
Electronic Thesis and Dissertation Repository

1-11-2013 12:00 AM

Reassembling Knowledge Translation Through a Case of Autism Genomics: Multiplicity and Coordination Amidst Practiced Actor-Networks

Julia J. Bickford
The University of Western Ontario

Supervisor
Dr. Jeff Nisker
The University of Western Ontario

Graduate Program in Health and Rehabilitation Sciences
A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy
© Julia J. Bickford 2013

Follow this and additional works at: <https://ir.lib.uwo.ca/etd>



Part of the [Translational Medical Research Commons](#)

Recommended Citation

Bickford, Julia J., "Reassembling Knowledge Translation Through a Case of Autism Genomics: Multiplicity and Coordination Amidst Practiced Actor-Networks" (2013). *Electronic Thesis and Dissertation Repository*. 1097.
<https://ir.lib.uwo.ca/etd/1097>

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlsadmin@uwo.ca.

RE-ASSEMBLING KNOWLEDGE TRANSLATION THROUGH A
CASE OF AUTISM GENOMICS: MULTIPLICITY AND
COORDINATION AMIDST PRACTICED ACTOR NETWORKS

(Spine title: «Reassembling Knowledge Translation: A Case of Autism Genomics »)

(Thesis format: Monograph)

by

Julia Bickford

Graduate Program in Health and Rehabilitation Sciences

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctorate in Philosophy

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

© Julia Bickford 2013

CERTIFICATE OF EXAMINATION

Supervisor

Examiners

Dr. Jeff Nisker

Dr. Sandra DeLuca

Supervisory Committee

Dr. Allan Pitman

Dr. Marilyn Evans

Dr. Regna Darnell

Dr. Carol Herbert

Dr. Janice Graham

The thesis by

Julia Joy Bickford

entitled:

**Re-Assembling Knowledge Translation Through a Case of Autism
Genomics: Multiplicity and Coordination Amidst Practiced Actor-
Networks**

is accepted in partial fulfillment of the
requirements for the degree of
Doctorate of Philosophy

Date

Chair of the Thesis Examination Board

Abstract

Knowledge translation (KT) has become a ubiquitous and important component within the Canadian health research funding environment. Despite a large and burgeoning literature on the topic of KT, research on the science of KT spans a very narrow philosophical spectrum, with published studies almost exclusively positioned within positivism. Grounded in a constructionist philosophical position and influenced by actor-network theory, this dissertation aims to contribute to the Canadian KT discussion by imagining new possibilities for conceptualizing KT.

This is an empirical-theoretical study which is based on eight months of data collection, including interviews, participant observation, and document analysis. This data collection took place in a basic science laboratory, a clinic, and amongst families involved in genomic research pertaining to Autism Spectrum Disorder in a Canadian city. Interviews were transcribed verbatim and organization of the data was aided by QSR Nvivo software. Theoretical insights put forward in this dissertation are based on a detailed description of the everyday, local, micro-dynamics of knowledge translation within a particular case study of an autism genomics project. Through data collection I have followed the practices of a laboratory, clinic, and family homes through which genomic knowledge was assembled and re-assembled.

Through the exploration of the practices of scientists, clinicians, and families involved in an autism genetics study, I examine the concepts of multiplicity, difference, and coordination. I argue that autism is practiced differently, through different technologies and assessments, in the laboratory, clinic, and home. This dissertation closes with a new framework for and model of the knowledge translation process called the Local Translations of Knowledge in Practice model. I argue that expanding the range of theoretical and philosophical positions attended to in KT research will contribute to a richer understanding of the KT process and move forward the Canadian KT agenda. Ethics approval for this research was obtained from The University of Western Ontario and from the hospital in which the data was gathered.

Keywords

Autism Spectrum Disorder, Knowledge Translation, Genomics, Actor-Network Theory, Practice theory, Constructionism, Multiplicity

Acknowledgments

Keeping in mind all of the ideas and concepts I have learned from Actor-Network Theory, this dissertation might aptly be described as a “black box”. My name printed in black letters across the title page gets to stand in for all of the work, conversations, readings, seminars and coffee breaks with teachers, friends and family members throughout the last five years. This is what the acknowledgements section is really about, “de-centering” the author and making visible all the hidden work, all of the people who have helped me at various points and places during this degree.

First of all, I want to thank the many people at Laboratory X and the Autism Clinic for allowing me to hang around and talk with them. Despite their own tight deadlines and busy schedules, they were extremely patient and willing to help me conduct my research. Two people in particular, a post-doctoral fellow involved in sequencing and a PhD student involved in microarrays were especially helpful in reading drafts of my descriptions, correcting where I had inaccurately presented the procedures involved in these two technologies. They are, however, in no way responsible for any remaining inaccuracies or blind spots in my descriptions. I am especially thankful to the laboratory director and the director of the clinic for taking a chance on me and letting me enter into these spaces. Their willingness to be vulnerable, to let me into the “back-stage” workings of their day-to-day work in the interest of pursuing an understanding of knowledge translation was remarkable. They allowed me to watch them, talk with them, attend meetings; they shared slides, emails, articles, and invited me to talks and presentations. They did all this without any control over the final written product, without any silencing of findings. Their willingness to allow me to conduct my research was an enormous act of trust and I hope I have succeeded in demonstrating that this trust was not misplaced.

I thank the parents whom I observed and interviewed for inviting me into emotionally-charged meetings and appointments and for their honesty and candour in the interviews. The feedback sessions I observed were, in many cases, probably pivotal moments in family members' lives, short but defining events through which changing individual and family identities were initiated. For some, the hour-long visit in which feedback was given might be one of those highly remembered events that persist in a family's collective identity, talked about or carefully avoided for years to come. I am so grateful to have had the privilege to sit quietly in these sessions and to learn from them.

To my supervisor, Dr. Jeff Nisker, I am grateful for his unfailing confidence and support throughout this process. He gave me the guidance and direction I needed while also accommodating my preference to work independently. He waited patiently while I took not one but two maternity leaves of absence since beginning this degree. It was also Dr. Nisker who provided the initial connection with autism genomics and helped to negotiate my entrance into the field sites. Had I not had the privilege of working with such a supportive supervisor I might easily have given up long ago.

I am also thankful for the many discussions and helpful feedback from the members of my advisory committee: Dr Regna Darnell and Dr. Allan Pitman. The careful consideration and thoughtful insights you provided, each from your own disciplinary perspectives, were integral to the analysis and writing process and I am deeply indebted to you for moving this process forward.

I also want to acknowledge the many classmates and teachers with whom many of the ideas and theories in this dissertation were initially explored. Actor-network theory, being a relatively marginal approach, was initially a solitary adventure for me. However, finding a few others who were interested in ANT was extremely helpful and enriching, as I regularly

met and discussed ideas with Dr. Allan Pitman, Dr. Farrukh Christie, Richard Booth, and Dr. Akbar Saaed. I especially want to acknowledge my friend and classmate, Dr. Jodi Hall, who inspired me as another mother and PhD student; our discussions often spanned disparate topics from breast feeding to performance studies. Also my friend and fellow graduate student, Dr. Mark Dolson, in anthropology with whom I have had many theoretical discussions has helped me maintain connections to my anthropological roots despite leaving my disciplinary homeland.

I am thankful for the three years of funding I received from SSHRC during this degree. This funding made it possible for me to balance a full-time PhD workload with birthing and parenting two young children.

Finally, I want to thank and acknowledge my family. My parents and siblings have always encouraged me to pursue my academic interests. My mother was especially supportive, frequently taking care of my children while I attended classes or seminars. To my girls, Beatrice and Eliza, I thank you for giving me a new perspective as a mother. Holding you as babies, watching you learn and engage with the world, playing with you as you've grown into toddlers and pre-schoolers have enriched my life more than you'll ever know. Most of all, I want to thank my husband, Ben, for putting up with me these last five years. Your encouragement and support has been boundless. Your companionship through this PhD process has made the stressful moments less strenuous and the positive moments even more fun.

Table of Contents

RE-ASSEMBLING KNOWLEDGE TRANSLATION THROUGH A CASE OF AUTISM GENOMICS: MULTIPLICITY AND COORDINATION AMIDST PRACTICED ACTOR NETWORKS.....	i
CERTIFICATE OF EXAMINATION	ii
Abstract.....	iii
Acknowledgments.....	v
Table of Contents.....	viii
List of Tables	xi
List of Figures.....	xii
List of Plates	xiii
List of Appendices	xiv
Preface.....	xv
Chapter 1	1
1.1. Finding an Entrance	1
1.2. Research Questions.....	8
1.3. Purpose.....	9
1.4. Autism or ASD?.....	10
1.5. Doing Fieldwork	12
1.6. Methods.....	14
1.7. Process of Interpretation and Representation.....	19
1.9. Quality Criteria.....	24
Chapter 2	29
Groundwork: Philosophical Footings	29
2.1. First Layer: Theoretical Position.....	31
2.2. Second Layer: Methodology.....	37

2.3. Third Layer: Epistemological Mooring	54
2.3.b Epistemology or Ontologies?: Practiced Knowledges, Practiced Realities	60
2.4. Relating my Philosophical Position to Knowledge Translation	70
Chapter 3: Research Ethics	73
3.1. Approaching Anonymity.....	74
3.1b Anonymity when “studying up”?.....	79
3.2 Tensions in the research process: anonymity? "thick description"? or something in between?	85
3.3. Expectations of Research Participants	91
Chapter 4	94
Inside-Out and Upside-Down: Tumbling into the World of Autism Genomics	94
4.1. Diagnosing Autism	95
4.2. Genomic Constructions of Autism.....	97
Chapter 5: Translation as Transformation	107
5.1 Setting the Stage.....	109
5.2. From Individual to Blood.....	116
5.3. From Blood to DNA	121
5.4. The Microarray Process: From DNA to CNVs.....	124
5.5. Validation – From CNVs to <i>Real</i> CNVs.....	143
5.6. From CNVs to SNPs - Next Generation Sequencing.....	150
5.7. From Data to the Report.....	165
5.8. Exit the Laboratory: The Feedback Session.....	169
5.9. Back into the Clinic.....	173
5.10 Setting the Stage: The Autism Clinic.....	175
5.11 Entrance: Into the Family Home	188
5.12 Summary	197

Chapter 6: From Problematization to Mobilization: An Actor-Network Theory Account of Translation	199
6.1. Overview of Callon’s Framework.....	201
6.2. Problematization in Autism Genomics Research.....	203
6.3. Interestment in Autism Genomics Research	204
6.4. Enrolment in Autism Genomics Research	206
6.5. Mobilization in Autism Genomics Research	214
6.6. Conclusion	217
Chapter 7: Translations Amidst Difference and Multiplicity	219
7.1. Overview of Key Concepts	221
7.2. The Practiced Individual with Autism	226
7.3 Autism(s) in Practice(s)	248
Chapter 8: Reassembling Knowledge Translation	270
<u>8.1. Reassembling Knowledge Translation</u>	271
8.2. Knowledge Translation According to the CIHR.....	275
8.3. Time for a New Conceptualization of KT?.....	281
8.4. Comparing the KTA and LTKP Frameworks.....	293
8.5 Conclusion	297
Appendices.....	325
Appendix A: Key Concepts in Genomics	325
Appendix B: Some of the Equipment Needed for Next Generation Sequencing	327
Appendix C: Knowledge Translation in Autism Genomics.....	328
Appendix D: The Local Translation of Knowledge in Practice (LTKP) Model.....	329
Curriculum Vitae	330

List of Tables

7.1 Anonymity or Description	86
8.1 Comparison of the KTA and LTKP frameworks	293

List of Figures

3.1 Ethics Documents Statements Pertaining to Confidentiality	90
4.1 Wet Laboratory	112
4.2 Flow Chart Depicting CNV Interpretation Process	136
4.3 Example of a DGV slide	163
6.1 Image of Maps Pinned to Laboratory X Bulletin Board.....	233
6.2 Pedigree.....	261
8.1 The CIHR KTA Process	277

List of Plates

2.1 Situated Author	30
2.2 Rock Strata	31

List of Appendices

Appendix A: Key Concepts in Genomics	325
Appendix B: Some Equipment Needed for Next Generation Sequencing	328
Appendix C: Knowledge Translation in Autism Genomics	329
Appendix D: The Local Translations of Knowledge in Practice (LTKP) Model	330

Preface

"Ring, ring, ring!"

I race to answer the phone at a speedy *I-just-got-the-baby-sleeping* pace. Hurdling a Sesame Street play toy I grab the phone from the charger and press talk.

"Hello?" I say, trying not to sound out-of-breath.

"Julia. It's Jeff. How are you doing?"

"I'm great. How are you?"

"Good. Is this a good time to talk?"

"Um-hum, sure."

"Ok great. I'm actually in the middle of a Genome Canada meeting and I had to call you.

We're just having a 10-minute break and I stepped out of the room. There is this guy named Bob Lorenz [pseudonym] who just presented his current research and it's really amazing stuff. He's got some really interesting findings on copy number variations and autism. I just had to call and tell you about it..."

This was the beginning of a conversation that took place in the winter of 2008 which subsequently propelled my research in its current direction. Upon first applying to enter the PhD program I had tentatively proposed a research site in Montreal at a clinic providing pre-implantation genetic diagnosis (PGD). At this point, my partner was still looking for a teaching position and was relatively free to move around; we also did not have any children. Fast-forward 18 months and we had a baby, a mortgage, and Ben had found a much-coveted teaching position - moving to Montreal for 8-12 months suddenly didn't seem so feasible. I was just returning from a maternity leave and I needed to find another research site. I was still interested in knowledge translation and genetic research and hoped to find some way of exploring the day-to-day practices or micro-dynamics of translation. I was especially

concerned with the narrow theoretical scope from which knowledge translation was being explored in the health sciences literature. I wanted to find a field site that could act as a case study in which to approach knowledge translation from a constructionist position, in contrast to the taken-for-granted positivist positions which seemed to dominate KT discussions. I hoped to be able to demonstrate how knowledge translation could be approached from a different epistemological and methodological position in order to ignite discussion amongst those entrenched in positivist approaches to KT. When Jeff called, I jumped at the opportunity and began to explore autism genomics as a potential case study through which I could re-assemble KT.

The year following this phone call from my supervisor was spent finishing my course work and writing my comprehensive exams. In December of 2009 my supervisor and I met with Dr Lorenz at his lab to talk with him about my ideas and to get a sense for how willing he might be to have me hanging around his laboratory for the better part of a year. Waiting outside his office, I remember feeling nervous. This Dr Lorenz [pseudonym] was obviously one of the top guys in this field. The space was beautiful, modern, state-of-the-art. An enormous lab filled with machines and bustling white lab coat clad bodies spanned the length of one side of the main hallway. Jeff told me that Dr Lorenz had previously been named one of Canada's "Top 40 under 40" for scientific minds in this country. His office door opened and we sat down at a round table. Dr Lorenz was very friendly and low-key. He seemed amused or perhaps bemused that an anthropology/ health sciences student would be interested in his laboratory as a site that warranted ethnographic investigation. We talked for about fifteen minutes and by the time we left it was just a matter of doing the necessary REB paperwork before I could begin fieldwork as far as Dr. Lorenz was concerned. Before leaving his office, he also invited me to attend an annual meeting that was happening with all the

people involved in the autism genetics project across the country. It just so happened that this all-day meeting was to be held in his laboratory conference room in two days time.

Two days later I found myself sitting in a chair pushed against a wall of a very crowded conference room. There were people from across Canada, both basic scientists and clinicians. A woman rushed in at the last minute as the doors were closing. She sat down on the only seat left in the room, which happened to be beside me. We went around the room quickly introducing ourselves and I came to realize that this woman beside me was actually Dr Felicia Morten [pseudonym], the director of the Autism Clinic. She was the very woman with whom I was hoping to talk about extending my field site into her territory. Needless to say, people quickly shuffled around and space was made for her at the table in the centre of the room. She was a major player in the Autism Genetics Project and her ability and need to speak at the table signified her importance. At a break for lunch I did manage to chat with her for about two minutes about my research and she said she would be happy to discuss it further with me. I ended up meeting with her again for about twenty minutes in the kitchen of the genetics laboratory before one of the subsequent Monday morning meetings about a month later. She was interested in this approach to examining knowledge translation and agreed to have me extend the fieldwork into the autism clinic.

This dissertation describes some of what I have learned in the two years since these initial meetings.

Chapter 1

- 1.1. Finding an Entrance
- 1.2. Research Questions
- 1.3. Purpose
- 1.4. Autism or ASD?
- 1.5. Doing Fieldwork
 - a) Location
 - b) Timeline
 - c) Participants
- 1.6. Methods
 - a) Types of Data Collected
 - b) Limitations to Data Collection
- 1.7. Process of Interpretation and Representation
- 1.8. Reflexivity
- 1.9. Quality Criteria
 - a) Authenticity
 - b) Ethnographic Validity
 - c) Deploying Actors as Networks

1.1. Finding an Entrance

First Entrance

I opened the London Free Press newspaper this morning and depicted on the front page was a photograph of a 5000 year old body found mummified in an Italian glacier. Scientists have just completed sequencing this man's DNA and found him to be lactose intolerant and to have a predisposition for coronary problems. Strung out, letter by letter, his DNA sequence appears to be quite similar to that of the many human genome sequences created from amalgamations of people living today. The article mentions that the DNA sequence is being

openly shared on a website so that specialists from different disciplines can analyze it as there is more than a lifetime of work in analyzing this mummy's sequence. I only scanned the article briefly as I was also bouncing Eliza on my knee and eating a bagel but I need to follow up on it when I get a chance. I'm not sure how, but I think perhaps this article might provide an entrance into my dissertation.
(JB journal entry, March 2nd, 2012)

Genomic research is entering the public imagination and has been for several years. Popular movies (for example, *Gattaca*, *Bladerunner*), fiction (for example, Ian Douglas's *Inheritance Trilogy*, 2009) and popular TV shows (for example, *Bones*, *CSI*, *Who is my Baby's Daddy?*) are bringing the idea of genomics into the living rooms of many Canadians. Scholarly articles covering genomic findings filter through to daily newspapers, discussed over coffee and toast around the breakfast table. Of course, much of the genomic work carried out in laboratories across Canada is not on 5000 year old mummies. Within the purview of health research, genomics has been given the task of uncovering the secrets of single gene disorders such as cystic fibrosis (Kerem et al., 1989)(Riordan et al., 1989) and Huntington's (Gusella et al., 1983) and is now moving on to complex polygenic conditions such as schizophrenia (Xu et al., 2012) and Autism Spectrum Disorder (Leblond et al., 2012). I like this newspaper article (Rose, 2012) on Otzi man's genomic profile. Perhaps I am influenced by the summers working on archaeological digs during my undergraduate degree, the monotonous hours of sifting through dirt punctuated by instances of excitement in finding a clay pipe bowl or post-holes. The public sees the "Indiana Jones" exhilaration of finding amazing insights into our past. The vast majority of work that lays behind these findings remains eclipsed. These images conjured up out of archaeology appeal to me; they seem relevant to the hundreds of movements repeated over and over in the laboratory in order to map a genome sequence, occasionally yielding something the scientists find "interesting".

Most of the work being conducted inside the genomics laboratory is beyond the view of the public. What really goes on in a genomics laboratory? How does this genomic research relate to clinical work and to individuals diagnosed with autism and their families? How is it translated? What if, instead of focusing on the findings, we focus on all the day-to-day work that lies behind them? If we keep in mind the bottles and beakers, buffers and pipettes, slides and chips, computers and people, the messiness of the practices in the laboratory, we might understand better how genomic research is constructed and how it relates and translates to the equally messy practices of the clinic and the family home.

This is one way I could introduce the reader to my research, but there are other possibilities to consider as well.

Second Entrance

It is April, 2011. I have been invited by one of the senior clinicians in the clinic where I will be doing my research to sit in on a conference for parents of children with ASD. A large screen at the front of the room is showing a movie taken from a hidden camera in a school yard. In the movie, it is recess and the camera microphone detects a cacophony of children yelling and playing, seemingly enjoying themselves. There are children running around or just standing in groups talking. The presenter at the front of the room takes her laser pointer and tells us to “keep your eyes on this boy in the movie”. The boy in the movie is sitting alone on the side of the track and field track. He is bent over with his chin resting on his knees. It looks like he is holding a stick and is drawing in the dirt. Another boy comes toward him and kicks him, spraying dirt in his face, and then walks away. A minute later another boy yells at him and calls him a “loser”. The boy is wearing a hidden microphone but the sound is still kind of muffled amidst all the background noise. The bell rings shortly after and the boy slowly gets up and walks, head down, back toward the school. Another group of

kids approaches him and he is shoved hard. A teacher stands near-by but doesn't seem to notice with the activity of rounding everybody back inside after recess. The movie ends and the presenter, a child psychologist, tells us that this boy is diagnosed on the autism spectrum. He and many other similarly diagnosed children often endure verbal and physical bullying. Her research has studied the school experiences of children with ASD and she wants to raise awareness of bullying in the education system.

At the coffee break I talk to some of the people sitting near me. They all have children with autism. Their children are different ages, some toddlers, school aged, or young adults. Many of these parents have changed their lives, quit their jobs even, trying to cope with the challenges that face their children. I meet a woman who works at the autism clinic that I am studying for my research. She too has an adult son with autism and she has been an advocate for him and others like him for a long time. She explains that he is entering into a stage of life, adulthood, which will bring a whole new set of challenges for someone living with ASD.

This is another entrance, through the lives of the people living with ASD. How is genomic research related to them and the activities they engage in? Many of the parents are keen to sign up for genetic research while others are more ambivalent, worried about what genetic findings might be used for in the future. How is genomic research changing the lives of people and families living with ASD? How does it translate into their everyday world?

Third Entrance

Autism was first diagnosed by Leo Kanner in 1943 (Kanner, 1943). Since then, it has become entangled in and constructed through a wide variety of networks of associations, from psychodynamic to genetic. During the 1950's and 1960's a psychodynamic approach to autism was predominant. Through this approach autism was believed to be caused by

destructive interactions between a baby and his/her mother. One of the main proponents of this approach was Bruno Bettelheim (Bettelheim, 1967). Bettelheim believed that the causes of autism were environmental and could be traced back to infancy. He proposed that an anxious mother was unable to adapt her reactions to her baby's cues. He suggested that children who were quiet and isolated in their first year of life may become autistic in their second year of life, upon learning to speak and walk, "when their reaching out to relations led to what they viewed as destructive responses. This, in my opinion, is why they gave up all initiative" (Bettelheim, 1967). Thus, for Bettelheim, autism was a defence mechanism, a learned response to a hostile environment. He went so far as to compare the home environments of autistic children to concentration camps: "In the German concentration camps I witnessed with utter disbelief the nonreacting of certain prisoners to their most cruel experience...like others who have worked with autistic children, we were again and again confronted with a parallel blotting out of all pain"(Bettelheim, 1967).

In *The Empty Fortress* (1967), Bettelheim describes the relationship between a mother and her autistic child as "destructive and inescapable...because of the one single relation that propelled him out of a position of love and ambivalence with overwhelming force he became, so to say, glued to hate" (Bettelheim, 1967). Bettelheim directed an institution, The Sonia Shankman Orthogenic School at the University of Chicago, for the rehabilitation of children with emotional disturbances. Among the residents, autistic children were taken from their parents and placed in the School, often living there for years. Bettelheim (Bettelheim, 1955) felt that "when a child is securely established at the School and accepts it as a reliable frame of reference for his life, he becomes able to deal constructively with the experiences he had in a less secure world, with past failures and disappointments". Thus, for several decades following Kanner's initial description of infantile autism in 1943, Bettelheim and the

psychoanalytical approach prevailed, blaming so –called “refrigerator mothers” for autism.

Since this time, there has been a complete reversal in how autism is constructed in the clinic. Mothers are no longer blamed by psychologists for causing autism in their children. During the 1970’s, as twin studies were published, the genetic underpinnings of autism gained acceptance amongst the scientific community. Since this time many technological advancements in microbiology have changed the way that genomics is practiced. How are recent genomic findings in the laboratory seeping into the clinical practice of autism? How is autism constructed in the clinical context? Who and what are the various actors that reassemble autism in the various spaces and activities of the clinic?

Each of these entrances provides a different context from which to explore genetic research in autism. In setting out to do this study, I wanted to understand how genetic research translates within and amongst each of these contexts: the laboratory, the clinic, and the homes of individuals and families living with autism. I wanted to tell a story about autism genomics as it is assembled and reassembled in these different spaces. But how should I do this? How do I tell a story about the *translations* between these places? Stories are often linear affairs, with a beginning, middle, and an end. The audience is gently coaxed along a particular trajectory until they arrive at a conclusion. Much of the messiness, the collisions between voices and the branching off of alternative trajectories, is left untold.

In reading this dissertation, its organization might be interpreted in several different ways. Upon first glance, the chapters appear to conform to the standard layout. An introduction and background gives way to some new findings and a conclusion is reached. A single story is made to unfold. There are other ways of reading this, however. Each chapter is also its own story containing its own trajectories and voices. For example, the ways in which the notion of *translation* is registered varies amongst the chapters in the body of this

dissertation. In Chapter Four, translation is described as a process of transformation as I follow the enactment of an individual diagnosed with autism, and then blood, then DNA, computational outputs and graphical representations, PowerPoint slides, reports, feedback diagrams, scores on clinical assessments, and then back to the individual and his/ her family. In Chapter Five, translation in autism genomics is described as a predominantly political process in which human and nonhuman actors are enrolled in a network and mobilized or fronted by spokespeople. In Chapter Six, translation is again reassembled; here I explore the idea of translation as coordination amongst different enactments of reality. While each of these chapters is ostensibly about autism genomics, on another plane of analysis I am also critically engaging with the concept of knowledge translation; each of the chapters highlights aspects of translation (i.e., transformation, the political, coordinating multiplicity) that are largely absent in the KT discussions found in the Canadian health sciences literature.

There are connections and coherences percolating amongst the chapters. They interfere and interact with each other. There are philosophical and theoretical stories entwined within these pages as well. There are also ruptures, deep crevices that hint at the friction among various voices and trajectories. A break in chapter headings might signify a break in the cartography of assumptions, and with it the landscape of autism genomics changes, multiplies. Again, on another plane of analysis, these frictions and ruptures are also the spaces that hold the potential for new possibilities for imagining knowledge translation.

In reading this dissertation this way, I hope to not only describe multiplicity and difference within the context of autism genomics, I also want to perform this multiplicity. The word *I* is very important here. It is my performance. Each chapter enacts another way in which I have come to understand autism genomics. All of the accounts are mediated and

performed through my own body. Some researchers include a separate section or story describing how the topic of study relates to them personally. I have chosen not to do that. To do so might risk the creation of a binary opposition between that which is personal and subjective and that which is impersonal and objective. Such distinctions would be inconsistent with the constructionist assumptions underpinning this research.

1.2. Research Questions

According to Eakin and Mykhalovskiy (2003) in qualitative inquiry the research question often "functions more as a compass than an anchor, and is sometimes not really known until the end of the research. The following questions are those that I have attempted to address in this dissertation:

1. Within the context of recent findings about copy number variations, how is genetic knowledge about autism constructed through the various practices, places, and spaces in the laboratory?
2. How is this genetic knowledge *translated* amongst the laboratory, autism clinic and families involved with autism genetics at Hospital X?

Drawing on constructionist, practice theories, this research adopts the view that knowledge is inseparable from the practices through which phenomena are known. Knowledge does not merely reflect the world, but also constructs the world. Different knowledge practices construct different objects. In the context of my research, it is not only knowledge about autism that is being constructed and translated within and amongst the laboratory, clinic and home, but also autism itself. Knowledge is viewed as a practice, entangled in the material reality of the world. Following from this assumption, several other research questions have emerged in this research:

1. How is autism constructed in the laboratory, clinic and family homes involved in the

autism genetics research at Hospital X?

- a) Who/ what are the actors that are assembled around "autism" in the laboratory?
- b) Who/ what are the actors that are assembled around "autism" in the clinic?
- c) Who/ what are the actors that are assembled around "autism" in the home?

2. How is "autism" coordinated/ translated throughout the Autism Genetics Study?

- a) Where are there controversies/ discrepancies in the practices of "autism" across the autism genome research at Hospital X?
- b) What are the strategies for coordination between scientists, clinicians, and parents of individuals diagnosed with autism?
- c) How is "autism" practiced in the shared/ hybrid spaces within the autism genetics research?

1.3. Purpose

The purpose of this research is to re-conceptualize knowledge translation within the particular context of autism genomics, considered from a constructionist philosophical position and as informed by actor-network theory. It is a descriptive agenda. My hope is not to prescribe a set of rules or steps to follow when engaging in KT. Rather, I will explore how knowledge translation can be described and explored when approached from this theoretical and philosophical position. Description in this context is simply empirical enquiry persuasive to scientists as well as to participants in the study whose work it hopefully informs.

The need for a broader conceptualization of KT has been suggested by Greenhalgh et al (2004), with specific calls for more theory-driven approaches (McWilliams, 2007; Reimer Kirkham, Baumbusch, Schultz, & Anderson, 2007). Following these critiques, the purpose is to demonstrate how KT can be re-conceptualized and re-positioned within a broader range of theoretical and methodological approaches, which could complement (or potentially disrupt)

the current understanding and models of KT predominant in the health sciences literature. In this way, I hope to ignite a discussion about the limitations of existing orientations to KT, and offer an alternative approach, thereby expanding the philosophical and methodological breadth of the Canadian KT agenda.

1.4. Autism or ASD?

Throughout this dissertation I have chosen to use the word “autism” rather than Autism Spectrum Disorder (ASD). ASD is a complex and heterogeneous diagnosis, a spectrum with an enormous range of clinical manifestations. In the practice of autism genomics, however, the complexity of this diagnosis is reduced. As I observed and formally and informally interviewed members of the laboratory, autism was referred to in a binary manner. In practice, the complexity of the spectrum is reduced to a binary phenomenon: individuals diagnosed with autism, siblings, parents, family members in an extended pedigree were either on or off the spectrum, diagnosed with autism or not. This is not to say that the complexities of diagnosis and differences and variation within the spectrum were not discussed and practiced within specific circumstances and locations within the clinic and home. However, as autism pertained to genetic testing, the complexity and diversity of the spectrum was reduced.

To some degree, this simplification and reduction of the autism spectrum is also being reflected in changes being made to the Diagnostic and Statistical Manual V (DSM-V), forthcoming in May 2013. Particularities and sub-classifications are being reduced. This also reflects my experience of how clinicians and scientists talk about and think about ASD in the context of genetics. Participants frequently used the word “autism” to stand in for everything on the spectrum. In almost all of the conversations and observations I had, participants talked about autism in a binary way, either you have it or you do not.

Furthermore, my research is not focused on how autism is clinically diagnosed. Throughout my fieldwork I never observed a clinical diagnosis being given. The issue of variations and the differences within the autism spectrum are an entire other realm of complexity that warrants its own empirical investigation that is well beyond the scope of the focus of the present research. In all cases that passed through the unit and laboratory that I observed, the individual already arrived with a diagnosis of ASD. Thus, if I have reduced the complexity of the autism spectrum to a simple binary opposition in my interpretation and representation it is because that is the way autism was practiced by those whom I observed and interviewed in the context of autism genetics. Put in another way, my use of the word “autism” reflects its emic construction (how it is used and practiced by the people I observed within the specific contexts of autism genetics), which may not reflect the formal definition of autism found in medical text books. For example, one clinician described autism in this way:

Now, the tools that we use, you still need to use clinical judgment. Because the tools, like for example, you're either on the spectrum or you're not. But it doesn't mean, sometimes you need to use your clinical judgment to determine, is it autism, is it Asperger's, is it PDD-NOS, which is going to be irrelevant with the next DSM. So it's going to be ASD or not. So there won't be those classifications any more. It's changing. That's why sometimes the clinical diagnosis and the research diagnosis may or may not be the same. But typically you're either on or not on the spectrum.

Thus, there are many areas in the autism clinic in which much attention is focused on sub-classifications within ASD. Certainly, clinicians spend a great part of their day arriving at specific diagnoses within the spectrum. The clinic that became my field site was a research

clinic with a wide variety of research studies. Some of the projects the clinicians were working under were not connected to genetic research, while other studies were intimately tied to genetics. Throughout the day, clinicians had to shift between opening up or black-boxing the complexity of ASD as they moved between activities that were not part of genetic studies and those that were. Within the specific context of autism genomics, which is the focus of my present research, the distinctions and particularities within the diagnosis tended to be re-scripted as a binary classification. Following this, I have adopted the word autism throughout the text. In the few spaces of my descriptions and interpretations where sub-classifications on the spectrum are evoked, I consciously turn to using the term ASD.

1.5. Doing Fieldwork

a) Location

This research took place within a hospital in a Canadian city. In order to preserve the anonymity of participants, all names of places and people have been altered. The hospital will be referred to as the Hospital. Within this hospital, data collection was carried out in an applied genomics laboratory and in an autism research clinic. The laboratory will be called Laboratory X and the clinic will be referred to as the Autism Clinic.

b) Timeline

Final ethics approvals from The University of Western Ontario and from the hospital research ethics board were granted in February of 2011. As I was on a maternity leave, data collection did not commence until June of 2011. Much of the data was collected throughout the summer months between June and September in which I tried to travel to the field sites at least once or twice a week. Much of the observational data was collected in this time. Between October and March, many of the interviews were conducted with less emphasis on

observational data collection. During these months I would travel to the field site a few times each month. Data collection was completed in March 2012. However, following this, several key informants were contacted to review the written sections of my dissertation for feedback. I wanted to ensure that the descriptions of the activities in the laboratory and clinic, in particular the descriptions in Chapter 4, were being described accurately. I state this, however, recognizing at the same time that the descriptions are partial and contain less technical detail than “native” inhabitants of the laboratory or clinic would use.

c) Participants

Participants at Laboratory X had a variety of educational backgrounds including molecular biology, genetics, zoology, and bioinformatics. They represented a variety of positions at Laboratory X including post doctoral fellows, PhD students, project coordinators, laboratory technicians, facility managers, assistant directors and the director. These participants varied in the amount of time they had been working at the laboratory, from eighteen months to fifteen years. The laboratory scientists whom I recruited into this study were purposively sampled. In order to be able to follow DNA as it moves through the laboratory, I approached people who were experts at each stage of the genomic experimental process from DNA extraction to report writing.

In the autism clinic, participants included psychology PhD students, psychologists, developmental paediatricians, project coordinators, a parent liaison, genetics counselors, and clinical geneticists. The participants from the autism clinic had been working there for a range of one year to ten years. The clinicians who participated in this research do not represent a sample. They are an entire population as I interviewed and observed everyone in the clinic who carried out clinical work as part of the autism genomics project.

Parents of children with autism had all participated in genetic testing at the hospital

and had received feedback about the results of those genetic tests. In total, six parents participated in an interview, five mothers and one father. Genetic results varied for each of the families. While each child had been reported to have a copy number variation (CNV), the location of the CNV was different amongst families; different genes were affected from one family to another. Moreover, while five of the families received genetic feedback indicating the genetic variant was inherited, one family had results indicating a *de novo* (or spontaneous and non-inherited) variant. All participants were at least 18 years of age and all of them spoke English. When children were in the room while I was observing at the autism clinic, for example when I observed the Autism Diagnostic Observation Schedule (ADOS) and intelligence testing, parents signed consent forms on the child's behalf. When possible, children signed an assent form. The parents were chosen based on a convenience sampling strategy in which I approached anyone whom I was aware of being given genetic feedback during the time I was in the field.

1.6. Methods

Data collection included document analysis, participant observation, and interviews with three groups of people: basic scientists working at Laboratory X, clinical researchers working through at autism clinic, and parents of children diagnosed with Autism Spectrum Disorder who were participants in the genetic research taking place within Laboratory X and the autism clinic. All of the people working or studying as part of the Laboratory and autism clinic were also part of the same hospital.

a) Types of Data Collected

i) Laboratory X

I conducted seventeen semi-structured interviews with eleven people at the

Laboratory over the course of data collection. All of the semi-structured interviews were digitally audio recorded and transcribed verbatim. Interviews ranged from fifteen minutes to over two hours, with most lasting approximately 45 minutes. I also carried out several informal interviews, chatting in the hallway before or after meetings or asking quick questions during observations. I also went down to the cafeteria with participants for lunch on several occasions which prompted further opportunity for discussion. None of these informal interviews were recorded or transcribed. Instead, I took field notes either during or directly after these interactions.

Data collection also included participant observation, or “deep-hanging out”, in which I followed participants around and made notes on what I was observing as they went about their daily routines and tasks in the laboratory. I observed different kinds of meetings, including Monday morning meetings, laboratory meetings, and Exome sequencing meetings. I was able to observe laboratory experiments taking place such as PCR, microarray and Next Generation Sequencing (NGS). Almost every time I conducted a semi-structured interview with someone at the Laboratory, they walked me through the laboratory, taking me through the various steps in an experiment and showing me the instruments used or the various data print-outs produced along the way.

Several types of documents were included in analysis, such as PowerPoint presentations, NGS protocol, meeting agendas and meeting minutes, as well as peer-reviewed publications that were either authored by Laboratory X members or discussed at meetings. Email was often used to announce interesting articles being published in the scientific literature. In addition, several of the web-sites used in the Laboratory X for genomic analysis were scrutinized for this research, for example, The Database of Genomic Variants (<http://dgvbeta.tcag.ca/dgv/app/home>) and the 1000 Genomes Project

(www.1000genomes.org).

ii) The Autism Clinic

I conducted nine semi-structured interviews with nine participants at the Autism Clinic. All of these interviews were digitally, audio recorded and transcribed verbatim. Interviews varied in length from 30 to 60 minutes. I also informally chatted with clinicians while walking to and from meetings or while eating lunch in the lunchroom. I observed meetings, presentations, intelligence testing, ADOS testing and assessment scoring and genetic feedback sessions. I also analyzed various documents, such as patient consent forms, PowerPoint presentations, peer-reviewed articles authored by Autism Clinic employees, and ADOS assessment forms.

iii) Parents of Individuals diagnosed with Autism

Data collection with parents included observation of genetic feedback sessions as well as subsequent semi-structured interviews, which were digitally audio recorded and transcribed verbatim. I was able to observe four feedback sessions with parents, individuals diagnosed with autism (called *probands*), and siblings. In addition, I conducted semi-structured interviews with parents at least 2 months after they received the genetic feedback. These interviews were between 25 and 40 minutes in length. Ideally, I would have liked to engage in participant observation within the homes of these individuals and families. However, in discussions with my supervisor and the director of the autism clinic, it was decided that this form of data collection in the home would be too intrusive and burdensome for families.

b) Limitations to Data Collection

i) Laboratory X

One of the biggest limitations was my ability to observe inside the laboratory. Several of the experiments have steps that require intense concentration for the person running the experiment. They cost up to twenty five thousand dollars per run and I was told, understandably, that certain steps would not be open to observation because of this. As a result, I was reluctant to casually walk into the laboratory and observe without setting up a formal appointment for being there. I did not want to walk up to a participant working over a lab bench unannounced and inadvertently introduce error into an experiment.

ii) Autism Clinic

As with the laboratory, there were limitations in my ability to casually “hang-out” in the Autism Clinic. The area is small with most employees working in cubicles. Telephone conversations with parents were being conducted in these spaces and so any talking or informal interviewing would have been distracting for employees trying to carry out their daily activities. There was physically nowhere for me to stand that was out of the way as hallways were unusually narrow in this space. The large lunchroom was the only open space where I felt I was not in the way. The other problem with casually dropping in to observe at the autism clinic was that a locked door stood between the front waiting room and the rest of the clinic. On the few times I tried to drop-in to causally observe, I ended up waiting for hours in the waiting room before anyone realized I was there. This is because there are some days when there is no receptionist sitting at the waiting room sliding window. If patients are not booked for a morning or an afternoon on these days, there is no reason to check if anyone is in the waiting room. Observations, therefore, took place at pre-arranged times such as for a specific assessment, feedback session or meeting.

This limitation to accessing participants, to conducting participant observation, is faced by many anthropologists, but is perhaps particularly characteristic of research that attempts to engage relatively elite people and institutions. As Gusterson (1997, pp., 115) has noted, “participant observation is a research technique that does not travel well up the social structure”. As such, Gusterson called for anthropologists to break with a “fetishistic obsession with participant observation” (Gusterson, 1997, pp., 116) and instead adopt a more “polymorphous engagement” of participants which entails collecting data eclectically from dispersed sites, and across disparate sources. Following this vein, in my own research participant observation was not hierarchically positioned as more valuable or insightful than interviews or document analysis.

iii) Family Home

One of the limitations of recruiting parents into my study was that there were very few parents receiving genetic feedback regarding ASD. In the first three months of fieldwork only two families received feedback and I was only able to observe one of these. (The research coordinator forgot to tell me about the other feedback session. So I did not know it had occurred until after the fact.) Fortunately, there were a few more feedback sessions that occurred between November and January. Thus, while my sample of parents might appear small this is because the entire population from which I was recruiting was extremely small. Indeed, two of the parents interviewed had been given genetic feedback over a year earlier but had heard about my study through their ongoing involvement with the autism clinic. With so few families receiving genetic feedback during my fieldwork, I chose to interview these two mothers as well. Important to note, many of these families had been waiting for nine or ten years since their blood was first collected for genetic testing. It is only with recent technological advances that clinically significant variants are being detected.

Overall, the most significant limitation in my ability to collect data was the distance between where I live and where Laboratory X and the Autism Clinic were located. It took a two hour train ride as well as a subway ride or half hour walk in order to get from my house to my field site. As a result, I could not participate in the kind of day-to-day, deep hanging out that typically characterizes ethnographic field work. I also had a young, nursing infant as well as a toddler at home throughout this fieldwork. While there were weeks when I commuted back and forth every day, I typically went in only once or twice a week.

1.7. Process of Interpretation and Representation

In the social sciences there is only interpretation. Nothing speaks for itself. (Denzin, 2004)

The ongoing process of interpretation and representation consisted of a constant manoeuvring back and forth between books and articles I was reading and the data I was collecting in an effort to make sense of what I was learning in the field. All of the data I collected - interview transcripts, documents, participant observational field notes - were gathered together in QSR Nvivo 9. This software is purely an aid to organization and allowed me to hold together, in one place, all of the data I was amassing. From a constructionist standpoint the researcher is intimately involved and implicated in the interpretation of data. In the interpretation process relations are made between literature and data. The conceptual tools, the theoretical assumptions adopted by the researcher precede the *doing* of ethnography and shape what is seen in the field and written in a text (Van Maanen, 2004). At times it is about reading through the data with the literature in mind and at other times it is about reading through the literature with the data in mind.

I found the train rides to and from the field sites to be particularly productive times, in

which I would reflect on the relationships between what I was reading and observing and hearing. My field notebook contains many jottings and bursts of insight that often raised further questions. These entries came to be known to me as Train Thoughts. The train ride was a liminal place, between the spaces in which data was collected and the formal writing space of my “office”. By reading back over these train thoughts I can trace the various trajectories of my thinking and follow which lines of inquiry were left as loose ends, questions unexplored, and which I ended up pursuing within this dissertation. As it is for many, the interpretation was done through the activity of writing (Richardson, 2004), whether this writing took the form of expanded field notes, jotting in Train Thoughts, or more formal attempts to solidify my ideas in drafts of this dissertation. As Denzin asserted, “a situated, writing self structures the interactions that take place among the writer, the text, and the reader” (2004).

Through interpretation, the researcher imposes an order on the world being studied. Denzin outlined four phases in the process of moving from the field to a written text: sense making, representation, legitimation, and desire. Sense making concerns how the researcher moves from field notes to the actual writing process. I used the time riding on the train to write out descriptions of how what I had just experienced in the field related to particular concepts or ideas I was reading in the science studies literature. It was in these “Train thoughts” that I began to try out theoretical orderings on my field notes. Representation, according to Denzin, deals with the issue of voice, and reflexivity as the author positions herself within the text. At the end of this chapter, I describe in more detail the issue of reflexivity. Legitimation concerns how a text makes claims for its own authority. Reliability, validity, and generalizability are typical hallmarks of legitimation in post-positivist texts but are not appropriate in constructionist texts. Verisimilitude or truth is established through

detailed descriptions of field experiences. Denzin stated, “authentic understanding is created when readers are able to live their way into an experience that has been inscribed and interpreted” (2004). I have dealt with this issue of legitimation in further detail in the section below on quality criteria. Desire pertains to the issue of making a reader enjoy a text, making it vital and gripping. I have tried to make the text readable by attempting to portray vivid descriptions of the places and people I encountered.

The codes I developed were not seen as inherent within or emerging out of the data itself but rather as signposts to the ideas and concepts about which I was reading. I interpret codes as a nexus between author, data, and influential literature. I developed coding schemes for each of the three sub-groups (laboratory, clinic, family) within my study. I was then able to compare across these three coding schemes to look for similarities and differences amongst them. I further coded the instances and circumstances in which the actor-networks of these three sub-groups came together. As such, the coding scheme and the way the data were approached is directly related to the research questions, with three coding schemes focused on each of the spaces (lab, clinic, family home) as separate actor-networks and another coding scheme focused on the hybrid spaces in which networks became entangled. What I have written is a complex entanglement of field notes and memories that have been assembled and reassembled through the art of interpretation. The theoretical ideas presented in this dissertation are not new; there is nothing original in writing about post-humanist constructions of scientific knowledge; these concepts are borrowed from the published literature. My contribution is to take these ideas and to begin to relate them to another arena of discussion in which I have not seen these ideas surface before, that of Knowledge Translation (KT).

1.8. Reflexivity

According to Kinsella & Whiteford (2008), reflexivity "goes beyond pragmatic reflection to embrace a critical dimension and to carefully interrogate the very conditions under which knowledge claims are accepted and constructed. Reflexivity recognizes the sociality of the process of knowledge generation". With this definition in mind, science studies or the sociology of scientific knowledge (SSK) is synonymous with a reflexive endeavour; the *raison d'être* for this field of study is to explore how science actually works, its assumption and practices on the ground which contribute to the making of scientific knowledge.

Lynch (2000) asserted that there are actually many different meanings and uses of reflexivity, depending on who is doing the reflecting, on what they are reflecting and what are the intended outcomes or goals of reflecting. In Lynch's words, each kind of reflexivity "involves some sort of recursive turning back, but what does the turning, how it turns, and with what implications differs..." (2000).

Reflexivity is utilized by Latour (1988) to indicate "any text that takes into account its own production and which, by doing so, claims to undo the deleterious effects upon its readers of being believed too little or too much" (Latour, 1988). Infra-reflexivity, supposes that no amount of layering of self-consciousness will ever bring a text closer to a referent. For Latour, infra-reflexivity is a process of "displaying the knower and the known and the work needed to interrupt or create connections between them" (1988). Since any account is always a story, Latour proposes that we add as many genres and styles of narration as possible. He stated (1988) "the reflexive character of our domain will be recognized in the future by the multiplicity of genres, not by the tedious presence of 'reflective loops'". In this

way, the knower or the writer is pushed off stage and the spot light is turned once again to things in themselves.

According to Latour the Actor-Network Theory (ANT) account "has to be able to register differences, to absorb multiplicity..." (Latour, 2005), much the same way that Woolgar calls for sustained uncertainty and the juxtaposition of multiple interpretations. The text itself is a mediator in ANT. Here, then, more recently Latour has recounted his claim that all we can do is write stories. He laments the claim that just because there is no absolute Text, all texts are relative. Instead, he contends that "textual accounts are the social scientist's laboratory and if laboratory practice is any guide, it's because of the artificial nature of the place that objectivity might be achieved..." (2005). The artificial and the objective, truth and fiction are not set in opposition to one another but instead are intimately mixed together. Latour continues by stating:

A good text is never an unmediated portrait of what it describes - nor for that matter is a portrait. It is always part of an artificial experiment to replicate and emphasize the traces... The simple act of recording anything on paper is already an immense transformation that requires as much skill and just as much artifice as painting a landscape or setting up some elaborate biochemical reaction (2005).

As described previously in this chapter, this dissertation attempts to perform multiplicity, to register differences in the ways that I experienced, approached, and interpreted the activities I encountered during field work. I have tried to keep myself, as author, in focus, to show how I was entangled in the activities amongst the different spaces I entered. My feelings, anxieties, naivety break through the surface of various descriptions and interject, *in an italic font*, another voice. My body, clumsy and unfamiliar with the choreographed rhythms and movements of the laboratory or the clinic, offered another vehicle from which to register and compare the practices in these different spaces. As such,

data was not only gathered through listening or observing but also through my body as a physical object that had to squeeze between, hover around, had to become partially disciplined in the fashion of these various spaces so as not to bump into temperamental machines, for example. I had to learn when I could ask questions and when I needed to remain silent. Thus, as will be explored in the following chapter, knowledge production was experienced as a fleshy, corporeal event rather than a mental bi-product. From this perspective, knowing becomes a practice, an activity intimately tied to the material world. Reflexivity, then, is about keeping those connections and ties in focus and refusing to allow insights to be black-boxed and severed from the bodies, machines, feelings, and tools through which they are constructed.

I can not claim to offer *the* story of autism genomics. This is because the interactions and activities I observed cannot be reduced to a single story. Moreover, the observations and conversations I entered into were confined to a single year and doubtless some of the actors have changed already. It is not a story about what autism genomics is, but instead, I aim to tell a story about the tensions and differences in the way that autism genomics is becoming. It is a story of the *doing* of autism genomics.

1.9. Quality Criteria

The whole point of 'evoking' rather than representing is that it frees ethnography from mimesis and the inappropriate mode of scientific rhetoric that entails 'objects', 'facts', 'descriptions', 'inductions', 'generalizations', 'verification', 'experiment', 'truth' and like concepts that, except as empty invocations, have no parallels either in the experience of ethnographic fieldwork or in the writing of ethnographies.
(Geertz, 1988, p. 136)

How does one assess the quality of research? What are the standards or criteria for discerning

a high-quality versus a low-quality text? As will be described further in the following chapter on Philosophical Background, I argue that actor-network theory is a methodological approach very much akin to ethnography. As such, I put forward two key criteria for assessing the quality of research, which are typically associated with ethnographic works. These two criteria are authenticity and ethnographic validity. In addition, I propose an ANT-centred quality criteria, that of deploying actors as networks.

a) Authenticity

Ethnography is about trying to "persuade readers....that what they are reading is an authentic account by someone personally acquainted with how life proceeds in some place, at some time, among some group" (Geertz, 1988). The quality or 'author'ity of an ethnographic text rests in its claim to authenticity. The ethnographic text must persuade the reader that "I was there". This can be done in different ways. Geertz is often quoted for his example of *thick description* (2001). Similarly, Atkinson describes the rhetorical device called *hypotyposis* as a key means of establishing a narrative contract. Hypotyposis is:

the use of a highly graphic passage of descriptive writing, which portrays a scene or action in a vivid and arresting manner. It is used to conjure up the setting and its actors, and to 'place' the implied reader as the first-hand witness (P. Atkinson, 2001, p.98).

Thus, one criterion for a good ethnographic account is authenticity - the ability to persuade the reader that "I was there".

Chapter four is a detailed account of the activities that I observed in the various spaces of the laboratory, clinic and family home. I have tried to leave the reader with my sense of what these spaces are like and what it is that people do in these spaces. There are, without doubt, huge gaps in my understanding of what is going on in these spaces. My interpretations of the practices that occurred as DNA passed through these spaces are based

on my understanding as someone who is not a genetic scientist, not a clinician, and not a parent of a child with autism. Many of the complexities and details with which insiders might be grappling in their daily work remain beyond my understanding. And yet, with the fundamental, basic insights that were shared with me in each of these spaces I am able to offer descriptions which begin to open up the complexity of translation.

b) Ethnographic Validity

The issue of validity is one discussed amongst post-structuralist social scientists with much ferment (Lather, 1993). The positivist definition of validity rests on a correspondence model of truth. This view of validity does not resonate well with a research project underscoring ontological multiplicity and non-coherence. Instead, validity must be repositioned as “multiple, partial, and endlessly deferred” (Lather, 1993, p.675). Richardson (1993), for example, describes a “transgressive validity” using poetry to “make visible both context and labour” (Richardson, 1993, p.696). Validity, then, involves illustrating the process through which a researcher comes to construct a particular representation.

According to Sanjek (1990) there are three canons on which ethnographic validity rests: theoretical candour, the ethnographer's path, and field note evidence. These all point to a reflexive stance in which the researcher engages with the process of constructing a textual account of the field site(s).

i) **Theoretical Candour** - A good ethnographic account will discuss how theory guides the process of fieldwork. The ethnographer cannot attend to everything at once while in the field. The ethnographer makes choices about what he/she attends to and these choices are guided by theory. In order to establish validity, an ethnography must be explicit about the theoretical reasoning behind these choices (Sanjeck, 1990).

In my research, I am interested in *how autism is practiced and translated through the*

assembling together of human and nonhuman actors in the laboratory, clinic and home settings. Thus, participant observation is integral to my research. Semi-structured interviews alone would not allow me to describe the mundane day-to-day practices of autism in the laboratory and clinical contexts. In my research, practice theory has implications for my choice of data collection methods. The interpretation and representation of the data that I have presented is also influenced by several theoretical concepts such as multiplicity and difference.

ii) **The Ethnographer's Path** - Ethnographic validity, according to Sanjek (1990), is also established by a detailed account of how the ethnographer was introduced to various people and contexts. The ethnographer's path is a kind of road-map to the fieldwork process, allowing the reader to follow along from point of first contact through to exiting fieldwork. The path brings the reader along, exploring how the ethnographer became connected to the people and places explored in fieldwork.

iii) **Field note Evidence** - The third canon of ethnographic validity requires the ethnographer to be explicit about the relationship between the field notes and the written text. Like the Ethnographer's Path, the issue of field note evidence is concerned with explicitly stating how the notes of the field inform the final text. This third canon might also draw on what Ottenberg called 'headnotes': "the notes in my mind, the memories of my field research" (Ottenberg, 1990, p.144). As Sanjek explained,

[W]e come back from the field with fieldnotes and headnotes. The fieldnotes stay the same, written down on paper, but the headnotes continue to evolve and change as they did during the time in the field...the headnotes are more important. Only after the anthropologist is dead are the fieldnotes primary (1990, p.93).

Ethnographic validity, according to Sanjek, requires that the ethnographer reflect on this process of how hundreds of pages of hurried scratches jotted in the field amount to the

chosen impressions and examples unfolded in a text.

In this dissertation, the various chapters draw from different experiences and interpretations of field work. For example, the story that unfolds in chapter four in which I map out and follow the route of genetic information as it is translated amongst laboratory, clinic and home is one way of ordering my fieldwork experiences. However, chapters five and six draw on particular theoretical concepts such as Callon's (1986) notion of translation, Mol's (2003) idea of multiplicity, and Law's notion of coordination. Thus, each of these chapters pulls out different experiences, allowing me to present different ways of assembling or ordering the data.

c) Deploying Actors as Networks

A good ANT account will deploy actors as networks (Latour, 2005). This means that the account must follow the translations and transformations of actors as they move in and out of various networks. An actor and the networks through which actors become associated are not conveyed as rigidly bounded or stable but rather are imagined as moving, changing, and in flux. Heterogeneity and complexity proliferate as the ANT account re-constructs the pathways through which actors move, subverting certainties about what any actor *is*. In my own research, I have attempted to trace the transformations of actors as they move through the networks of laboratory, clinic and family home in the context of autism genomics.

In the next chapter, I unfold the intricate layers of philosophical assumptions which have guided data collection, interpretation, and representation.

Chapter 2

Groundwork: Philosophical Footings

2.1. First Layer: Theoretical Position

- a) Theories of Practice

2.2. Second Layer: Methodology

- a) Actor-Network Theory (ANT)
- b) Criticisms of ANT
- c) How does ANT as a Methodology relate to Ethnography?

2.3. Third Layer: Epistemological Mooring

- a) Constructionism
- b) Epistemology or Ontologies?: Practiced Knowledge, Practiced Realities
- c) Both Constructed and Real

2.4. Relating my Philosophical Position to Knowledge Translation

"It is not a matter of looking harder or more closely, but of seeing what frames our seeing"
(Lather, 1993, pp. 693).



Plate 2.1: Situated Author

In this chapter I will attempt to position myself and make explicit the assumptions underpinning each stage of this research. These assumptions have informed the questions I have asked, the methods for data collection, the theories influencing the analysis of the data, and the way I have performed and presented the research in this written text. In this chapter I have organized these assumptions into three layers. To be sure, there are issues and debates which cut down through these philosophical strata, at times overlapping and folding these layers like the convoluted striations on a mountain rock face. As I work down through these philosophical layers in this chapter, these percolating issues and debates will be followed and mapped out as well.



Plate 2.2: Rock Strata

The top strata I will address are *theoretical*. Theories of practice have influenced this research. If we dig down a little deeper, we find the second layer, which is *methodological*. Although the word *theory* is embedded within Actor-Network Theory, I argue that this is actually a methodological stance. I will also discuss how this research relates to another methodological approach, that of ethnography. I argue that ANT and ethnography are overlapping methodologies. Finally, digging further, we find the third layer, which is *epistemological*. A description of the epistemological position I have adopted, constructionism, reveals assumptions about knowledge and the relationship between the knower and that which is known, subject and object.

2.1. First Layer: Theoretical Position

2.1a Theories of Practice

Practice theories are a heterogeneous response to structural determinist theories (Ortner, 2006). Ortner (2006), for example, traced the history of practice theories and described how practice theory emerged as an alternative to three major paradigms (symbolic anthropology, Marxist political economy, and French structuralism) which were all essentially theories of constraint. Through these three paradigms human behaviour was seen as shaped by external cultural forces. Practice theory, as it emerged in the late 1970's and early 1980's sought to explore the processes that produce these cultural constraints. Early practice theorists attempted to define a "dialectical, rather than oppositional relationship between the structural constraints of society and culture on the one hand and the practices of the social actors on the other" (2006). Ortner described practice theory as evolving over the last few decades, addressing the issue of power and the situatedness of practices in a historical context. Furthermore, the concept of culture is reworked through practice theory (Ortner, 1999). Culture is "loosened up" and tied less to geographically defined groups of people, acquiring a geographic and temporal mobility.

There is no single, unified approach underlying practice theory. However, while there are important distinctions between various theories of practice, at the core these theories all insist that human action is both constrained by a social or cultural order *and* that human action makes, reproduces, and transforms that socio-cultural order (Ortner, 1996). As such, practice theories tend to reject the dichotomy between macro and micro, structure and individual, instead reformulating these positions as mutually constituting one another through practice. It is through practice that dichotomies between subject and object, micro and macro might be described as being mangled (Pickering, 1995). It is through the central issue of agency that some of these dichotomies will be explored in this section.

Before delving into these issues and distinctions within practice theories, I first consider what is meant by practice. According to Schatzki (2001), “practices are arrays of human activity”. These activities are embodied and materially mediated. The embodied nature of practice is crucial as it is the body that is assumed to be the meeting place, the point of connection between the individual and the social, the micro and the macro. The material nature of practices is taken up by some more than others. In particular, Latour and those who engage with actor-network theory are especially concerned with a focus on non-humans in the study of practices. Most practice theorists also approach practice as shared, collective actions. A distinct social ontology has arisen in which practice theories approach the social as “a field of embodied, materially interwoven practices centrally organized around shared practical understandings” (Schatzki, 2001). The social then, can be understood by exploring how humans (and non-humans) interact with one another through shared practice. Barnes (2001) stressed that practice theories are not compatible with individualism, noting how humans “cannot be understood as independent calculative social agents, they stand revealed in their practice as profoundly interdependent, mutually susceptible social agents”. Thus, practice theories aim to show both how the social influences individuals and how individuals, through practice, make the social.

i) Where does agency lie?

Pickering (2001) outlined how agency is situated in a post-humanist theory of practice. Distinct from most social theory in which key concepts revolve around humans, a post-humanist position “recognizes from the start that the contours of material and human agency reciprocally constitute one another” (A. Pickering, 2001). In *The Mangle of Practice* (1995), Pickering sets out to describe how science is practiced in real-time. Rather than exploring how science *represents* nature, Pickering prefers to adopt a *performative* idiom. He

starts from the position that the world is constantly doing things; it is filled with agency. Science is a means of coping with this agency. Scientists, as human agents, build machines to “capture, seduce, download, recruit, enrol, or materialize that agency, tamping and domesticating it, putting it at our service” (1995). Through examples from old and new particle physics, Pickering describes the reciprocal process of “tuning” between human and non-human agency. He further describes this process as a “dance of agency”, which is elucidated in this quote:

Scientists tentatively construct some new machine. They then adopt a passive role, monitoring the performance of the machine to see whatever capture of material agency it might effect. Symmetrically, this period of human passivity is the period in which material agency actively manifests itself. Does the machine perform as intended? Has an intended capture of agency been effected? Typically the answer is no, in which case the response is another reversal of roles: human agency is once more active in a revision of modelling vectors, followed by another bout of human passivity and material performance” (1995).

This dance between agencies is a dialectic of resistance and accommodation. The world initially resists some human attempt to capture it and in turn humans accommodate this material agency and modify their instruments and machines. It is through this dialectic, this constant shifting back and forth between human and material agency, that Pickering’s post-humanist position on agency emerges. This dialectic which he calls the *mangle of practice*, attempts to keep in view simultaneously human and non-human agency. In this post-humanist space human and material agency are intertwined and reciprocally defined. This post-humanist space is one in which “the human actors are still there but now inextricably entangled with the nonhuman, no longer the centre of the action and calling all the shots” (1995).

Knorr-Cetina (2001) has further elucidated the post-humanist position in the context

of epistemic practices. According to Knorr-Cetina, epistemic practices are based on a form of relationship, a relationship between subjects and objects. Scientific objects, objects of knowledge are those things that are at the centre of investigation, that are in the process of being defined through research. They “are characteristically open, question-generating and complex. They are processes and projections rather than definitive things” (Knorr-Cetina, 2001). In this way, knowledge objects are different from objects that we encounter in everyday life, such as tools or goods that can be characterized as a closed box. Conversely knowledge objects are characterized by their lack of completeness as they are in the process of being materially defined. She describes epistemic objects as having an “unfolding ontology” which highlights changes in these objects over time. She states that inquiry tends to increase rather than reduce complexity of knowledge objects.

Moreover, epistemic objects often exist in a variety of forms simultaneously. For example, in her field of high-energy physics, Knorr-Cetina notes how the detector “continually circulates through a collaborating community of physicists in the form of partial simulations and calculations, technical design drawings, artistic renderings, photographs, test materials, prototypes, transparencies, written and verbal reports” (Knorr-Cetina, 2001).

Knorr-Cetina approaches epistemic practices as a type of relationship between subject and object. When epistemic objects are in the process of being materially defined scientists attempt to capture the object, to represent it. Through initial experiments an object is partially defined and the representations often imply what is still missing, suggesting directions from which to approach the object in future. Knorr-Cetina describes this desire to capture the object as a “chain-of-wanting”. This structure of wanting between the scientist and the epistemic object offers a view of practice that is embedded in relational dynamics. Through practice objects and scientists are mutually engaged: “objects provide for the chain of

wanting through the signs they give off and what they still lack and scientists (subjects) provide for the possibility of the unfolding of the objects through experiment. In this way, practice is oriented toward the future as the nature of an epistemic object unfolds through the successive attempts of experts to pin it down. Knorr-Cetina points to the emotions, the excitement and pleasure, involved in epistemic practice through which subject and object are mutually engaged.

The issue of how agency emerges in this dichotomy between individual actors and over-arching structure is addressed by Latour more recently through the idea of scripts (Latour, 2012). Individual actors are involved in several competing scripts simultaneously. At times our actions are guided by scripts and at other times we write those scripts. At times we live under the script; here the script delegates instructions to us to be carried out. At other times we live above the script and as such we insert instructions into the script. Latour proposes, however, that we are “never simultaneously but always sequentially fabricators and fabricated, and we shift roles at specific deadlines that are themselves scripted” (2012). The individual-structure dichotomy is made more complex here as Latour interrogates the concept of the individual, instead highlighting the possibility for a single actor to take the form of many characters inscribed into different, and often contradictory, scripts. The structure is nothing more than what is written in these various scripts. The relations between individual and structure are registered through flip-flopping below and above the scripts over time.

In this research, I have adopted a theoretical position based on practice theories. In particular, I have been influenced by post-humanist theories of practice, which acknowledge the agency of both humans and nonhumans in the activities of science. This dissertation adopts the position that individuals make the social and that the social influences and

constrains individuals. Thus, practice theories enable one to simultaneously focus on divergent ends of the individual-social and subject-object dichotomies. As will be explored more fully in the discussion of methodology and epistemology, this bi-focal perspective is achieved by foregrounding nonhuman actors. While practice theories ideally illustrate both how the social constrains the individual and how individuals make up the social, this research has focused on the latter. The methodological approach found within actor-network theory, explored below, details why only one half of the practice theory agenda has been dealt with in this research, as the social (or cultural) is viewed as a category that needs to be explained rather than one that is used to explain other things.

2.2. Second Layer: Methodology

2.2a Actor-Network Theory

Methodology denotes how the would-be knower, the researcher, can go about finding out whatever he or she believes can be known (Guba & Lincoln, 2004). As Crotty (1998) explained, methodology is “the strategy, plan of action, process or design lying behind the choice and use of particular methods and linking the choice and use of methods to the desired outcomes.” Actor-Network Theory (ANT), I argue, can be considered a methodology, one that shares similarities with ethnography. ANT surfaced in the 1980’s in the field of the social studies of science. It was initially put forward by Bruno Latour. Law (1999) has described ANT as the semiotics of materiality or relational materiality; “It takes the semiotic insight, that of the relationality of entities, the notion that they are produced in relations, and applies this ruthlessly to all materials – and not simply to those that are linguistic” (1999). Further, ANT proposes that these relations between materials are not inherent by themselves but that these relations have to be performed. It is through semiotic materiality and performativity that ANT becomes a methodology informing how researchers approach a

research question and the desired outcomes of research.

In this section I will outline some of the main components of ANT: actors, networks, and the tension between actors and networks. I will discuss how this methodology informs one's plan for carrying out investigations and the intended outcomes of using this methodology. I will also briefly address one of the key criticisms levied against ANT regarding its ability to address issues of power and politics. Finally, I will briefly address how an ANT methodology might be described as overlapping with ethnography.

i) Actors

Anything that modifies a state of affairs is an actor. In actor-network theory, the activity of acting is spread widely; it is not only humans that act. For example, in the context of genetic research on "autism", actors might include equipment, tools, tests, statistics, print-outs, journal articles, blood samples, and granting agencies along with technicians, administrative personnel, and scientists. Each of these could be considered a potential actor depending if and how they are drawn into controversies. Thus, ANT studies often describe both *human* and *non-human* actors as they are entangled with one another. Instead of assuming objects are passive, ANT focuses on how the material world pushes back on people (Latour, 1992). This is not to suggest that ANT confers intentionality to non-living objects, but rather that action loses any humanistic assumptions. Nonhuman actors can be anything that forces others to do something. For example, the flashing or beeping seatbelt signal that warns a driver to put on his/ her seatbelt when starting a car could be a nonhuman actor (B. Latour, 1992). The same language of agency is used to describe objects on either side of the traditional dichotomy between things that belong to nature and things that belong to society. This is arguably one of the most defining characteristics of ANT - the inclusion of non-human actors.

Latour wrote about the "underdetermination of action...the uncertainties and controversies about who and what is acting when 'we' act" (2005). Just as an actor on a stage in a theatre is never alone (there are props, backstage crew, lighting, audience reactions, a script, a playwright...the list could go on), the word "actor" in actor-network theory indicates a *dislocation* of action. Latour suggested that we should "remain puzzled by the identity of participants in any course of action" (2005) instead of deciding too quickly who and what is doing the acting. Latour has described ANT as "a very crude method to learn from the actors without imposing on them an *a priori* definition of their world-building capacities" (1999b). It is in this sense that ANT can be approached as a methodology rather than a theory. As Latour stated, it is "simply a way for the social scientists to access sites, a method and not a theory, a way to travel from one spot to the next" (1999b).

ANTs approach to studying non-human actors is not without its critics. There have been several arguments and discussions within the field of science studies addressing this inclusive definition of the "actor". For example, Yearly and Collins (1992) questioned how, as humans, we can speak for non-human agents who cannot speak for themselves. They chastised Latour for what they called his "absence of methodological control over fantasy" (1992). Moreover, they were concerned about the essentialist implications of taking non-human actors too far:

If non-humans are actants, then we need a way of determining their power. This is the business of scientists and technologists; it takes us directly back to the scientists' conventional and prosaic accounts of the world from which we escaped in the early 1970s (Yearly & Collins, 1992).

Thus, Yearly and Collins, along with Bloor (1999) and those in the Edinburgh school, prefer to adopt a humanist approach. Jensen recapitulated Yearly and Collins's position and stated:

On the one hand the epistemological realist position of science is granted, but it is then doubled by the position of the sociologist who is able to really point to how realism is the result of the open and negotiable work of scientists (but notably *not* the open and negotiable work of natural entities) (Jensen, 2004, p. 239).

Thus, for Yearly and Collins it is the sociologists who are really able to provide an account of science and how it works.

Latour's aims are different, choosing to trace the networks between human and *non-human* actors, all of whom have agency. Similarly, Pickering (1995) has portrayed the practice of science as a "mangle" in which "the dance of agency...takes the form of a dialectic of resistance and accommodation" (1995). He elaborated on his concept of the mangle by noting that from this perspective science is seen as an "evolving field of human and material agencies reciprocally engaged in a play of resistance and accommodation in which the former seeks to capture the latter" (1995). Thus, contrary to the Edinburgh school which, for the most part, obfuscated the role of non-human agency in science, Pickering and Latour call for a gaze that captures both human and non-human agency simultaneously.

Actors become *Black-Boxed*

One of the difficulties with following actors is that many actors quickly become *black-boxed* once a controversy is resolved or an innovation is taken for granted. Black boxing is a process in which an idea/ knowledge is rendered "distinct from the circumstances of its creation" (B. Latour & Woolgar, 1986). This process of black-boxing is also referred to in the ANT literature as 'punctualization' (Akrich, 1992). As an example, we might say that the double-helix model of DNA is a black box. It is taken for granted. All the actors - discussions, models, alternative hypotheses, people, tools, and tests - that were part of the context in which the double-helix model was developed have dropped from the description. DNA *is* a double helix: order is created out of disorder. In other words, as a network

becomes stronger and more stable a network can be treated as a point or a node rather than a network.

When phenomena are black-boxed it is tricky for the ANT analyst to unpack those boxes and recover all the important actors. In this light, Latour (2005) has offered a few suggestions on how to attune oneself to situations in which actors are more likely to become visible. For example, one suggestion is to study *innovations* (e.g., the scientists' laboratory), where objects are not yet taken for granted and are made visible through meetings, plans, sketches, and regulations. A second setting in which actors become more visible is in *accidents* or *breakdowns*. At these times, objects that were a moment before taken-for-granted, automatic, and invisible are suddenly scrutinized and quickly made visible.

In my research on knowledge translation in the context of autism genomics I have adopted this approach. Autism as a genomic object is still in the process of being constructed and in this sense its construction is visible. It has not yet become black-boxed, allowing me to trace how it is assembled in the networks of the laboratory, clinic, and family home.

ii) Networks

"...[T]he elements bound together in a network (including people) are constituted and shaped by their involvement with each other" (Lee & Brown, 1994, p. 775).

In ANT, the actor is not explored in isolation. Rather, actors *act* in relation to other actors within a network. The word network in ANT has a very specific meaning that was intended to convey two key attributes: instability and transformation. Deleuzian concepts such as the “fold” and the “rhizome” underpin the ANT notion of the network (Jensen & Rodje, 2010). "Network" is a common-place word today and has lost the meaning that was intended when actor-network theory was first named. Specifically, Latour explained:

At the time, the word network, like Deleuze's and Guattari's term rhizome, clearly meant a series of transformations - translations, transductions - which could not be captured by any of the traditional terms of social theory. With the new popularization of the word network, it now means transport *without* deformation, an instantaneous, unmediated access to every piece of information. That is exactly the opposite of what we meant" (Latour, 1999b).

Latour (2005) described "double-click" information which is associated with the internet. Double-click information travels from one user to another without change; inputs and outputs are the same. Unlike a network of highways which is stable and transports vehicles from one place to another without any change, in ANT, actors are modified by their involvement within a network. The second characteristic of networks in ANT is that they are unstable and ambiguous. Actors can have multiple ties to many networks simultaneously (Singleton & Michael, 1993). If actors leave a network it will change or even fail altogether.

The work by Williams-Jones and Graham (2003) on genetic testing demonstrates two of the key attributes of the ANT network - transformation and instability. Williams-Jones and Graham (2003) demonstrated the ambiguity and instability of networks over time, underscoring the work needed to maintain the enrolment of actors. The network, in ANT, does not have to be composed in a certain way; it could always be different; networks may fail and fall apart. These authors mapped the networks of 'BRCA-testing' which included actors such as technicians, geneticists, counsellors, patients, families, reagents, sequencers, laboratories, corporate interests, and stockholders. For a time, Myriad Genetics was able to hold together one version of the BRCA-test network; key actors such as the British Columbia government were enrolled. For example, public testing was halted through cease and desist letters as the British Columbia provincial government laboratories stopped providing public testing, instead referring patients to Myriad. However, in 2003, after a period of two years, the B.C. government reversed its position on gene patenting and resumed 'in-house' testing.

Thus, the network that Myriad had attempted to stabilize eventually broke down and changed as key actors left to join other networks.

In the example above, the two key characteristics of the network in ANT are apparent. First, the network is unstable. The BRCA-test network that Myriad Genetics attempted to hold together eventually broke down and changed altogether when the B.C. government bypassed the pharmaceutical company. The transformative nature of networks is also emphasized; for example, a genetic test is modified into a *commercial resource* in the Myriad network.

Networks and the Research Analyst

Networks do not just apply to the human and non-human actors brought together by the members of the groups we study. Consider Strathern's statement that the "theorists' interpretations are as much networks as any other combination of elements" (1996). In an ANT account, the analyst has been typically situated outside the network being described (Schwartz Cowan, 1987). This warrants further consideration. How do the networks of the analyst and the networks of the field site interact in the written account? How does the analyst situate him/herself in relation to the networks being traced? Law (2000) explored this issue directly. He contended that there are many different ways of ordering what we describe in our fieldwork, with different aspects of the personal being drawn into the stories we tell. He urges researchers to consider what he calls "narrative interference", to pay attention to how we are performing the stories we tell about our research site. Attending to our bodies as a site for ordering, in particular at times when different orderings cannot be aligned into a coordinated, singular story, we "become sensitive to the multiplicities of the world" (Law, 2000). As there are multiple ways in which the networks we study can assemble and change, so too can the network within which our account is situated. Thus, Law seems to suggest that

just as actors influence and are influenced by the other actors in a network, so too is the author/ researcher. We too become de-centred, located in different subject positions as we relate to different objects.

In other words, in ANT the analyst may be thought of as a network builder among network builders. Latour has stated, "the text, in our discipline, is not a story, not a nice story. Rather, it's the functional equivalent of a laboratory. It's a place for trials, experiments, and simulations" (B. Latour, 2005, p. 149). Here, Latour reframed Law's idea of performing narratives (2000); to Latour we are like scientists in a laboratory when we write. Considering *Laboratory Life* (B. Latour & Woolgar, 1986), by invoking a laboratory he implies that we very active in ordering our world(s).

One of the difficult decisions when adopting an ANT approach is in knowing when a network has been fully traced. How do we stop the network-tracing activity and declare data gathering and analysis to be finished? Strathern (1996) asked how to "cut" the network. She stated:

the power of such analytical networks is also their problem: theoretically they are without limit...one can always discover networks within networks; this is the fractal logic that renders any length a multiple of other lengths, or a link in a chain of further links. Yet analysis, like interpretation, must have a point; it must be enacted as a stopping place (Strathern, 1996).

Doubtless, there are probably many network-cutting possibilities. *Ownership* is one example offered by Starthern: "...[B]elonging divides and property disowns. So where technology might enlarge networks, proprietorship can be guaranteed to cut them down to size" (1996). She considers the example of an invention; the academic article outlining the invention may include 50 names, while the patent contains only six. The network is quickly cut and boundaries are inscribed through ownership. Thus ownership and authorship are one means

of truncating a network. Others have suggested "promoting incompleteness and ambiguity [are] positive aspects of a theoretical strategy (Neyland, 2006, p. 43). Interpretation could be treated as a multiple, disputable, ongoing, fluid affair. Moreover, the length of the dissertation also dictates when the network is cut. Latour stated, "you stop when you have written your 50, 000 words" (Latour, 2005, p. 148). Elsewhere, Akrich and Latour have commented, "It is never clear where the 'real' limits of a setting are even though it has inscribed precise walls to itself - a book does not end with the word 'end'" (Akrich & Latour, 1992, p. 261). Perhaps the question to be concerned with is not where and how the network is cut but how the connections are traced within the part of the network explored. The text either does or does not capture the movement, activity, and translations in the actor-network being studied.

iii) Holding onto the Tensions in the "Actor-Network"

Micro-macro, local-global, individual-collective: there are many possible dichotomous positions that could be held in the space-holder of the "actor-network". The hyphen between actor and network in ANT implies that these two terms are brought into relation with one another. Law (1999, p.1) has described the actor-network as an "intentionally oxymoronic term".

This is perhaps the source of much confusion about just where an ANT approach is situated. According to Latour (2005), one of the main difficulties with these dichotomies is that they imply a *change of scale*. He described the tendency of social scientists to explain the local by jumping up to "social context", "frameworks" or "structure" and then later swinging back down to the individual setting. For Latour, the question is "to decide whether the actor is 'in' a system or if the system is made up 'of' interacting actors" (B. Latour, 2005,

p. 169). In ANT, one is not led away from the local; the macro/ global/ collective are described by focusing on the interconnections between many local sites. "Macro no longer describes a *wider* or a *larger* site in which the micro would be embedded like some Russian Matryoshka doll, but another equally local, equally micro place which is connected to many others..." (Latour, 2005, p.176) For Latour "there exists no place that can be said to be 'non-local' (Latour, 2005, p. 179). The network half of the *actor-network* term does not denote a larger "context" but rather describes the connections between the actors.

In ANT a researcher does not attempt to decide whether a phenomenon or interaction is best described as micro or macro. Instead, "scale is the actor's own achievement" (Latour, 2005, p. 185). The job of the ANT researcher is to trace how scale is achieved by following the actors themselves. This means that the tensions between large and small, individual and collective, micro and macro are not *overcome* by ANT; rather, these tensions become even more emphasized. The purpose of ANT is precisely *not* to overcome these dichotomous positions but rather to follow and describe how these positions are constructed through the process of *translation*.

In another example of how the tensions between dichotomous positions are held together in ANT, Law and Callon (1997) explained that anything can be thought of as simultaneously a point (an individual actor) and a network (a collective). This is because, according to these authors, an individual actor can be conceptualized as a black-boxed network. If we look closely at any actor, we begin to see the connections between a great number of elements assembled together. The authors explain that a black box:

"translates the various materials that make it up. It translates them by coordinating them, by fronting them, and by standing for them in a simple and coherent form. This means that for the moment the fronted network acts as a single unit" (Law & Callon, 1997, p. 170).

In this way, the actor and the network, the individual and the collective - each of these is understood in relation to the other. We do not want to have to choose one half of the dichotomy over the other as each is crucial to understanding the process of translation. ANT attempts to hold onto the tensions that emerge between two ways of seeing, simultaneously following both the individual and the collective, the actors and the networks. One does not replace the other; rather they are like two sides of a single coin.

iv) Context

Law and Callon (1992) suggested that "the notions of context and content ... may be transcended if projects are treated as balancing acts in which heterogeneous elements from both 'inside' and 'outside' the project are juxtaposed" (1992, p.22). Here Law and Callon move away from the idea of a *determined* actor and a *determining* structure; instead they aim to show how networks and actors are mutually shaped. They do this by exploring the development and eventual abandonment of a military aircraft called the TSR.2.

In the production of the TSR.2, the local network consisted of designers, designs, production teams, management, subcontractors, engine and wing positions, and the like. Initially, the global network included the Ministry of Defence, the Treasury and the Navy. New actors joined the global network, however, and threatened the success of the local network in carrying through with the construction of the TSR.2. For example, the Labour Party became a new actor, when they won an election over the Conservatives; moreover, an alternative aircraft called the F111 comparable to the TSR.2 was already in production in the US. Law and Callon (1992) point out that the success or failure of a technology rests on the ability to build and maintain local and global networks. Therefore, *context* amounts to the *associations*, the connections, between various actors in different networks. The context changes as new actors are introduced or old actors are called into question.

b) Criticisms of ANT

A primary criticism frequently levied against ANT is the claim that ANT is amoral and apolitical. However, there are many different ways of measuring politics. ANT perhaps captures the political in an unconventional way. According to Mol and Mesman (1996, p.436), "it generates new axes of difference. It creates new political categories". ANT pays attention to how a particular order is generated. By detailing the micro dynamics of how a particular order is achieved, ANT brings to the foreground places and times when alternative orderings could have arisen; the current ordering is not inevitable and networks of associations between actors can always fail.

Latour (1986) specifically addresses the issue of power, distinguishing between diffusionist and translational models of power. In the diffusion model, power rests on an initial force. In this model, one focuses on those who *have* power and those who do not. Power is used as an explanation. The translation model of power focuses on how power is shaped and transformed. It emphasizes the chain of actors needed for power to exist. For example, Latour proposed, "people who are 'obeyed' discover what their power is really made of when they start to lose it. They realize, but too late, that it was made of the wills of all the others" (1986, p.268). In this way, Latour understands power to be a *consequence* (a consequence of enrolling, convincing) rather than a cause of collective action. Thus, according to Latour, power is not something that can be possessed, but rather is practiced and made. The key point in moving from a diffusion model to a translational model of power is that power is not used to explain something else; instead, it is power itself that requires explaining.

Latour's account highlights the work involved in maintaining power; yet, ANT also records how some networks become robust, irreversible (M. Callon, 1991) and standardized

(Star, 1991). Star examined how stabilized networks exclude some actors. Specifically, she stated, "part of the public stability of a standardized network often involves the private suffering of those who are not standard - who must use the standard network, but who are also non-members of the community of practice" (Star, 1991, p.43). Star (1991) also acknowledged, however, that the multiple memberships any actor has in several networks simultaneously could be regarded as a mechanism for resistance. Thus, contrary to criticisms of being amoral or apolitical, I interpret ANT as having the potential to offer novel ways of exploring power and politics. Of particular relevance to this dissertation, I argue that the political is explicitly brought to the fore in an ANT-informed discussion of knowledge translation. The ANT notion of the political in the context of autism genomics and knowledge translation will be further explored in Chapter 5.

c) How Does ANT as a Methodology Relate to Ethnography?

"The only viable slogan is to follow the actors themselves" (B. Latour, 2005).

ANT is a methodology in so far as it guides the inquirer as to how to approach a question. ANT proposes that we trace the inter-connections between actors and that it is these connections which constitute the social. Latour has described ANT as "simply an attempt to allow the members of contemporary society to have as much leeway in defining themselves as that offered by ethnography" (2005). Inquirers have to engage in the world-making activities of those they study without deciding in advance who the actors are and what makes them act (Latour, 2005). Much like ethnography, the ANT inquirer must follow the actors themselves, follow the natives. So the ANT inquirer has the task of tracing connections between actors, registering differences in the ways that actors come together around controversies.

An ANT inquirer starts in the middle of things, in *medias res*. This methodology

points to certain methods such as conducting interviews, taking notes, leafing through documents, and clumsily loafing around (Latour, 2005). Through these methods the inquirer traces how actors become connected in different ways within different networks. In this way, the goal or intended outcome of an ANT account is descriptive rather than prescriptive. The task is to deploy actors as networks. A good account will perform the social, will bring together various actors into a collective (Latour, 2005).

All of this is very similar to and compatible with ethnography. I would suggest that ANT and ethnographies are over-lapping methodologies. Ethnographer means, literally, “writing culture”. An ANT methodology similarly aims to write an account of the social. They have different vocabularies but in practice an ANT inquiry is very similar to an ethnographic study. Perhaps, it would be helpful to describe ANT as a particular type of ethnography, one that focuses on culture or the social as a network of materially heterogeneous related entities. Indeed, many of the leading proponents of ANT have claimed to be engaged in ethnography (Latour & Woolgar, 1986; Latour, 1987). Others have described this methodology as a type of “praxiography” (Mol & Law, 2003). While there are similarities between ANT and ethnography, to be sure, there are also instances in which ANT is distinct from ethnography. These instances are described in the following section.

The Ambiguous Relationship between ANT and Ethnography

Disciplines define and redefine themselves interactively and competitively. They do this by inventing traditions and canons, by consecrating methodological norms and research practices, by appropriating, translating, silencing and holding at bay adjacent perspectives. They articulate, in tactically shifting ways, the solid core and the negotiable edge of a recognizable domain of knowledge and research practice (Clifford, 1997).

Ethnography and ANT are dynamic and changing methodologies. Neither of them is fixed and therefore it is difficult to outline the boundaries of one in relation to the other.

Further adding to the complexity, ethnography refers both to “the manner in which observations are made and to the process of compiling a description” (Strathern 2000, accessed at <http://virtualsociety.sbs.ox.ac.uk/GRpapers/strathern.htm>). In presenting an argument that ANT can be a distinct methodology, I am not proposing that ANT and ethnography are necessarily mutually exclusive in all circumstances. Certainly, many, perhaps most, scholars engaged in ANT research propose that they are simultaneously engaged in ethnography (Bruni, 2005; Heath, 1998; Hine, 2007; Latour & Woolgar, 1986; Neyland, 2006; Williams-Jones & Graham, 2003). I merely want to pause before making the knee-jerk genuflection to ethnography and ponder; can ANT stand on its own legs as a distinct methodology? I argue that while there are ways in which ANT and ethnography coincide, there are also tensions between the two methodologies; ANT can push hard against the limits of ethnography, compelled me to situate my own research within ANT specifically and more tenuously in relation to ethnography.

There are two principal reasons why I am uncomfortable with claiming the ethnographic label. The first is the centrality of prolonged participant observation to the ethnographic endeavor. While the role of participant observation as a necessary element of ethnography has been challenged over the last few decades, deep hanging out over and extended time remains an iconic right of passage for the ethnographer. The second reason why ethnography does not fit well with the approach I have taken to my research is the emphasis on meaning-making at the core of ethnography. Each of these tensions (long-term field work, and meaning-making) is discussed below.

i) Long-Term Participant Observation and the Ethnographic Psyche

Ethnography is not an easily bound methodology. Indeed, Atkinson et al (Atkinson, Coffey, Delamont, Lofland, & Lofland, 2001) celebrated the idea of “unity in diversity”. The borders of ethnography are being stretched and blurred with a growing proliferation of ethnographic sub-types (auto-ethnography, critical ethnography, cyber-ethnography, institutional ethnography, multi-sited ethnography, etc.), which each have their own particular emphases and contexts. The practice of ethnography typically conjures up images of prolonged contact with research participants in which the method of participant observation is paramount. Classic ethnographies such as Malinowski’s *Argonauts of the Western Pacific* (1922), Margaret Mead’s *Coming of Age in Samoa* (1928)(1928) or Evans-Pritchard’s *Witchcraft, Oracles and Magic Among the Azande* (1937) reinforce long-term participant observation as a requirement to claim the identity of ethnographer. However, since Nader’s (Nader, 1969) call for increased ethnographic research on the powerful (such as corporations, federal bureaucrats, political leaders), this expectation for prolonged participant observation as an integral aspect to ethnography has been challenged. Such expectations are not feasible in many of the field sites that arise when one chooses to “study up”. For example, the power dynamics and gate keeping involved in Gusterson’s (1997) study of a nuclear weapons laboratory presented significant obstacles to participant observation. While deep hanging out and prolonged engagement with research participants may be typical, ethnography cannot be reduced to a particular method. However, the focus on prolonged and deep engagement with a field site has left some science and technology scholars who “study up” more sensitive and less confident in their assertions that they are doing ethnography. Some have found it necessary to describe their studies as having “ethnographic sensibility” (Star, 1999). Meanwhile, Hine (2007) somewhat tongue-in-cheek,

described her methodology as “a methodologically eccentric historico-ethnographical autobiographically-inflected thematic analysis of the material and communicative cultures of systematics rather than simply ethnographic”(Hine, 2007). My own disciplinary movement from anthropology to health sciences has left me with less confidence in claiming the label of ethnographer given the way in which I have engaged with my topic of investigation, pushing hard against and perhaps transgressing what traditionally counts as ethnographic.

ii) Meaning-Making

The dynamics of doing fieldwork in private and privileged spaces, “studying up”, has perhaps loosened the grip that participant observation traditionally held around ethnography. Long-term participant observation may be an example of what Clifford (in the quote above) has described as the “negotiable edge” (1997) of research practice. If ethnography is not merely participant observation, then what is it? I argue that central to an ethnographic methodology is the practice of describing *meaning-making*, often in relation to the notion of culture. Geertz’s *Interpretation of Culture* (1973), for example, explores culture as semiotic. He wrote,

Believing, with Max Weber, that man is an animal suspended in webs of significance he himself has spun, I take culture to be those webs, and the analysis of it to be therefore not an experimental science in search of law but an interpretive one in search of meaning (Geertz, 1973).

Thus, meaning-making is perhaps an example of the “solid core” (Clifford 1997) of ethnographic research practice.

Why ANT is not necessarily Ethnographic

The primary tension between Actor-Network Theory, as I have engaged with it, and ethnography is this fundamental aim of ethnography to describe “meaning-making” through

the notion of culture. From my perspective, where ethnography and ANT rub up against each other with some friction is in how “culture” or the “social” are imagined. Through the interpretive turn, led by Geertz, culture came to be recognized as socially established structures of meaning embodied in symbols (1973).

The thing to ask about a burlesqued wink or a mock sheep raid is not what their ontological status is...The thing to ask is what their import is: what it is, ridicule or challenge, irony or anger, snobbery or pride, that, in their occurrence and through their agency, is getting said (Geertz, 1973)

Thus, meaning, meaning-making, the meaning-ladenness of cultural life are central to the ethnographic agenda. By claiming that ANT and ethnography are overlapping, I am, perhaps, pushing hard against this ingrained meaning-centredness of ethnography. This is because I have not explicitly focused on what autism genetics *means* to those in the laboratory, clinic, and family home. I have instead focused on how it is done, enacted, practiced in the material world. Even as I write this I am uncomfortable with this, as obviously meaning is intimately related to and tied up in practice. I stress however that in this dissertation I am more concerned with the objects themselves - DNA, autism, the patient - and how they are *done* through practice rather than focusing on the meanings that humans attach to these phenomena. Contrary to Geertz’s (1973) assertions in the quote above, I propose that the (multiply emergent and sometimes ambiguous) ontological status is precisely the thing to ask about autism! Thus, I have chosen to focus on ANT as a distinct methodology, albeit a methodology that shares many similarities with ethnography.

2.3. Third Layer: Epistemological Mooring

[W]e are not denying the existence of real, painful stress and suffering. There is, of course, a biological reality, but the moment that efforts are made to explain, order, and manipulate that reality then a process of

contextualization takes place in which the dynamic relationship of biology with cultural values and the social order has to be considered.

(Lock & Gordon, 1988)

Epistemology is concerned with knowledge, how we come to know what we know about the world and how this knowledge relates to nature. The dichotomy that comes to mind in the context of epistemology is that between realism and idealism. If one imagines various epistemological positions as being stretched out along a single axis with realism at one end and idealism at the other end, constructionism would be somewhere in the middle. Also central to a discussion of constructionism is the dichotomy between subject and object, and natural and social. Indeed, these dichotomies are intimately related to one another. I have tried to tease them apart in the discussion that follows.

a) Constructionism

Constructionism is often preceded by the word “social”. According to Hacking (1999), the underlying aim of social constructionist arguments is to raise consciousness. Specifically, these arguments critically examine how whatever it is that is said to be socially constructed is not inevitable; “that X as it is at present, is not determined by the nature of things” (Hacking, 1999) and it could always be different. Social constructionist arguments usually appear when X is taken for granted and seems to be inevitable. Hacking identified six grades of constructionism ranging from historical, ironic, reformist, unmasking, rebellious to revolutionary. In the historical vein, X is contingent upon historical events. Those who adopt this position are usually noncommittal about whether or not X is good or bad. The ironic commitment to constructionism follows that X is a contingent product of history but yet X is something that we cannot, at present, avoid in our interactions. Reformist feel that X is quite

bad and by demonstrating how it is constructed and not inevitable we might be able to change some aspects of X. The unmasking commitment to constructionism seeks to expose the function of X and thereby strip it of its authority. A rebellious constructionist believes that X is not only constructed but that X is bad and we would be better off without X. Finally, a revolutionary commitment tries to change the world in respect of X (Hacking, 1999).

In examining Hacking's six categories of commitment to constructionism, I find that my own position does not fit anywhere. While I would describe this research on autism to be perhaps most akin to Hacking's ironic category, it does not quite work. This is because, as Hacking states, "X, which we thought to be an inevitable part of the world or of our conceptual architecture, could have been quite different" (Hacking, 1999). Approached from within theories of practice, however, I feel that there is perhaps another category of constructionism that could be teased out: multiplicity. A multiplicity category explores how X is contingent and not inevitable. It also aims to show that not only *could* X be quite different, but that X *is* quite different. In a commitment to constructionism as multiple, the aim is to unpack how different constructions of X exist and interact with one another, how they might resist, conflict and at times relate and borrow from one another. Thus, approached from theories of practice and a methodological stance of actor-network theory, I am committed to construction as multiple.

i) What is it that is constructed?

Again, I draw on Hacking (1999) to clarify what I mean when I position myself in a constructionist epistemology. Hacking distinguished between objects, ideas, and what he calls "elevator words". The boundaries between these three classifications are tenuous and

slippery but the distinction is helpful, I think, in clarifying what precisely I am referring to as being constructed. The first category of objects are in the world, according to Hacking. Autism can be examined as an object, as can DNA and individual people. The second classification is called ideas and includes ideas, concepts, beliefs, attitudes to and theories. Ideas can be shared or private. Autism could also be approached as an idea; one could study how the idea of autism has been constructed differently over time or in various contexts. For example, disability rights constructions of the idea of autism differ greatly from the ideas of autism held by some parent-driven groups such as Autism Speaks, which seek to cure autism. The third category is elevator words. Elevator words include facts, truth, reality, and knowledge. These words, suggested Hacking, are not objects in the world but say something *about* the world and the way we think about the world. One could, for example, study the construction of knowledge within a particular context, like autism genomics.

Throughout the chapters of this dissertation that which is being explored as constructed differs. For example, in chapter 3, I describe how the idea of autism has been constructed through technological advancements in genomics. In chapters 4 and 5, I explore how knowledge is constructed within the contexts of autism genomics. In chapter 6, I unpack how the nature of autism, its ontology, is constructed multiply in the laboratory, clinic and family home.

ii) Can something be Constructed and Real?

I am very concerned that in taking a constructionist approach this research might be misinterpreted as taking the position that autism and the objects of science under investigation are not *real*. I want to make clear my position - that I hold autism to be real, very real. I contend that it is, however, both real and constructed. To say that the idea of

autism or knowledge about autism is constructed is perhaps less risky. However, in chapter 6, I also explore how the nature of autism, its ontology, is constructed. It is here that I must be most clear in how I relate and connect a multiply-constructed object to one that is also, in no uncertain terms, real.

Here, I want to draw on Pickering and Latour again to help me elucidate what I mean when I say that autism is both constructed and real. The issue of realism, as has been discussed above, is usually problematized by knowledge on the one hand and the world or nature on the other hand. The central question is whether or not and to what degree knowledge is able to represent or correspond to the real world. Pickering (1995) enlists his concept of the mangle of practice in a position he calls *pragmatic realism*. In my reading of Pickering, scientific knowledge is real in so far as scientist are engaged in this dialectic of resistance and accommodation with nature, in so far as knowledge is finely tuned to the world.

The problem is that humans can be engaged in this dance of agency with the world in different ways. The various tools, the technologies, and the machines that are used by humans allow us to become entangled with the world in different ways. As will be demonstrated in this dissertation, for example, autism is constructed in the laboratory through a process in which scientists use various machines, tools, and objects (e.g., DNA) to explore the world. Here, not only knowledge about autism but in certain instances autism itself is constructed in terms of genes and DNA. At the same time, autism is constructed in the clinic through a very different process in which clinicians use tools and technologies (e.g., tests and observation schedules) to engage with the world. Through practices of the clinic autism is constructed behaviourally. Both of these constructions are at once real; knowledge from the

laboratory and knowledge from the clinic can both be described as particular ways of practicing or ordering autism.

In this way the world can simultaneously support multiple entanglements and dialectics of resistance and accommodation. Even though, at times, these constructions may in certain ways conflict with one another. Two constructions may actually be incommensurable; that is, there may be no common yardstick from which to measure and compare two constructions, two different ways of approaching and engaging with the world. Yet, they both may be real. Sometimes these constructions coexist temporally and in other examples one way of engaging with the world overtakes another. I feel that it is through the process of knowledge translation that we shift and maneuver between and amongst various entanglements with the world.

Like Pickering, Latour also focuses on nonhumans as central to dismantling the dichotomy between subjects and objects, culture and nature. By considering associations of humans and nonhumans in a state of uncertainty, Latour attempts to end the volleying back and forth between subject and object (2004). I draw on Latour also as he points out that once an object becomes a fact, once it is given a name, once it has been probed and prodded through various tools and practices, it becomes real; it assumes an ontological weight, so to say. In this way ontology is intimately related to practice. The nature of an object is determined through practice, through various "socio-technical assemblages". At this point we must take it for granted as being real. It becomes a closed box. Latour, for example, analyzed a scientific experiment by Pasteur (Latour, 1993a) and contends that an experiment is "an action performed by the scientist so that the non-human will be made to appear on its own... The experiment creates two narrative planes: one in which the narrator is active, and one in which the action is delegated to another character, a nonhuman one" (Latour, 1993a).

We constantly shift between frames of reference. Latour described how Pasteur acted so that the yeast could act alone. Depending on which of these two actors is stressed, the same text becomes constructivist or realist (1993).

When an object comes to be defined through various trials in the laboratory, an act of ventriloquism arises. At first, when the contours of the object are still uncertain, the scientists speak for the object. Later, after the object has been established as fact, the object speaks for itself (Latour, 2004). It is real. If and when a new controversy opens up around an object, a new paradigm or new technology is developed that allows the object to be probed and prodded in different ways, the question of its constructed nature opens up once again. The arena in which it is come to be known, the technologies, the field of practices that constrain how scientists accommodate nature's resistance – all of this becomes visible again. After a while some agreement is reached and the apparatus of practice fades away again leaving nature to seemingly exist independently of the tools and practices through which we engage with the world.

2.3.b Epistemology or Ontologies?: Practiced Knowledges, Practiced Realities

David Bloor, a sociologist in the Science Studies Unit at the University of Edinburgh, has been a major champion of the *Strong Programme* in sociology. The key idea attributed to the Strong Programme is the symmetry postulate. Bloor has explained this postulate as follows:

Both true and false, and rational and irrational ideas, in as far as they are collectively held, should all equally be the object of sociological curiosity, and should all be explained by reference to the same kinds of cause. This requirement was formulated in opposition to an earlier prevailing assumption, still defended in many quarters, which has it that true (or rational) beliefs are to be explained by reference to reality, while false (or irrational) beliefs are explained by reference to the distorting influence of society (Bloor, 1999, p.

84).

This postulate marked a radical shift in science studies. As a result, all knowledge and beliefs could be explained in the same way. The concern for Latour, however, is that this postulate is limited to epistemological concerns. It proposes symmetry of knowledge and ideas about the world, but continues to uphold the traditional view that the world (reality) itself is out there, untouched. The world (reality) is not within the purview of social science; only descriptions of the world should be subjected to sociological scrutiny:

The important point is to separate the world from the actor's description of the world. It is the description that is the topic of enquiry, and the proposed separation is one of our resources. This is all just another way of saying we must respect the distinction between the object of knowledge and the subject of knowledge (Bloor, 1999).

The preceding quote points to Bloor's modern separation between subjects and objects, human representations and things-in-themselves. As such, Bloor restricted his research to scientific *knowledge*, rather than the broader domain of science itself. Scientific knowledge could be explained by society. As the following passage suggests:

All knowledge always depends on society. This is because, as I have argued and as case-studies demonstrate, society is the necessary vehicle for sustaining a coherent cognitive relation to the world (Bloor, 1999).

Meanwhile, Latour claimed that Bloor and other champions of the Edinburgh school's Strong Programme assume "*unequally* the sources of uncertainties, so that all the uncertainties reside with humans, while the sensory inputs remain utterly neutral" (Latour, 1999a, p.117). Latour aimed to problematize nature itself. Latour claimed, "Bloor aligns himself with the most reactionary philosophers of science who insist that science studies is all very well as long as it sticks to epistemological questions and leaves entirely aside—that

is to the scientists!—the ontological ones" (1999a, pp.122). Alternatively, Latour insisted that instead of leaving aside nature, we should focus squarely upon it. He stated, "the alternative I would prefer is to engage in a complete reworking of the origin of the notion of 'nature'. Nature is the concept to topicalize. It is through nature that the whole history of absolutism has been developed" (1999a, p.127).

For Latour, nature and society can be explained by things themselves if we follow, step-by-step the chains of association, which include "psychological, ideological, cognitive, social, and material entities, many of which are non-human agents. Along these chains, each element takes the meaning given to it by the adjoining elements in the series" (B. Latour, 1999a). Latour depicted Bloor, the Strong Programme and those in the Edinburgh unit of Social Study of Scientific Knowledge as subjectivist (emphasizing the role of society or culture) and at the same time realist (not questioning the ontological status of things in themselves). In this way, it is assumed that there are different types of causalities attributed to different types of reality; a wedge is driven between nature and society, object and subject and each side of the chasm is explained according to different standards. Latour, on the other hand, aspired to push the symmetry postulate one step further, eschewing this divide between subject and object, a relic from the modern project. His aim was to illustrate how this divide is produced. For example, Latour and Callon aimed to introduce an alternative ontological axis, one that would break the tug of war between natural realism and social realism. They contended:

Our general symmetry principle is thus not to alternate between natural realism and social realism but to obtain nature and society as twin results of another activity...network building...we have to make ninety-degree turn from the SSK yardstick and define a second dimension" (Latour & Callon, 1992).

Thus, instead of *starting* with nature and society, for Latour and Callon, these divisions were

an *end* result of the activities and networks of humans and non-humans. Later, Latour (1993b) further explicated this alternative ontological dimension. This north-south dimension "registers variations in the stability of entities from event to essence" (1993b). In other words, the vertical dimension traces the historical process through which a *thing* becomes stabilized. The essence of the *thing* is the trajectory that links all of the events in the thing's history. Thus, Latour's project is to focus on the process and practices through which things become stabilized. Latour later offered a more sophisticated explanation of his deviation from the traditional subject-object dualism (Latour, 2008, p.105). He stated: "in the first frame, all the attention is concentrated on two loci: the object intact 'out there' and the subject that has shifting versions 'in there'. In the second frame, the two anchors have disappeared: there is no longer one subject and there is no longer one object. Instead there are threads woven by the crisscrossing pathways." Thus, he was interested in "successive temporally marked versions of the objects and subjects" (Latour, 2008). In this way, Latour has granted ontological status to knowledge activity. Truth becomes an event and knowledge a trajectory.

The notion of time becomes paramount. When one takes a synchronic snapshot of the relationship between subjects and objects, they appear frozen, hardened in opposition to one another. The subject looks outward at objects as they are already recognized. In a diachronic, historical view, we can see how the "things" (not necessarily subjects or objects) are continuously shifting in relation to one another.

Likewise, according to Pickering, pragmatic realism subverts the realist/ idealist debate, claiming instead that "the world will support an indefinitely diverse set of ontologies and bodies of knowledge" (1995). In this way, Pickering, like Latour, is at once realist and relativist. What Pickering highlighted within this pragmatic realist perspective, is the

importance of time. For example, Pickering described the "irremediable historicity of scientific knowledge (and culture in general): what counts as knowledge now is a function of the specific historical trajectory that practice has traced out in the past" (Pickering, 1995).

Latour echoed this emphasis on time and went so far as to position facts and knowledge as having ontological status or weight; they are events that can be marked and traced through time. Thus, what counts as an object or a subject is a result of a particular stabilization of practice over time. In this way, it seems to me, that ontology can only be understood in relation to epistemology. To say that something is ontologically multiple, is to say that the nature of that thing is multiple. But nature is only apprehended through interaction with the world and that interaction, I am arguing, is in the form of practice. Ontology is practiced; it is not given *a priori*. This is how it can be said that an object exists ontologically in multiple ways, because it exists through multiple practices. This is not to say that the object is not real. Its existence can only be understood through practice, through our interactions with the world, and these interactions are mediated by and through tools, technologies, and practices.

In exploring multiple ontologies, I am exploring knowledge. Ontology and epistemology are conflated. How so? They are conflated through the idea of practice. Specifically, the notion that knowledge is practiced upsets the dualistic opposition between inside and outside, subject and object. Instead, when knowledge is regarded as practice rather than understood as something which lives in the human mind, knowledge becomes a materially heterogeneous activity. Knowledge is thus imbued with an ontological status. Casper Bruun Jensen (2004) further explores this move in ANT, emphasizing the comingling of humans and nonhumans, subjects and objects as challenging traditional epistemology: "

because activities such as observing or representing are not seen as distinct from intervening or constructing...in this way epistemology collapses into ontology and the sciences are reformulated as practical activities aimed at rebuilding the world by adding new elements with new capabilities and new relationships to it" (Jensen, 2004). As Latour has suggested "we have abandoned, as illusory, the demarcation between ontological and epistemological questions" (Latour, 1999c). This is a crucial point, that realities and knowledges of realities are constructed together. As Law has recently stated, "we need to replace an attitude of innocence with the recognition that our knowledges are complicit and collusive in the real...knowledges are embedded in and enacted alongside and together with realities that they purport to describe" (Law, 2012). Similarly, Latour describes knowledge as a "mode of existence" (2008).

Mol (1999; 2000; 2002) in her work on the ontological politics of atherosclerosis, described how a disease is enacted differently through different practices in the same hospital. The different realities of atherosclerosis butt up against one another, sometimes they are held within one another, and other times they are contradictory. The key point is that there is no single coordinated network to support a singular reality of atherosclerosis. There are actually multiple modes of ordering reality. So the construction metaphor no longer works. Reality is much too tentative and fragile, too fluid and relational to be described through images of concrete and steel conjured up by the word "construction". The project is no longer to describe the construction that could have been constructed otherwise, but rather, to describe the ways in which several simultaneous realities being performed at once hang together. Ontology is multiplied along with ways of knowing and doing. As Law has similarly stated, "if practices and knowledge practices are performative, then...reality is also heterogeneous: it, the real (or they, the reals), is (or are) simply being done differently in

different places” (2012).

Mol (2002) described how the different practices and enactments of atherosclerosis are distributed over different local spaces. When they do run into each other, when traffic between sites forces one reality to come up along side another, there are forms of coordination. They manage to coexist together. Mol, for example explores two different technologies and how they are coordinated. An angiographic image shows the vessel lumen while a duplex gives information on blood velocity; the objects of these two techniques are different but they are made comparable. There are ways to translate them. Velocity increase is translated by a technician into loss of vessel lumen. Thus, as Mol (2002) contends "the threat of incommensurability is countered in practice by establishing common measures. Correlation studies allow for the possibility (never friction free) of translations."

Mol explained,

the knowledge incorporated in practice does not reside in subjects alone, but also in buildings, knives, dyes, desks...This then may be a way out of the dichotomy between the knowing subject and the objects-that-are-known: to spread the activity of knowing widely...Instead of talking about subjects knowing objects, we may then, as a next step, come to talk about enacting reality in practice (Mol, 2002, p. 50).

A turn toward practice and activities precludes knowledge from living in the mind.

Knowledge is *done* - it becomes a fleshy, corporeal affair of the bodily world in which we move.

Reality, for Mol, is performed in a variety of practices and is therefore multiple. She writes of ontologies rather than ontology; the distinction is made, however, between multiple and plural, setting her viewpoint apart from those who espouse a perspectival or constructionist approach. According to Mol, perspectivalism "broke away from a monopolistic version of truth. But it did not multiply reality. It multiplied the eyes of the

beholders...And this in turn brought pluralism...While in the centre the object of the many gazes and glances remains singular, intangible, and untouched" (Mol, 1999). Alternatively, constructionist stories articulate the possibility for alternative constructions of reality that might have been by unpacking the processes through which accepted "facts" were produced and other potential facts were lost along the way.

Instead, Mol's description of multiple ontologies is contingent on the ideas of performance and practice: reality is "done and enacted rather than observed" (Mol, 1999). In this way, there are multiple versions of the object, multiple forms of reality itself. However, "[t]hese are not perspectives seen by different people - a single person may slide in her work from one performance to another...So they are different versions, different performances, different realities, that co-exist in the present" (Mol, 1999). She explained further that while these various realities may clash at some points, different performances of an object also depend on and collaborate with one another. Thus, they do not necessarily co-exist independently and side-by-side, but rather might be found inside one another.

While Latour emphasizes how constructions of reality could be otherwise, tracing how particular constructions arise through time, Mol concentrates on how reality is performed or practiced multiply in the present. Considering all the emphasis on time by Latour and Pickering, this dissertation is noticeably atemporal. Despite my indebtedness to Latour's ideas, it is Mol's concern for multiplicity and ontological politics in medicine that I find particularly relevant and generative in my pursuit to explore the concept of knowledge translation from a constructionist position. In this dissertation I seek to take up the issues of multiplicity and coordination as integral to a new way of framing the practice of knowledge translation.

c) Both Constructed and Real

In *Science in Action* (Latour, 1987) Latour unfolds the story of how objects are slowly made into being, first a fuzzy thing on which the tests must be conducted to define its edges, figuring out what it does what it doesn't do. Nature or objects do not come into being until after they are "isolated from the laboratory conditions that shaped them, things with a name now seem independent from the trials in which they proved their mettle" (Latour, 1987). Through this process, reality becomes reified. Thus, Latour alludes to the two-faced Janus. On the left side of Janus, Nature is cause, on the right side consequence. On the left side scientists are realists, on the right side relativists. On the left side science is cold, hard and certain. On the right side, science is warm, soft, and unsettled. Stengers (2010) reinterpreted the two-faced Janus as consisting of what she calls "bearded science" on the left and beardless youth on the right. She describes a:

"struggle for a less dissociated or amnesic personality than the Janus figure, for a bearded old man who would remember and celebrate the adventurous, intricate constructive processes that any scientific achievement entails, instead of describing the achieved result as the direct consequence of a normal, rational method" (Stengers, 2010).

The suggestion to shift between frames of reference allows Latour to adopt a realist perspective without absolutism. Things are real; they exist, whilst also being constructed.

i) Construction as Process

When we talk about a construction, we often imply a maker, an architect. What Latour wanted was to think not about an all-powerful creator, but rather the *process* of construction. He proposes that we think of engineers instead of architects; "learning how to become responsive to the unexpected qualities and virtualities of materials is how engineers will account for the chance encounter with practical solutions: they will never think of describing themselves as little kids moulding reality at will" (Latour, 2003). In other words,

by using the word “construction”, agency must be shared across a wide variety of actors and uncertainty introduced into the final construction. Adopting a constructivist position, according to Latour, means "to learn how to become sensitive to the contrary requirements, to the exigencies, to the pressures of conflicting agencies where none of them is really in command" (2003). A potter, for example, may throw a pot with a particular shape, but she is constrained by the properties of the clay (is the clay uniformly wedged, is it too wet or too dry), the speed of the wheel, or gravity's effect on abrupt curves. As any fledgling potter knows, certain shapes hold up better than others (pots collapse and fold at weak spots - so we learn which shapes are possible and which can be maintained). Thus, the potter constructs a pot, but not without the constraints of the material world.

Latour views constructivism as the only way to bypass the dichotomy between an unconstructed world that is "already there" and a world made purely of subjective value claims (Latour, 2005). Elsewhere, Latour (1993) has described science studies as situated in a no-man's-land between the two cultures of sciences and humanities, between absolute realism and absolute relativism. In the no-man's-land, relativism is relative and realism is more realistic. In this no-man's-land *relationism* comes to replace both terms (Latour, 1993). Empiricist notions of knowledge remain deeply cognitive and cerebral; detached minds gaze out at the world. Conversely, Latour and ANT hope to plug the wriggling brain back into the body; he stated in *Pandora's Hope* (Latour, 1999), "we no longer have a mind dealing with an outside world, but a lived world to which a semi-conscious and intentional body is now attached." In this way, the outside world is granted a warm, human, historical existence, a more realistic realism or relative relativity.

2.4. Relating my Philosophical Position to Knowledge Translation

Practice theories, actor-network theory and constructionism provide a set of concepts and ideas from which to draw upon when exploring knowledge translation. In closing this chapter, I would like to briefly outline how knowledge and translation (the two fundamental components of KT) are informed by the particular theoretical, methodological, and epistemological positions I have adopted.

a) Knowledge

In this research I have approached knowledge as a practice. Specifically, following practice theories, I suggest that knowledge is a materially heterogeneous practice with an unfolding ontology. Actor-network theory has been described as the semiotics of materiality, emphasizing how things are produced in relation to other things. An ANT methodology allows me to decentre knowledge and trace the connections between the various human and non-human actors that make up a particular enactment or practice of knowledge. Constructionism brings to the foreground the idea that knowledge is entangled with the way the world is enacted. Knowledge is conceptualized as a particular way of ordering the world. Different knowledge practices rebuild the world anew. In a constructionist approach, knowledge does not only describe reality but creates it. Thus, knowledge practices are not treated as distinct from ontological practices. When knowledge practices change or multiply, so too does reality.

This particular conceptualization of knowledge, informed by practice theories, ANT, and constructionism, can be contrasted with the conceptualization of knowledge that is typically found in the health science literature pertaining to KT. In my reading of this literature, I interpret knowledge to be predominantly conceptualized as a representation of

reality rather than a practice or construction of reality; a reified possession rather than a process; a black-boxed actor, rendered distinct from the circumstances of its creation, rather than a network of connections relating many actors to one another. This typical conceptualization of knowledge will be further explored through the example of the Knowledge-to-Action (KTA) model promoted by the CIHR in the final chapter of this dissertation.

Thus, in re-conceptualizing knowledge through a philosophical lens informed by practice theories, ANT, and constructionism I am altering what it is that is being considered as undergoing translation. The knowledge that I am considering in this thesis bears little resemblance to the knowledge that is considered in the health sciences KT literature. That which is under investigation differs from what is typically included in KT research.

b) Translation

Following these changes in the conceptualization of knowledge, my understanding of translation is also markedly different from the dominant conceptualization of translation in the health sciences literature. Informed by practice theories, ANT, and constructionism, my view of translation implies a process in which different knowledge practices are related to one another. Following ANT methodology, in describing translation I am describing how actors change as they enter new networks. An ANT-informed understanding of translation requires that I register differences in the way that actors come together as they move amongst different networks. In my conceptualization, translation and transformation are synonymous. As my conceptualization of knowledge relates knowledge practices to the construction of ontological realities, it follows that translation also entails creating connections between multiple ways of enacting reality. Drawing on the notion of multiplicity, following Mol, I

will suggest that hidden within the process of knowledge translation is an ongoing process of ontological politics.

It is in this notion of ontological politics that my conceptualization of translation differs from the translation that is discussed in the health sciences KT literature. In this literature, translation is not generally approached as a political process. Further, while many models discuss the need to adjust knowledge so that it can be adopted to a particular context, translation is not typically defined by change and transformation of knowledge. Rather, it is assumed that at its core knowledge being translated remains constant and unchanged when moved from producers to users. Finally, as implicated in the previous sentence, translation often entails two distinct groups of people: those who produce knowledge and those who use it. In the health sciences literature the translation process implies an intentional and directed attempt to move knowledge from producers to users.

In relating my philosophical position to a discussion of KT I have highlighted the differences between the ways in which I have approached knowledge and translation and the ways in which they are conceptualized in the health sciences KT literature. The body of this dissertation, which draws on my field work experience, explores autism genomics as a case study in which to examine KT using particular conceptualizations of knowledge and translation that are informed by practice theories, ANT, and constructionism. I argue that developing theory-driven approaches to KT, as I have done in this dissertation, will enable a larger network of KT researchers to think critically about what is typically included and precluded from investigation and open up possibilities for re-configuring what KT entails.

Chapter 3: Research Ethics

3.1. Approaching Anonymity

7.1a Anonymity of individuals diagnosed with autism and their family members

7.1b Anonymity when "studying up"

3.2. Tensions in the research process: Anonymity? "Thick description"? Or somewhere in between?

3.3. Expectations of Research Participants

At the end of a Monday morning meeting on March 6th 2012 a genetic counsellor relayed to the group that in a recent feedback session one of the probands had withdrawn his consent and no longer wished to participate in the autism genetics research. This proband happened to have a particularly interesting copy number variation. A discussion ensued about how to best go about the withdrawal process. One person in the room, a post doctoral fellow in bioethics who had been invited to work with the group, noted the impossibility of retrospectively taking data out of past compiles. Others noted the need to trace where the proband's information had gone as it had been part of a central public repository used by other scientists internationally. Still others noted the implications of his withdrawal, that they could no longer publish the results. This conversation led to the above statement made by the director of the laboratory:

“You can see that ethics is overtaking the science now”
(Director, Laboratory X – March 6, 2012, Monday morning meeting).

In this chapter I would like to take this statement made by the Director and apply it

specifically to an ethical quandaries that emerged from my research, that of providing context of the research participants while at the same time providing anonymity in the context of knowledge translation of genomic science from the laboratory to the clinical setting and back again.

3.1. Approaching Anonymity

The word “anonymity” has been used to specifically describe the protections to prevent the identifiability of participants (Walford, 2005; Tilley & Woodthorpe, 2011). Tilley and Woodthorpe (2011, p.198), for example, make the distinction between confidentiality and anonymity stating, “confidentiality refers to the management of private information...anonymity refers specifically to removing or obscuring the names of participants or research sites, and not including information that might lead participants or research sites to be identified”. Confidentiality is a broader concept that entails more than merely protecting the identity of research participants and sites. For example, confidentiality also includes issues pertaining to security measures for protecting data, and foreseeing legal reasons to disclose information to third parties (TCPS, 2010). These broader issues associated with confidentiality are not being challenged in this chapter. Rather, following Tilley and Woodthorpe (2011), this chapter specifically focuses on the issue of *anonymity* in the context of qualitative inquiries. Anonymity, according to Walford (2005, p.85),

[M]eans that we do not name the person or research site involved, but, in research, it is usually extended to mean that we do not include information about any individual or research site that will enable that individual or research site to be identified by others.

In the Canadian research context, the Tri-Council Policy Statement (TCPS) 2 2010 is the joint ethics policy guideline prepared by Canada’s three federal research agencies (Canadian Institutes of Health Research (CIHR), and Natural Sciences and Engineering Research

Council of Canada (NSERC). The TCPS2 is guided by three core principles: respect for persons, concern for welfare, and justice. In the TCPS2 (2010), the notion of anonymity is not defined and is instead subsumed within the concepts of privacy and confidentiality, which are important aspects of these three core principles. According to the TCPS2, “privacy risks in research relate to the identifiability of participants, and the potential harms they, or groups to which they belong, may experience from the collection, use and disclosure or personal information” (2010, p.55). Confidentiality refers to the obligation to safeguard entrusted information; specifically, ‘researchers shall safeguard information entrusted to them and not misuse or wrongfully disclose it’ (2010, p.56). While the TCPS2 does not use the word anonymity, it does acknowledge, however, that confidentiality “can be a particular challenge in qualitative research because of the depth, detail, sensitivity and uniqueness of information obtained” (2010, p.143-44). Here the TCPS2 demonstrates sensitivity to the unique challenges involved in protecting anonymity for highly descriptive research methodologies.

Anonymity of research participants are commonly demanded across Research Ethics Review Boards at Universities and other institutions (Giordano, O'Reilly, Taylor, & Dogra, 2007). However, the orthodoxy of anonymity is beginning to be questioned in qualitative research (Kaiser, 2009; Kelly, 2009; Snyder, 2002; Van den Hoonaard, 2003; Walford, 2005). Van den Hoonaard (2003, p.141) argued that anonymity “is a virtual impossibility in ethnographic research” and pointed to the marked differences between the “front-stage” promises of anonymity made to REBs and the “back stage” reality of research in practice. Complicating the issue of anonymity, Walford (2005) argues that while the identity of a particular site or community might be concealed, pseudonyms will probably not conceal the

identity of individuals in relation to others from that same site or community. For example, there have been studies in education research (Burgess, 1985) in which pseudonyms did little to protect participants from colleagues and principals discerning individual identity. Walford (2005, p.88) warned,

The head teacher and other teachers will know which teachers were involved in the research and few details may be sufficient to identify the person being quoted. . . Moreover, the people who are in a position to identify individuals are exactly those to whom exposure has the greatest potential risks of harm or embarrassment.

Scheper-Hughes (2000) has written similarly:

I have come to see that the time-honoured practice of bestowing anonymity on ‘our’ communities and informants fools few and protects no one—save, perhaps, the anthropologist’s own skin. And I fear that the practice makes rogues of us all—too free with our pens, with the government of our tongues, and with our loose traditions and interpretations of village life (Scheper-Hughes, 2000), p.128.

Thus, the typical way in which anonymity is preserved (pseudonyms) ensures what Tolich (2004) has described as external confidentiality (to the outside world). However, as Kaiser (2009 pp.1636) has noted, “this approach does little to ensure that persons with whom respondents have relationships such as spouses, coworkers or neighbors will be unable to identify respondents”. Meanwhile, Tilley and Woodthorpe (2011) raised concerns about the challenges of maintaining anonymity amidst increasing pressure to disseminate and translate research findings in an on-line era. These authors suggested, “it is now common practice for a lot of information about research activities to end up in various places, especially on the internet. . . the sheer volume of this information can challenge the principle of anonymity in identifying sites” (2011, pp. 205).

Nespor (2000) has identified other problems with anonymity. In particular, he suggested that strategies to improve anonymity, such as glossing over details, invite the

reader to generalize the findings of a particular study to any place and time. Readers might be more apt to apply findings to other situations or sites, without considering important and unique socio-historical contextual factors. Concerned for the anonymity of participants in my own study, I considered the idea of removing any traces of the particular context of autism and instead using [] in place of the world autism throughout my dissertation. Nespor's (2000) concerns regarding the decontextualizing of findings and the risk for readers to generalize findings into other contexts influenced my choice to remain close to the particular context in which my research was situated.

My research involved engagement in a genomics laboratory and autism clinic. While a pseudonym might hide the identity of the participants in the short-term, any description of the spaces and the technologies in those spaces narrow the range of possibilities immeasurably, such that the laboratory and by extension the clinic are quickly identifiable. Such description, however, is essential for a serious discussion of the construction of genomic knowledge and its translation amongst the various participants in the laboratory and clinic. Moreover, actions taken to hide or gloss over the particulars of the research site in the interest of preserving anonymity would simultaneously impede my ability to demonstrate authenticity (showing the reader that I was there) and thereby threaten my own claims to research quality. In my research, the challenges associated with anonymity differed between and among individuals diagnosed with autism, family members, scientist, and clinician participants and are explored separately below.

3.1a Anonymity of individuals diagnosed with autism and their family members

One of my primary concerns is ensuring that individuals diagnosed with autism and their families are not identifiable within my writing. This was actually more difficult to

achieve than I had initially anticipated. The main difficulty in ensuring anonymity of the families that participated in my research is that there have been so few families given genetic feedback in the Autism Genetics Study, as it moves from the basic science laboratory to the clinic. In order for social science to accompany rather than follow cutting-edge basic and clinical research, as has been argued (Timmermans & Berg, 2003), social research must begin with a small group of participants, and thus strategies to address the related complexities of anonymity should be pursued. Feedback has only been given in the last three to four years with less than a total of twenty families actually involved. This is because parents only receive feedback when a genomic variant is found which is of “clinical significance”. Most of the genomic variants that are found in the laboratory are either not clinically significant (these variants are common in control populations) or, increasingly, they are what are termed “unknown clinical significance”.

Trying to provide anonymity increases in complexity when one considers the many different people for whom a research will seek anonymity. For example, in my research I hope to ensure the individuals diagnosed with autism and their family members are not identifiable. This becomes complex in relation to other family members, friends, co-workers, or acquaintances as well as from the researchers and clinicians in the autism genetics study. To promote anonymity I have used pseudonyms and modified demographic information as much as possible. However, pseudonyms do little to protect the anonymity of individuals with autism and their family members from the clinicians and scientists in the autism genetics research. With so few parents involved in my study, and so few families having received genetic information from the Autism Genetics Study, clinicians would quickly be able to identify who said what. This concern is further complicated by the fact that these scientists and clinicians were listed as co-investigators on my research project, as per

research ethics board requirements; as such, they have access to signed consent forms clearly identifying the parents who participated. The parents were aware of this, as the information letter and consent form has the names of the clinic and laboratory directors at the top. In parts of my dissertation, parents may offer concern regarding the clinical genetics feedback process, offering potentially useful suggestions about the need for continued opportunities for follow-up meetings with the genetic counsellor. In the interest of increasing anonymity from the scientists and clinicians in the autism genetics research, I have tried developing composite descriptions, based on stories from several research participants that have been combined. For example, when I describe the process of meeting with a genetics counsellor to receive genetic feedback, the story is told from the perspective of a mother. The experiences and feelings recounted here are morphed together from several different mothers I interviewed and from the four different feedback sessions that I observed. I have thus collected data verbatim but to promote the anonymity of the research participants I have brought together, and reassembled it.

3.1b Anonymity when “studying up”?

While I had anticipated the challenges to anonymity for individuals diagnosed with autism and their families early on in the research process, the difficulties related to anonymity for the scientists and clinicians became increasingly apparent as I began to write descriptions of the spaces in which they were working. There are few people involved in autism genomics research in Canada with the resources and infrastructure to carry out the types of cutting-edge experiments I describe, let alone on such a large scale. The laboratory and its director have an impressive public presence in the world of autism genetics research and, as such, are highly visible. With a little effort, anyone who reads my dissertation could probably figure out the group I was studying if they really wanted to. Considering this and

that there is only one director of the laboratory and one director of the clinic, anonymity becomes difficult, if not impossible, to achieve.

Over forty years ago, Laura Nader (1969) called for anthropologists to “study up”, to focus on the elite individuals and institutions with power. She identified four factors which contributed to the paucity of studies focused on those with power: access, attitudes, ethics, and methodology. Traditionally, in many anthropological studies, the researcher traveled to a distant country and had relatively more power than the research participants. Participants may not have spoken the same language in which the anthropologist would eventually publish findings and would have little opportunity to scrutinize the interpretations made by the researcher. While anthropology “at home” has become increasingly common in the last few decades, many researchers continue to focus their studies on relatively marginal or disenfranchised people. As Gusterson (1997) has noted, “In many cases, anthropology’s traditional taste for the marginal and exotic has not so much been transgressed as imported and transposed upon American society, leaving us with more studies of scientologists and crack dealers than of federal bureaucrats and corporate executives” (1997, p.114).

Recently, Edwards (2007) focused squarely on the challenges that emerge when “studying up”. Edwards (2007) conducted an ethnography of the Japanese women’s soccer team and the broader issue of corporate sports. She quickly found herself dealing with corporate scandal involving Japanese mafia and some of Japan’s most powerful and elite. The taken-for-granted power imbalance that traditionally favours the anthropologist was reversed creating complex new ethical questions that were not yet explored in the literature. “What happens”, Edwards (2007, p.564) has asked, “when the power vector points in the other direction?” The novice researcher is left in uncharted waters, with little guidance on the ethical or methodological issues pertaining to researching those with more power than

ourselves. My aim is to contribute to the nascent conversation about the ethical challenges that may arise when one engages in this activity of studying up, across, and down. In particular, I explore some of the issues I confronted in the context of doing a multi-sited study with a heterogeneous mix of participants who had varying degrees of power vis-à-vis myself as researcher.

Arguing against the automatic adoption of anonymity of research participants, Walford (2005) suggests a process in which the participants are themselves given a platform in which to present their interpretation alongside the researcher, an idea previously put forward elsewhere by Lawless (1992). Such an exchange, in which the researcher and researched present ideas alongside one another, would indeed be another source of data and might possibly lead to ongoing interpretations.

Giordano et al (2007) considered the possibility of allowing participants the choice of maintaining anonymity and confidentiality. These authors describe the debate between retaining anonymity of participants and revealing identities as a collision between different constructs of agency. Giordano et al raise several important questions in the debate whether or not to offer the choice to refuse anonymity to participants. For example, is the participant a vulnerable participant who needs to be protected or is the participant also an individual, separate from the study, who may benefit from giving voice to their own experiences? Can a participant recognize and predict the implications and ramifications of choosing to be identified as a research participant?

The issue of choice regarding anonymity is made more complex when considering research with multiply positioned participants who are linked by association with one another. There is often an unspoken assumption that research participants in a single study are a homogeneous group (Edwards 2007). However, when purposefully including a diverse

range of participants is integral to your research questions, what might be ethical research practice for some participants may in fact confer risk, harm or stress on other participants within the same study. In my research on autism genomics, for example, allowing scientists to waive anonymity and naming the laboratory might, by association, implicate the few families who have received genetic feedback pertaining to autism involved in my research. While conducting fieldwork I came to realize that the scientists and clinicians who participated in my research had the expectation that they would be co-authors on publications that arose out of my dissertation. Journal articles in genetics begin with lengthy lists of authors, name after name, sometimes filling an entire page. Anyone who has contributed in any way is included as an author. Thus, of course, I came to realize it was natural for them to assume that by letting me hang out in their facility and clinic, interview them and generally take up their time they would expect to be authors on publications related to this project. I realized it would be a cultural faux-pas not to include them as co-authors and I would probably be regarded by them as “not playing by the rules”.

So the scientists and clinicians expect to be named, along with the laboratory and clinic sites. But what risk would their identification confer on the few families who have received genetic information from this laboratory and clinic? While some parents I interviewed had no problem being identified, indeed they openly appeared in journal articles previously published by the autism genomics researchers, there were other parents and families for whom anonymity was important. The issue of waiving individual anonymity reveals tensions and complex dynamics, not only between different groups of participants (scientist/clinician or family) but also within single families. One family, for example, had several adult siblings involved in the genetic testing process and two of these siblings were identified as being on the autism spectrum. During one of my observations, one sibling

revealed to the genetic counselor that he no longer wanted to be a part of the research. During this observation in which feedback was being given to the family, this individual looked very unhappy and had in fact been several hours late for the appointment. It seemed to me that he was attending the feedback session under duress, as other family members were very keen on the project.

How would offering choice of anonymity work in this case, in which participants are related. Let us say, hypothetically, that one sibling chooses to be identified, waiving their right to remain anonymous. However, let us suppose that the other sibling does not want to be identified and wishes to remain anonymous. When the topic of the research is genetics, entire families are implicated by association with an individual who might choose to be identified. Identifying oneself as having a genetic marker associated with autism is also by extension opening the doors for speculation about one's family members. While for one sibling, being identified might be an empowering and positive experience in the research process, for the other sibling identification may confer risk, harm or stress. Thus, the concern over offering participants the right to waive anonymity is more complex in the context of genetics as a tension could arise between an individual participant's wishes and the preferences of other family members who may be implicated. Nisker and Daar (2006) have suggested increased precautions and protections for individuals and family members in the context of genetics-based narratives. Likewise, the TCPS (2003) stated in Article 8.2,

Because the potential for gathering genetic knowledge about biological relatives or groups by studying only a few individuals is unique to genetic studies, an individual may not be assured of privacy within the group, unless extra precautions are taken.

Many of the scientists and clinicians who participated in my project expected to be identified, while some individuals diagnosed with autism and families expect to remain

anonymous. However, identifying scientists and clinicians (and therefore the particular laboratory and clinic) could also identify the individuals with autism and their families, of whom there are so few who have received feedback to date. Again, the Tri-Council Policy Statement (2010) offers some help.

In some instances, participants may waive anonymity (e.g., if they wish to be identified for their contributions to the research). Researchers should obtain the consent of these participants, and negotiate agreements with them that specify how they may be identified or recognized for their contribution. Where an individual participant waives anonymity but other members of the participant group object because identification may cause harm to the group, researchers shall maintain anonymity for all members of the participant group (2010, p.58).

The implication of this TCPS statement for my research is that, despite scientists' and clinicians' expectation to be identified, I should maintain anonymity of all participants since some expect to remain anonymous. With so few people being given clinically significant genetic feedback to date, I feel that I must at least refrain from divulging the actual names of the hospital, laboratory, and clinic. Likewise, I have chosen not to include the names of participants, whether they are people working in the laboratory, clinic, or the names of individuals diagnosed with autism and their family members. While the descriptions of the spaces in which I carried out my research might be identifiable to those within the Canadian autism genetics community, and indeed the international community of genomics researchers, it is unlikely that anyone outside of the autism research group I studied would be able to identify specific families from the descriptions I provide in this dissertation. Moreover, sensitive to this issue of ensuring anonymity, this dissertation was printed out and couriered to examiners so as not to risk electronic transfer of information.

What is more challenging, however, is trying to maintain anonymity of participants amongst each other. In practice, using a pseudonym alongside descriptions of the activities of participants does little to hide their identities from each other when there may be only one

project coordinator or a few psychology PhD students. What are the ramifications for “Claudia” who questioned the possible end uses of the genetic results or for the liaison who condemned the “cure speak” of the laboratory director? These participants talked about important issues that have yet to be openly discussed amongst members of the laboratory and clinic and dissemination of these findings could potentially instigate fruitful discussions therein. Alternatively, these questions raised by some participants could perhaps contribute to a straining of relations between these participants and the directors, their employers. While my consent form clearly stated that data and findings would be accessed by members of the research team (including the directors of the laboratory and clinic listed on the consent form), did the participants understand the ramifications of this, that their anonymity vis-à-vis their co-workers would be difficult to preserve?

3.2 Tensions in the research process: anonymity? "thick description"? or something in between?

Thus far in this chapter, I have tried to unpack some of the challenges to anonymity in the dissemination of qualitative research findings that include descriptive nuanced accounts of highly identifiable people and spaces. The process of working through the issues surrounding anonymity has brought into relief the inherent tensions in the research process, tensions between doing everything one can to protect anonymity of participants (such as using square brackets rather than the word autism) on the one hand and on the other hand, the value of in-depth, rich or "thick" descriptions of the particular contexts in which fieldwork is carried out. In anthropology, the discipline in which I feel most at home (although I have been nomadic in my PhD), there is great value in providing detailed and nuanced accounts of particular spaces and events and to unpack the complex socio-historical particularities of those spaces and events. Moreover, an Actor-Network Theory account requires descriptions

of the local assemblages of actors as they move from site to site. Maintaining anonymity could be difficult when recounting the detailed minutia of a setting in which actors come into contact with one another. As social scientists travel into new domains of research, including cutting-edge genomics, ethical issues, such as those surrounding anonymity, may require us to reconsider those practices which have traditionally defined us.

In Table 3.1 I have taken excerpts from my dissertation and considered how these excerpts might be re-written to strictly protect participants' identities. The first example in Table 7.1 illustrates how anonymity might be better protected by removing the name of the particular condition (autism) from the dissertation, such that the easily identifiable people and places associated with autism genomics research in Canada might remain anonymous. A generic condition [-] is made to stand-in for the actual context in which field work was conducted. In the second example, details of the physical space in which my field work took place are truncated in order to hide the identity of Laboratory X from those within the broader autism genomics research community who have visited Laboratory X for annual meetings. In the third example, the types of activities and work that occur in the Laboratory are deleted as is the number of employees, as the fee-for-service facility and the magnitude of the staff may be another way for readers to figure out where the research was conducted.

Table 7.1

Anonymity Protected	Description and Contextual Information Preserved
1. i) Individuals diagnosed with [] and their family members give blood in the blood lab located on the main floor of the hospital. The genetics project coordinator, Claudia from the [] Clinic, typically walks them over to the triage area in the new atrium of the hospital.	1. i) Individuals diagnosed with autism and their family members give blood in the blood lab located on the main floor of the hospital. The genetics project coordinator, Claudia from the Autism Clinic, typically walks them over to the triage area in the new atrium of the hospital.

<p>ii) Thus, the genetic variation in one individual with [] is likely to be distinct from the genetic variance of another individual with []. In reviewing the literature, several genomic loci were described as contributing to susceptibility for [].</p> <p>iii) I often wonder does that gene impact on, my question, I have a number of questions. So what it does is it brings forth more questions about myself. So because I have the gene I am the carrier or do I have [] on a lower part of the spectrum? What does it exactly mean is my question?</p>	<p>ii) Thus, the genetic variation in one individual with ASD is likely to be distinct from the genetic variance of another individual with ASD. In reviewing the literature, several genomic loci were described as contributing to susceptibility for ASD.</p> <p>iii) I often wonder does that gene impact on, my question, I have a number of questions. So what it does is it brings forth more questions about myself. So because I have the gene I am the carrier or do I have autism on a lower part of the spectrum? What does it exactly mean is my question?</p>
<p>2. i)The laboratory is housed in a Medical Research Centre. It's on my right as I walk along Rainier Street now. A beautiful old building sits stalwart on my right. A shadow is cast down on the rugged stone bricks by a tall, smooth, modern tower now joined at a seam onto the far end; this is the Medical Research Centre. As I approach, a custodian is cleaning the glass of the revolving doors so I push open the swinging door. The noisy street is shut behind me and my footsteps echo in the vast foyer as I walk through toward the elevators. To my right is a set of stairs that leads down into the food court, the underbelly that joins the research tower to the hospital. I know if I head down the stairs the tables will be full with groups of people huddled together around laptops, chatting over morning coffee from Timmies.</p> <p>ii) Several framed photos hang from the walls at regular intervals. On closer inspection, they are not just photos but actually the covers of journals related to</p>	<p>2 i)The laboratory is housed in the Medical Research Centre. It's on my right as I walk along Rainier Street now. As I approach, a custodian is cleaning the glass of the revolving doors so I push open the swinging door. The noisy street is shut behind me and my footsteps echo in the vast foyer as I walk through toward the elevators.</p> <p>ii)</p>

<p>genomics or the first page of articles published by Laboratory X employees. One of the frames contains a photo with humans: two children – twins – one with the phrase “I’m with Nature” and the other with the phrase “I’m with Nurture” written in block letters on their matching T-shirts.</p>	
<p>3. About one hundred people work here at the Laboratory X, with the vast majority of those working in the service facilities. This is the business part of the facility which conducts fee-for-service genomic work. Only about ten or fifteen people are part of the academic team, which consists of principle investigators, post-docs and graduate students.</p>	<p>3. Only about ten or fifteen people are part of the academic team, which consists of principle investigators, post docs and graduate students.</p>

The purpose of this table is not to indicate how descriptive social science research should proceed with regard to protecting anonymity. Rather, my aim is to highlight the competing tensions in the research process that emerge when studying easily identifiable people and places. In my own case, it took time for me to gain an understanding of how the research site is positioned in relation to the broader national and international context. Upon entering the field I was not aware of how special and unique my particular field site was and thus I did not anticipate in advance the challenges involved in maintaining anonymity. It was only through the process of writing detailed descriptions (Richardson, 2004) that I came to understand the complexity involved in maintaining anonymity within descriptive social science research about easily identifiable participants. The two research ethics boards from which I obtained approval to carry out this research also did not probe me to think about this issue.

The statements in the Letters of Information indicate that no personal information about participants will be published and yet through the descriptions and contextual information about the field sites made throughout my dissertation personally identifying information could be figured out. In the lengthy ethics protocol submitted to the hospital ethics board I indicated that only pseudonyms would be used in place of the actual names of Laboratory X and the Autism Clinic. However, the data sharing agreement between the hospital where my research was carried out and my university ethics board contains back-to-back contradictory statements that underline the difficulty in safeguarding anonymity while meeting expectations for authorship. This data sharing agreement demands that I: i) not include personally identifying information, and ii) include investigators (lab and clinic directors) as authors in publications (thereby disclosing their identity as well as their institutional affiliation). Figure 3.1 illustrates that exact phrasing pertaining to confidentiality that was used in the Letters of Information and Data Sharing Agreement.

Figure 3.1: Ethics Documents Statements Pertaining to Confidentiality

Letter of Information for Families

We will respect your privacy. No information about who you are (your child is) will be given to anyone or be published without your permission, unless required by law.

Letter of Information for Scientists and Clinicians

We will respect your privacy. No information about who you are will be given to anyone or be published without your permission, unless required by law.

REB Submission

As an additional precaution to uphold confidentiality, the name and location of the laboratory and clinic will not be given in JB's dissertation or any written presentations of this research; instead pseudonyms will be used.

Data Sharing Agreement

RECIPIENT shall not include any personally identifying information in any publication or presentation. [Hospital] Investigator's contribution to the Study and authorship contributions, as applicable, shall be acknowledged appropriately in any such publication or presentation in accordance with academic standards.

Thus, the Letters of Information and REB submission promise to protect the identity of participants. However, descriptive details about the study sites along with nuanced accounts of the activities carried out by particular individuals may reveal the identity of participants to some readers. Furthermore, the data sharing agreement undermines these precautions being taken by suggesting that some participants (Directors of the laboratory and clinic) should be named as authors on publications, thereby revealing the names of the particular field sites.

As descriptive social science moves into field sites such as cutting-edge genomics where participants may be easily identified how can the friction between a descriptive methodology and the need for anonymity be lessened? What steps should be taken to satisfy

these documents and at the same time provide the nuanced descriptions and depth which make the research meaningful within a particular context? How do I comply with expectations for confidentiality and anonymity while at the same time meet the academic expectations surrounding authorship? Does the consent process need to change in order to inform participants about the limitations to anonymity in descriptive research that “studies up”? My research brings to the foreground the complex implications of engaging in descriptive methodologies amongst highly visible or easily identifiable participants with regard to anonymity and the need for a greater awareness of this issue amongst research ethics boards.

3.3. Expectations of Research Participants

While anonymity is my primary concerns in this chapter, there is one other issue to briefly address in relation to “studying up” that provoked my discomfort and concern at various times throughout my research. At times, I struggled with the interrelated issue of loyalty to my participants and “for whom is this research being written?” (Priyadharshini, 2003). For example, I have a particular interest in knowledge translation, specifically in developing new conceptual models of KT based on a constructionist philosophical foundation. Approaching KT from this lens has enabled me to interpret my field notes about observations and interviews in a way that is probably unfamiliar and unanticipated by the participants. For example, exploring knowledge as being constructed rather than discovered might be received as a critical attack on the values and assumptions underlying much of the work in the laboratory and clinic. I worry that not only might the participants not agree with my interpretation but that they would also not find such discussion valuable.

Priyadharshini (2003) has previously discussed this issue. He stated. “subtle constraints imposed on my research from the point of gaining access to the end of fieldwork contained

my natural inclinations and made it harder for me to wear the badge of critical researcher...” (2003, p.426). These subtle constraints about which Priyadharshini writes were present in my fieldwork experience as well. For example, early on, while establishing the laboratory field site I had a meeting with the director of Laboratory X. He made a passing remark at some point in our brief meeting that they did not need another theoretical or philosophical piece but rather he felt the findings should be “practical”. This brief statement caused me great concern over the course of my research. Will he find this dissertation “practical”? To me, thinking through knowledge translation from a different philosophical position is practical. It has practical implications for how KT is approached. I feel that my integrity as a researcher would be compromised if I were not able to critically explore the assumptions underpinning much of the work currently being done in the area of KT. On the other hand, those who participated in my project gave their time generously and I feel an obligation and a desire to have them appreciate the work I have done. I would hope that my research would have some meaning or use to the participants. What kind of loyalty or allegiance is assumed when you are allowed access to a field site? What responsibility do I have as a researcher to ensure that my findings have some sort of practical utility, that they reciprocate in some way for the many hours the scientists and clinicians have given me as research participants? These are questions that are equally important to researchers who are not “studying up”. Further, knowing that your participants can and probably will engage with what you have written and that they have the power to respond in an articulate and scholarly way is a sobering thought that makes these questions about loyalty and expectations all the more poignant to the fledgling researcher.

In this chapter I have discussed the concept of anonymity as it relates to multiple sets of research participants in new and emerging sites of inquiry where "studying up" brings to

the foreground a tension between methodological rigor and research ethics. In addition, questions surfaced regarding loyalty to participants and negotiating participants' expectations alongside a researcher's individual interests and aims. This chapter raises more questions than it answers and I suspect many of these issues will be ongoing in the future as I prepare sections of this dissertation for journal publication. Far from presenting tidy answers and conclusions, this chapter merely opens up a discussion about some of the ethical complexities that have emerged through an anthropologically-inspired study of genomics.

Chapter 4

Inside-Out and Upside-Down: Tumbling into the World of Autism Genomics

4.1. Diagnosing Autism Spectrum Disorder

4.2. Genomic Constructions of Autism

a) Research Paradigms

b) Linkage and Association Studies

c) The “Multiple Hit” Model

In this chapter, I will first briefly familiarize the reader with how autism is diagnosed today and some of the statistics pertaining to prevalence and incidence. While my research was not focused on issues of diagnosing autism (all of the proband participants had been previously given a clinical diagnosis of autism before engaging in genetic research) the clinical tools and technologies engaged in the process of diagnosis were very important actors in the network of the autism clinic in so far as they were used to establish an individual’s phenotype. Thus, this initial introduction of the diagnosis of autism will be followed in later chapters by a more in-depth description and discussion of some of the tools involved in the diagnostic process.

The second aim of this chapter is to provide the reader with a background understanding of the current genomic practices within which autism is being constructed today. An overview of the current genetics literature related to autism will prepare the reader with a baseline understanding of autism genetics to facilitate in following the descriptions presented in the subsequent chapters.

4.1. Diagnosing Autism

According to the DSM-IV, the umbrella term of Pervasive Developmental Disorders (PDD) is comprised of five related clinically defined categories. Three of these categories compose what is commonly called the autism spectrum, including: Autistic Disorder, Asperger's Syndrome (AS), and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Rett disorder and childhood disintegrative disorder (CDD) are less common but included within PDD. Moreover, a broad autism phenotype (BAP) has recently been applied to label subtle cognitive or behavioural attributes that are similar but less severe than those exhibited in Autism Spectrum Disorder (ASD) patients (Freitag, 2007). The diagnosis of ASD has become standardized with two instruments: the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord, 1989).

Leo Kanner first identified autism in 1943 (Kanner, 1943). Originally, Kanner defined "autism" based on two criteria: "autistic aloneness" and "insistence on sameness" (Kanner & Eisenerg, 1956). Recent diagnostic criteria for autism, as it is described in the American Psychiatric Association's DSM-IV (American Psychiatric Association, 2000) and the World Health Organization's International Classification of Functioning, Disability, and Health (ICF) (World Health Organization, 2001), are structured around the three core areas of social impairment, communication difficulties, and rigid and repetitive interests and activities. Typically, onset occurs before age three (Gillberg & Coleman, 2000). Asperger's syndrome is diagnosed when individuals meet the criteria, but without showing language deficits or "mental retardation"² (Lord & Spence, 2006). Many people with Asperger's syndrome may be regarded by their peers as odd, but not perceived as psychiatrically abnormal (Gillberg & Coleman, 2000). A diagnosis of PDD-NOS indicates milder

difficulties (Lord & Spence, 2006).

Nadesan (2005) has traced the historical changes in the classification of "autism", drawing attention to recent broader and more inclusive criteria for diagnosis which has led to the notion of a continuum or spectrum. Kielinen et al (2000) described a striking variation in the rates of "autism" that result when different diagnostic criteria are applied to the same survey data. It behoves us to bear this in mind when comparing measurements reported across time; different diagnostic criteria can result in radically different epidemiological statistics. For example, incidence (the number of new cases in a population over a period of time) is difficult to determine with diagnoses on the "autism" spectrum as several variables (i.e., changes in diagnostic criteria, increased public awareness and improved service availability) have not remained constant over time. Fombonne (2005) warns that upward trends in prevalence (the proportion of individuals in a population with a disorder) cannot be attributed to increased incidence because of the aforementioned variables. The prevalence estimates of Autistic Disorder is approximately 13 / 10 000 (Fombonne, 2005). Prevalence rates for Asperger's is about one fifth that of autism, approximately 2.6/ 10 000; however, epidemiological studies of Asperger's are very sparse, as it was only recently acknowledged as a separate diagnostic category (Fombonne, 2006). Meanwhile, PDD-NOS has a prevalence rate of about 20.8 / 10 000 (Fombonne, 2005). Most of the available statistical data which support prevalence rates are based on surveys conducted in urban areas (Fombonne, 2006). There is also a marked sex differentiation in autism, with a 4:1 male to female ratio (excluding Rett syndrome which is more common in females) (Bartlett, Gharani, Millonig, & Brzustowicz, 2005).

Comparing measurements of an ASD diagnoses is further complicated by the possible political ramifications of attaching this label or code to a child. Grinker (2007), for example,

highlights that an ASD code will usually get your child more services that benefit him - more hours of speech therapy, more aide support, more of almost everything the school has to give" (2007, p.267). Thus, a diagnosis may be sought in some situations. Defining and measuring "autism", therefore, is a complicated endeavour with many factors to be taken into consideration.

4.2. Genomic Constructions of Autism

In the 1970s, the first twin studies were conducted showing a significant difference between monozygotic and dizygotic concordance (Rutter, 2000). A major shift in the conceptualization of autism and its causes began to occur. Twin studies replicated these findings in the 1980s and 1990s presenting a 60% concordance rate for autism in monozygotic twins compared to a 5% rate in dizygotic twins (Rutter, 2000). Current heritability estimates for ASD are ~90% (C. Marshall et al., 2008), suggesting that "autism is one of the most heritable neuropsychiatric disorders" (Bonora, Lamb, Barnby, Bailey, & Monaco, 2006, p.51).

While there have been major advances in the study of genetics over the last decade, for example the mapping of the human genome and new technologies such as micro array analysis, there remains much to be explored in the aetiology of "autism" (Bonora et al., 2006). According to Pickler and Elias (2009) there are currently over two dozen genetic syndromes (e.g., Fragile X syndrome, Angelman syndrome and Rett syndrome) that have been associated with "autism", likely because "autism" is defined by such a heterogeneous mix of behaviours. Given this heterogeneity it is most likely that a large number of genetic

variations and possible epigenetic occurrences are involved in the development of ASD (2006).

4.2a Research Paradigms

Genetic research in the area of autism is typically conducted within one of two paradigms: common disease-common variant and common disease-rare variant (Cook & Scherer, 2008). The common disease-common variant model is *oligogenic* in that it assumes disease results from "the combined action of multiple interacting genes" (Abrahams & Geschwind, 2008, p.342). In this model, it is assumed that multiple alleles that are common to the general population each contribute small effects to the phenotype. Distinct characteristics of ASD (e.g., communication difficulties or repetitive and rigid behaviour) are related to independent genetic factors (Happé & Ronald, 2008; Ronald et al., 2006). This model has been supported by linkage studies indicating different locations for various traits or characteristics of "autism" (Schellenberg et al., 2006). Risch et al (1999), for example, argue for at least 15 susceptibility loci. Haple and Ronald (2008) described the idea of the "fractionable autism triad"; the idea of fractionability suggests that "different genetic loci may be associated with the different core behaviours that currently define the autism diagnosis" (Haple & Ronald, 2008). These authors raise the question of whether autism should really be conceptualized on one continuum, "or whether each individual should be mapped in a three dimensional space along three, perhaps orthogonal, dimensions: social interaction, communication, and RRBI [rigid and repetitive behaviours and interests]" (Haple & Ronald, 2008, p.299). The implications of the common disease - common variant model of autism are that genome-wide association studies which look for susceptibility genes would be more successful if they geared their search towards specific behaviours within the autism triad rather than searching for genes underlying autism as a whole. One of the key

challenges is the difficulty to define the phenotype, especially considering the broad spectrum of autism. Such a diverse and variable set of characteristics and behaviours would likely involve genetic heterogeneity, as well as epigenetic factors. Bartlett et al (2005) have considered this difficulty and stated:

While phenotypic heterogeneity does not necessarily imply genetic heterogeneity, the breadth of phenotypic variation, which cannot solely be accounted for by any one etiological theory, and the linkage findings converge on the same conclusion, that *autism is not a unitary phenomenon* (Bartlett et al., 2005, p.224).

The task is complex as genetic effects may operate on components of autism rather than at a syndrome or diagnostic level (Rutter, 2000). As Abrahams and Geschwind (2008) have suggested, "diagnostic categories used in clinical practice might not properly represent underlying genetic risk". Thus, the clinical diagnosis of autism can be thought of as a grouping of characteristics or traits which are not necessarily held together by the same genetic and biological markers.

Conversely, the alternative *common disease-rare variant* model emphasizes overlapping risk factors (Pritchard, 2001). This rare variant hypothesis posits that many alternative rare variants underlie susceptibility to common complex conditions (Cook & Scherer, 2008; Pritchard, 2001). Recent work in the area of *ne novo* (spontaneous) copy number variations (CNVs) is rooted in this model (PGCC Committee, 2009). (This common disease-rare variant model was the model that guided the research in Laboratory X, where I conducted my fieldwork for the present dissertation.) Copy number variations may include deletions or duplications of DNA segments. Several studies have examined whether copy number variations are more frequent in case subjects versus comparison subjects. For

example, Sebat et al (2007) found increased rare de novo (spontaneous) copy number variants in case subjects (10%) versus comparison subjects (1%). Several studies have also reported an increase in deletions or duplications on chromosome 16p.11.2 in case subjects versus comparison subjects (Kumar et al., 2008; C. Marshall et al., 2008; Weiss et al., 2008). While researchers typically work within one or the other model (common disease - common variant or common disease - rare variant), Abrahams and Geschwind (2008) have commented on the necessity for the integration of findings from each of these models.

I learned, when talking with a post-doctoral fellow in Laboratory X, that this distinction between theoretical approaches is also accompanied by a slight difference in language. Whereas those using the common disease- common variant hypothesis tend to talk about “polymorphisms” (single nucleotide polymorphisms or SNPs), scientists who adopt the common disease- rare variant model tend to use the word “variant” (SNVs). During my fieldwork it seemed that people were using these terms interchangeably. When I asked a post-doc if there was any real difference between SNPs and SNVs this was her response:

Ahhh! This is something that I find very irritating because many people are rather loose in their use of polymorphism and variant. It’s all about frequency; so a polymorphism (ie a SNP) is generally taken to be a position that varies commonly in the population usually with a given minimum frequency (eg 1%, 3% or 5%). Whereas a variant is something that is more rare and may never have been described before.

4.2b Linkage and Association Studies

An alternative way to unpack the genetic construction of ASD is to examine how genetic-related conditions are explored. Linkage studies and association studies are two primary means of analyzing the relationship between genotype and phenotype (observable

expression of genes). The purpose of linkage studies is to map genes in families in order to locate susceptibility genes. Linkage studies concentrate on affected sibling pairs in multiplex families (Abrahams & Geschwind, 2008). Linkage is defined as "the tendency for alleles close together on the same chromosome to be transmitted together, as an intact unit, through meiosis" (Freitag, 2007, p.7). Lander (1996) proposed that most single nucleotide polymorphisms (SNPs) are ancient and common to most people in a population. SNPs become common because they are neutral or favourable to survival and get passed down to the next generation; however some may have harmful effects. Linkage analysis, then, starts with a particular phenotype found in families and then tests genetic locations on the genome to find linkage between genes and phenotype (Bartlett et al., 2005). Linkage has also been called *reverse genetics*, as the scientist moves from the phenotype back to the genotype (Bartlett et al., 2005). Several chromosomal regions have been linked to an ASD phenotype. Some linkage studies have stratified their sample of individuals with regard to phenotypic traits. From these studies, chromosome 2q and 7q35 appear to influence language development, while 1q is linked with obsessive-compulsive behaviour (Freitag, 2007). Thus, according to linkage studies, different components of autistic behaviour may have different underlying causal factors. The difficulty with linkage studies is that any one gene has a small overall effect size. Thus, it may be difficult to achieve statistically significant results.

Association studies start with the genetic or genomic information (genotype) and then search for associations with phenotypes. In other words, they are genotype-driven rather than phenotype-driven. Association studies use high-resolution microarray technologies to detect balanced and unbalanced structural variants or copy number variations (CNVs) (C. Marshall et al., 2008). CNVs involve segments of DNA that are at least 1 kb in size. Balanced variations involve no loss or gain of genetic material (Buchanan & Scherer, 2008).

Unbalanced variations included deletions or replications. Locus 1q21.1, for example, is associated with duplications in a form of ASD (Cook & Scherer, 2008). CNVs can be *de novo* (spontaneously arising rather than being transmitted by a parent) or they can be inherited. Adding to this complexity, the position or context of CNVs within the genome can influence expressivity or penetrance (Buchanan & Scherer, 2008).

Marshall et al (2008) reported a 7.1 % and 2% rate of *de novo* CNVs in simplex and multiplex families compared with a <1% spontaneous CNV mutation rate in non-disease samples. These authors found that CNVs in ASD are often in loci with genes functioning in postsynaptic density and regions associated with mental retardation. SHANK3, NLGN4, and NRXN1-PSD are three genes involved in synaptic functions and have been shown to have CNVs in ASD probands. Berkel et al (2010) found *de novo* copy number variations in the SHANK2 synaptic scaffolding gene in patients with ASD and mental retardation (MR). Two loci for ASD CNVs overlap with mental retardation. In particular the 16p11.2 CNV region was found at almost 1% frequency in ASD samples and not controls (C. Marshall et al., 2008).

4.2c The “Multiple Hit” Model

According to Leblond et al (2012), while there are many diverse causes of ASD, the “main category of genes associated with the disorder is related to development and function of neuronal circuits.” Genes such as neuroligens (NLGN), neurexins (NRXN) and SHANK are important for formation and stabilization of synapses and coding for scaffolding proteins. Mutations in these genes have been widely reported in patients with ASD. The “multiple hit” model suggests that the co-occurrence of deleterious variations in multiple genes could act together in the same pathway to increase the risk of ASD. For example, Leblond et al (2012)

suggested that the NRXN-NLGN-SHANK pathway and CNVs in the 15q11-q13 might together increase susceptibility to ASD. Recent data suggest that common genes/ pathways are being identified across a broad range of neurodevelopmental disorders. For example, ASD, schizophrenia, ADHD, and obsessive compulsive disorder all have overlapping susceptibility regions (C. Marshall & Scherer, 2012). Lionel et al (2011) stated that there seem to be “common genes and pathways implicated in several disorders...[suggesting that] different human disease-phenotype groups might arise from overlapping molecular causation”.

Specific genes thought to be associated with "disease" are called candidate genes. There is no single gene for ASD; rather, there appear to be several different regions in the genome that may confer susceptibility to ASD when perturbed. For example, Levy *et al* (Levy & et al., 2011) stated:

A striking finding of all the studies of de novo mutation in children with ASDs is the apparent number of distinct target loci. Even discounting 25% of events as incidental (based on a 2% frequency in sibs and 8% in probands), there are a large number of target regions and few recurrences. Only CNVs at 16p11.2 are present in more than 1% of cases (ten out of 858 children).

Thus, the genetic variation in one individual with ASD is likely to be distinct from the genetic variance of another individual with ASD. In reviewing the literature, several genomic loci were described as contributing to susceptibility for ASD. For example, using extended family pedigrees from 42 extended ASD families, Salyakina et al (2011) reported twelve loci that co-segregated with disease which may be involved in ASD susceptibility. Screening for CNVs is often used as a method for identifying susceptibility regions in the genome.

One of the most recurring regions for variants in ASD is called 16p11.2. This region has been described by Čiuladaitė et al (2011), Kumar et al (2008), Marshal et al (2008),

Weiss et al (Weiss et al., 2008) and Barge-Schaapveld et al (2011). Ciuladaite et al (2011), for example, suggested that the 16p11.2 deletion is a recurrent genomic event and a significant risk factor for autism. However, a deletion in the 16p11.2 region is associated with a wide range of clinical phenotypes. Deletions in the 16p11.2 locus are risk factors for a variety of developmental and psychiatric conditions, such as MR (mental retardation), ASD, attention deficit hyperactivity disorder (ADHD), language delay and seizures (Ciuladaite et al 2011).

Recently, CNVs have also been found in individuals with ASD at the x-linked PTCHD1 locus (Pinto et al., 2010). All of these variations were inherited from unaffected mothers. Marshall and Scherer (2012) have suggested that these X-linked variants may provide an explanation for the skewed male to female ASD diagnoses. Females, with two X chromosomes, are protected by CNVs in this region; whereas males, with only one X chromosome, are not protected.

Given the range of loci involved in ASD, a “threshold” model has been proposed to understand the role of CNVs in ASD (Cook & Scherer 2008). Marshall & Scherer describe this threshold model as follows:

Some CNVs have a large impact on ASD susceptibility and these are typically de novo in origin, cause more severe ASD symptoms, are more prevalent among sporadic forms of ASD, and are less influenced by other factors like gender and parent of origin. Other CNVs have moderate or mild effects that probably require other genetic (or non-genetic) factors to take the phenotype across the ASD threshold (C. R. Marshall & Scherer, 2012; C. Marshall & Scherer, 2012).

Devlin & Scherer (2012) have suggested a possible multigenic threshold model for ASD in which multiple CNVs, smaller sequence variants, and variants in apparently non-coding

regions of the genome (intron) may all interact. This gene-gene interaction may work to push an individual over the ASD threshold.

The diverse phenotype and complex aetiology of ASD make replication of study results a difficult task. Bartlett et al (2005) explain two key concepts that have an enormous impact on the possibility for replication of findings. *Locus heterogeneity* describes a situation in which different genes may be involved in causing the same disease in different individuals. *Allelic heterogeneity* implies that different alleles of the same gene may confer susceptibility to the same phenotype. Thus, it is very difficult to achieve replication of a positive association between a candidate gene and autism. This challenge is compounded when one considers possible environmental exposures (Hertz-Picciotto et al., 2006; Lawler, Croen, Grether, & Van de Water, 2004) and multiple interacting genes.

The technology to assay the entire human genome has instigated a transition in the way scientists think about disease, highlighting the need to simultaneously integrate information from many sources. Paradoxically, while the sensitivity and resolution of new genetic technologies improve and enable scientists to interrogate specific alleles on particular genes, there is also an increase in uncertainty about the nature of disease. According to Schaaf & Zoghbi (2011), rare *de novo* CNVs account for 7-20 % of individuals with ASD, single gene disorders account for 5-7 % and metabolic disorders account for approximately 5% of ASD cases. This leaves at least 70% of all ASD cases for which a genetic cause cannot yet be identified. Schaaf & Zoghbi further stated, “It is very likely that there will be hundreds of autism genes and proteins; thus designing treatments for ASDs tackling one gene at a time will be a challenge” (Schaaf & Zoghbi, 2011). Marshall & Scherer (2012) have specified that the challenge is in the correct interpretation of the clinical significance of each variant. To

address this challenge, the International Standards for Cytogenetic Array Consortium has established a working group to develop an evidence-based process for evaluating and interpreting genetic finding so that they can be used to inform clinical practice (Riggs et al., 2012). Moreover, knowledge translation amongst scientist, clinicians and the public is increasingly being recognized as an important aspect of genomic research (Zwaigenbaum et al., 2011).

In reviewing the complex genetic aetiology of ASD, the need for research describing the process of translation amongst basic science, clinical, and family milieus is made evident. Drawing on concepts such as ontological multiplicity and the mangle of practice, outlined in the previous chapter, the remainder of this dissertation will explore the processes involved in translating amongst the heterogeneous groups of people, practices, places and objects that partially connect through the overlapping networks of the Autism Genetics Study at the particular sites in which I conducted fieldwork.

Chapter 5: Translation as Transformation

[B]ehind the texts, behind the instruments, inside the laboratory, we do not have Nature, not yet... what we have is an array allowing new extreme constraints to be imposed on 'something.'"

(Latour, 1987, p.89)

5.1. Setting the Stage

5.2. From Individual to Blood

- a) Collecting the Blood

5.3. From Blood to DNA

- a) Into Laboratory X

5.4. The Microarray Process: From DNA to CNVs

- a) Clinical vs. Research Microarrays
- b) Running a Research Microarray

5.5. Validation: From CNVs to *Real* CNVs

- a) fISH
- b) PCR
- c) From PCR to qPCR

5.6. From CNVs to SNPs: Next Generation Sequencing

- a) The Computer Pipeline
- b) Monday Morning Meetings

5.7. From Data to Report

5.8 Exit the Laboratory: The Feedback Session

5.9. Back into the Clinic

- a) Diagnoses: Clinical and Research

5.10 Setting the Stage: The Autism Clinic

- a) Assessments

5.11 Into the Family Home

- a) Demographic Information of Parents
- b) “Bobby’s” Daily Routine
- c) Becoming Diagnosed on the Autism Spectrum

5.12 Summary

5.1 Setting the Stage

The dry heat of the office building gives way to the cold November air as I push through the revolving doors onto High Street West. The wind feels crisp against my face as I step further out onto the sidewalk. Inhaling, I catch a brief hint of fragrant spices from the little East Indian restaurant across the road. A long line of cars stretches beside me as I walk quickly along the bustling, morning rush-hour sidewalk and round the corner onto Peele Ave. A large group of ESL students huddles outside the door of an International School. I weave through them and quicken my pace, hoping to catch the walk signal ahead. Just missed it. Standing at the corner waiting for the light to change, I can see the boney, finger-like branches of the trees reaching up around the hospital. As if misplaced by summer, two bronze women in sundresses hold down a bench, blossoming and rounded with their sculptured children playing at their feet. Four other hospitals huddle up to the street in this one small stretch of the block; if one was ever to find herself ill or injured, surely this would be the ideal location.

Passing a half-empty bank of Bixi bikes, I walk a little further and turn right on Rainier Street. It's 9:00 am and I'm heading to Laboratory X to find out if I can observe anything this morning. I've just come from the Autism Clinic and I have a follow-up interview scheduled in an hour from now with one of the genetics post-docs. The laboratory is housed in a Medical Research Centre. It's on my right as I walk along Rainier Street now. A beautiful old building sits stalwart on my right. A shadow is cast down on the rugged stone bricks by a tall, smooth, modern tower now joined at a seam onto the far end; this is the Medical Research Centre. As I approach, a custodian is cleaning the glass of the revolving doors so I push open the swinging door. The noisy street is shut behind me and my footsteps echo in the vast foyer as I walk through toward the elevators. To my right is a set of stairs

that leads down into the food court, the underbelly that joins the research tower to the hospital. I know if I head down the stairs the tables will be full with groups of people huddled together around laptops, chatting over morning coffee from Timmies. Many of them have probably been working for hours already, taking a break before heading back to the hospital or up to one of the laboratories in the tall medical tower.

Approaching the bank of elevators, I push the “up” button and see a poster advertizing an upcoming colloquium on stem cell research. The elevator dings and the shiny metal doors open. Several other people step into the elevator with me. There are sixteen floors and Dr Lorenz’s laboratory is on the fourteenth. All of the people in the elevator have name tags hanging around their necks, partially obscured by scarves and winter jackets. Some people are quietly talking about the snow forecast for later this week while three others appear to be deep in conversation about a recent conference. The elevator stops at several floors before the fourteenth. As the others step off the elevator they each pull out their name badge and swipe it across a security scanner to unlock an interior set of heavy beige doors before they can enter into the laboratories awaiting them.

The elevator dings for the fourteenth floor and I step out. It looks different from the other floors we’ve just passed through with their prosaic beige paint and uninviting locked doors allowing only a few to enter. Here, there is a black leather bench perched in front of a window as you step off the elevator and green leafy ferns in shiny black planters adorn the corners. It’s quiet. The clean foyer is bathed in natural light from the large square window, deeply recessed in the end wall. The heavy, security-protected double doors are wide open, inviting customers to enter. To the right of the double doors, slightly obscured by a plant, there is a sign warning that ‘This facility is under video surveillance’. The floor is glossy grey with a brightly coloured helix pattern winding through it, a subtle indication of the work

being done here.

This is what Erving Goffman (1959) would call the “front stage” of the laboratory. Clean and bright with carefully planned signs telling the client or visitor that this lab is well-funded, high-tech and state-of-the art. All of the messiness of doing genomics takes place “back stage”, behind the glass wall of the laboratory or behind closed-door conference room discussions.

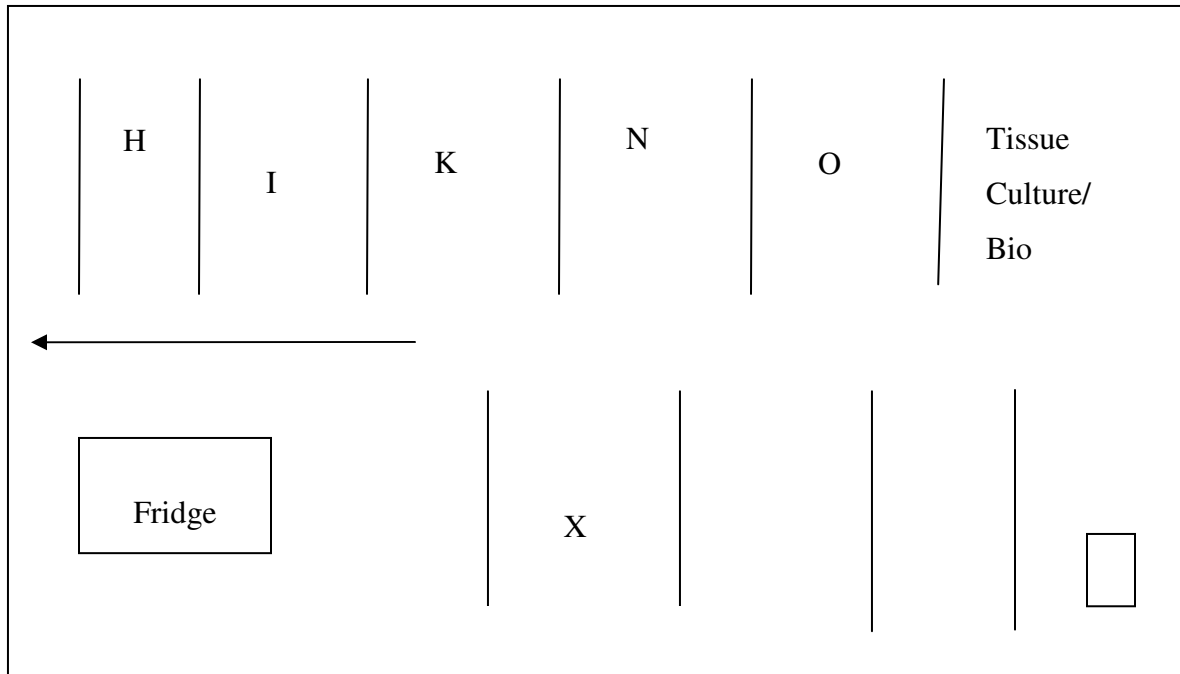
I follow the helix pattern through the inner double doors and pass a large window with sliding glass doors on the left with a sign above that reads “DNA sample drop-off”. All the samples that will eventually end up in the lab have to first pass through this window. The samples come from a variety of places; some from the DNA extraction lab in the hospital down the street that I just walked past a few minutes ago. Other samples are mailed from cities across Canada or from other countries. They can be from blood, tissue, or saliva. With luck the samples have been stored properly in the little glass tubes as they have made their various journeys to this window. If caps were not screwed on tightly they might have spilled and technicians will have to try to collect any remnants remaining in the surrounding package.

I look at the clock on the wall inside the small office on the other side of the drop-off window: 9:15. Brittany looks up and sees me. I wave and she smiles before turning back to her computer screen. Brittany is in her late thirties and has a PhD in molecular biology. She is thin, angular, but her soft, quiet voice bends in an unexpected way. She is precise, detailed, meticulous in the way she manages all of the records, accounting for all the samples that have been dropped off and delegating them to the various technicians in her the lab. She spends most of her time in this little office, receiving samples and managing the workflow of the microarray facility. One of her main tasks is to organize and keep track of all the orders

coming in on the Laboratory Information Management system, or LIMS. She is busy at this time of morning, as many samples have been dropped of by technicians as they begin their work day. The samples will continue to pass through the drop-off window all day. I continue to walk past the window.

If you were standing here beside me and looking straight ahead, you would see the laboratory, through a huge transparent glass wall. On the door leading to the laboratory there is a Biohazard sign that says “containment level 2”. There is also a sign informing sequencing costumers to proceed to aisle N. Through the glass, you would see rows and rows of machines with people wearing white lab coats and safety glasses standing bent over their work benches or perched atop stools gazing at computer monitors. The walls are white and the ceiling is made from white ceiling tiles interspaced with florescent lights. You would see that the laboratory is very bright, that the opposite side of the laboratory is also made of a large wall of windows letting in ample natural light even on this grey November day. The main part of the lab is just one large room divided by several aisles. Each aisle seems to loosely correspond to a certain activity; for example, there is an aisle where all the microarray data is done and another for Next Generation Sequencing (NGS).

Figure 5.1: Wet Laboratory



Legend:

Aisle H - Genome Resources

Aisle O – Genetic Analysis

Aisle I – Cytogenetics

Aisle X – Tissue Synthesis

Now, if you were to turn your head to the right and look down the hallway, immediately to the right you would see a swipe card machine for people to clock in and out as they start and finish their work day. About one hundred people work here at the Laboratory X, with the vast majority of those working in the service facilities. This is the business part of the facility which conducts fee-for-service genomic work. Only about ten or fifteen people are part of the academic team, which consists of principle investigators, post-docs and graduate students. Beside the swipe card machine there is also a magnet board with the academic's names on it and In/ Out beside them. Each person moves their magnet to "In" when they arrive and "Out" when they leave. I've frequently seen people doing this.

A little further down the hall to the right there are rows of grey lockers with locks

dangling. This is where lab technicians store their lab coats and other laboratory paraphernalia. *Indeed, the aisles between the workbenches in the laboratory are quite narrow. I always felt a bit like a bull in a china shop when I would come to the lab to do observations or interviews. I never knew where to place my backpack holding my laptop, books, notebook, as well as a coat or sweater.* Beyond the lockers is the large conference room that holds the regular Monday morning meetings, which I have often attended. Beside the door is a keypad entry. There is also a bulletin board which hangs on the wall beside the conference room. Here there are advertisements for all manner of instruments used in the lab. Everything from refrigerators that keep the samples cold, to reagents, to little gel dots. There are posters advertizing conferences and upcoming talks. Some of the talks are actually information sessions hosted by the companies that make the instruments for the lab.

On the other side of the conference room door, there is a large, four foot by four foot brightly coloured red sign against the white wall. The sign reads:

Finding disease-causing genes in DNA is 100,000 times harder than finding the white pins in this wall. We did it. Can you? Hint: use the microscope. Hospital X.

There are double helix images all over the sign. Further beyond the conference room is a section of cubicles and a few offices. A washroom is located a little further on and then beyond that are the offices of some other labs, not associated with the Laboratory X. I have heard that Laboratory X has, in the past, acquired some office space down there as other researchers have moved out of the building. Space is highly coveted.

Now, if you were to turn your head around to the left, looking down the hallway in the opposite direction, you would see a kitchen at the far end. This is a busy room with a fridge, microwave, sink, cupboards, table and chairs. It is morning and as I walk down the hallway toward the kitchen I am greeted with the smell of freshly brewed coffee. Several

framed photos hang from the walls at regular intervals. On closer inspection, they are not just photos but actually the covers of journals related to genomics or the first page of articles published by Laboratory X employees. One of the frames contains a photo with humans: two children – twins – one with the phrase “I’m with Nature” and the other with the phrase “I’m with Nurture” written in block letters on their matching T-shirts. Just to the left of the kitchen, near the end of the hall, is the door to the academic offices. Tyler, one of the senior research coordinators here, used to sit at the first cubicle but has recently been moved into his own office. He is still unpacking boxes. Penny, the main administrative assistant has an L-shaped desk in the middle of the room. Beyond this desk are more cubicles, primarily housing the bioinformaticians. The director of the whole laboratory has an office to the right of the admin desk. His office is fairly small, the size of a typical university academic office, but is adorned with a beautiful view out a large picture window.

For the most part, people in the academic office are sitting at their cubicles working on laptops. They do not have telephones (something I learned when trying to set up a telephone chat with one of the post-docs). The people who inhabit the research office do not wear lab coats or safety glasses. Everyone is dressed very casually, not surprising since many of these people are students of one sort or another. Jeans and a long sleeve jersey or sweater seems to be the preferred attire. There is beige carpet on the floor in here and the office somehow feels warmer and more relaxed than the rest of the facility.

I can hear Dr. Lorenz approaching the academic office. He is telling someone that he took the subway to work and was surrounded by people more sick than he. He is wearing a red sweater with a dress shirt collar neatly folded over the top along with blue jeans and black shoes. A large black leather shoulder bag/ brief case is slung over one shoulder, bulging. His brown hair is cut short and he looks tired this morning. He sneezes. There is a

group of people standing in the hallway. Tyler and Brittany are among them. Dr. Lorenz says jokingly, “I thought the meeting wasn’t happening until 9:30”. A woman approaches him and tells him that she is having a problem with someone who has not been showing up on time. Dr Lorenz and this woman disappear around the corner into his office.

So far you have met a few of the people that will become important in my recounting of the travels of DNA as it moves throughout the laboratory. I have given you a general description of the spaces that make up the Laboratory X, as you might see them upon entering the facility for the first time. Now, I will shift gears. I want to give you a more detailed account of a sample of DNA as it moves through the facility. I will move from describing not only what you would see with your eyes but also what is being done, with hands and robots and computers. I warn you, the number of actors you are introduced to is about to magnify significantly as we zoom in on the trail of a single DNA sample.

5.2. From Individual to Blood

And I think for their lab it’s a lot more biology and science and that kind of stuff, not clinical like it is here... sometimes they don’t understand what we’re doing or why it takes us so long to do things. So for us, I feel like we have to balance that a lot around here versus them, they just look at the data, they look at the blood. It’s more straightforward, cut and dry. (Excerpt from interview with psychology student/ research assistant at the Autism Clinic)

5.2a Collecting Blood

Just prior to the start of my data collection, the protocol for the genetics study changed. Previously, every participant was first “deep phenotyped” and then their blood was taken and sent onto the lab for genetic testing. The deep phenotyping included all the psychological assessments (i.e., ADOS, ADI-R) and took two days to complete. In the new protocol, however, only a brief phenotypic profile is gathered before blood is taken. The limited phenotypic data collected includes a photograph of the individual and the parents, as

well as having some questionnaires filled out by the parents. Deep phenotyping is now reserved for only the very few participants who have “interesting” genetic findings. In the new protocol, genetic testing comes first with phenotypic assessments after for select participants. I was told that this change in protocol was implemented in an effort to reduce costs, as phenotypic assessments are time-consuming and expensive.

Individuals diagnosed with autism and their family members give blood in the blood lab located on the main floor of the hospital. The genetics project coordinator, Claudia from the Autism Clinic, typically walks them over to the triage area in the new atrium of the hospital. I will recount one of the blood draws that I observed early on in my fieldwork; at this time everything was new to me and my notes are particularly detailed about this event.

Through revolving glass doors, we arrive at the new atrium with a mother named Jane, a father named Bruce and their teenage daughter, Alexis, who was diagnosed over ten years ago on the autism spectrum. Claudia takes Jane over to the desk where she has to fill out some paper work. A woman behind the desk takes all of their health cards and runs them through her computer. While Claudia stays with Jane I sit down with Bruce and Alexis on one of several green leather padded benches scattered in the waiting area. Alexis leans her head against her father’s shoulder while he puts his arm around her. Nestled against her father, her red hair pulled back in a pony tail, she begins quietly humming to herself. I can not tell if her eyes are closed or if she is just looking down. There are large glass windows all along the wall and plenty of natural light. The walls are painted green and yellow and lively murals depicting beach scenes surround the upper walls around us. This is the new part of the hospital. Lots of people come and go through the revolving doors behind us. From where we are sitting the reception/ check-in area is off to my right and to the left is a cafeteria. A large stairwell ascends to the second floor and a glass walkway spans the atrium above us, leading

to another part of the hospital. The ceiling is very high and everything echoes. I can hear the sound of water falling, coming from a fountain in the cafeteria. While we wait, I tell Bruce a little more about my study. After a while, Claudia comes back to our bench and asks Bruce if he could roll up Alexis's sleeve so that Claudia can rub a small amount of numbing cream onto her arm at the spot where the needle will later be inserted.

Claudia asks them to wait here where their daughter is comfortable while we rush ahead to the blood lab to make sure they are ready. We return to the atrium, bringing a wheel chair with us for Alexis. While we walk out of the atrium and down the hallway leading to the blood lab, I can tell that the mother and father are feeling a little anxious. Being poked by a needle in order to fill six or seven tubes is not fun for any of us, to say the least. For people with autism it can be extremely frightening and disturbing. Bruce must be anticipating this while we approach the blood lab because he reminds me that this is a very stressful event for them. He says I can observe but if Alexis gets very agitated I should leave the room. He might have to hold her down in order to do the blood draw.

There is an ethical issue here that I faced repeatedly throughout this research. Although I had obtained informed consent from each participant, I was constantly aware that observing these very intimate, private and stressful events (such as feedback sessions or blood and tissue collection) was an unbelievable privilege. I was a complete stranger to all of these people and they allowed me to follow them into highly emotional and private events. What right did I have to be there? Was my presence contributing more stress in an already stressful situation, just so that I could collect data for my PhD? I was constantly on the verge of apologizing for even asking to be there. In these situations I tried to make myself as small and unobtrusive as possible.

The hallway outside the blood lab is very busy and often noisy, as there is a constant

stream of hospital employees and patients walking past the lab in order to reach a bank of elevators located nearby. The canteen is also located down the hall from the blood lab. Once in the lab, Claudia gives the paperwork to the administrative assistant behind a desk. We all wait in a small, grey-walled waiting room with a television playing in the corner. The television helps to distract Alexis while Bruce and then Jane are taken out into the main room. A curtain is pulled around so that there is some privacy for the parents while their blood is drawn. Alexis is sitting in a wheel chair watching Toopy and Binoo on the television in the corner. She grows a little anxious when, for a few minutes, her mother and father are both out of the room getting blood samples collected. She holds on tightly to a small Fisher Price children's tape player. It sounds familiar: Raffi. Periodically she bends down to tap her fingers on one of her neon pink running shoes. She probably doesn't understand who we are or why she's here or where her parents have gone. Claudia reassures her that her mother and father will be returning to the room very soon.

After a few minutes her parents are finished with their blood draws and we all file into a small room. A hospital bed stands immediately to the left of the door. Rows of tubes are lined up across the starched white sheets pulled tightly across the bed. The tubes are each labelled and capped. The caps are different colours. Some are for clinical testing and others will be passed on to Laboratory X for genetics research.

It struck me that these tubes were significant. They marked a demarcation between the individual as a human body, whose emotions, behaviours and personal characteristics were perceptible and the individual as a number, a tag on a tube. Without that labelled number, the blood inside the tube would be unidentifiable from any other blood. The patient ID number becomes a place holder for all the individual characteristics that make a human an individual. In the language of actor-network theory, the ID tag is made to 'stand in' for the

individual, temporarily suspending a whole network of actors.

Alexis is wheeled into the centre of the room. There are six of us jammed in around her in this tiny space. One nurse brings over a DVD player to try to distract Alexis. Jane says “no thank you”; it probably won’t work for the needle. It’s better if her daughter can just listen to her mom’s voice. Alexis remains sitting in her wheelchair while a large, friendly and confident nurse rolls up the sleeve of the girl’s sweater and inserts a needle. Alexis pulls away slightly but is calmed by her mother who stands directly in front of her. The nurse keeps a friendly banter going. Alexis is doing very well. Her agitation was noticeable only through the noises she makes which grow louder and by the tears welling up in her eyes. Both her parents are touching her and talking to her to try to keep her calm. *I edge back closer to the doorway behind me, ready to leave if things start to escalate. I can feel that my heart is beating faster. I feel like such an intruder.* It only takes a few minutes to fill all of the tubes with dark red blood. After all of the tubes are filled, Jane gives Alexis a croissant as she has not eaten since dinner last night. It had been a fasted blood draw for her. The cheerful nurse reassures Alexis that it is all finished and praises her for doing so well. We all quickly walk back to the new atrium and say good-bye. Alexis is tired and needs to eat and go to bed. The parents had to medicate her with Ativan prior to arriving today. I am exhausted after just observing the event as a “detached” outsider. I can only imagine how tired the parents and child must be feeling.

We walk the family back to the atrium of the hospital. While they drive away in a grey sedan, their collected blood remains behind. For the family, the ordeal is over for now. They go home to recuperate. Their work is done. For the little tubes of blood, the journey is just beginning. At this point, the tubes with different coloured caps go their separate ways. Some of the tubes go to the clinical lab at hospital where information is collected pertaining

to iron or thyroids but unrelated to the genetics investigation. Another set of tubes that was collected will go to the Laboratory X for biobanking. Here an “immortalized” cell line is established and refrigerated indefinitely, a back-up source of DNA. Still a third set of tubes will first move through the DNA extraction lab before making their way into Laboratory X for genetic testing. It is this third set of tubes that I followed.

5.3. From Blood to DNA

The DNA extraction lab is located in the hospital in the Department of Paediatric Lab Medicine. DNA extraction for the autism genetics project is performed by a robot, an automated machine called Autopure, made and distributed by Ciagen (formerly Gentra). The Autopure is the size of a large laboratory refrigerator, perhaps five feet tall and four feet wide. One of the laboratory technicians explained the extraction process from her perspective: you just “pour your blood into barcoded tubes, scan them, load them and then when it comes off in about an hour and a half, it’s DNA!” When pressed to describe what she and the robot do with the blood in more detail the story unfolded in this way:

First, the DNA extraction lab receives one eight millilitre tube containing the blood from an individual with autism. If the blood is fresh and “uncompromised”, they log it into their database and assign it a DNA number. They check the identifiers on the tube to make sure they match with what is written on the requisition form. For clinical bloods they require two identifiers. For research, however, they allow just one identifier, a study number, to accommodate the concerns over confidentiality enforced by the ethics review board. The Autopure extracts DNA in batches of sixteen. At the front of the machine there is a rack of sixteen large 50 ml red-capped tubes, two rows of eight, each with a small barcode on the top. The technician scans the barcode and matches each one with the DNA sample number. The blood is poured into the barcoded tubes, the lids are closed. Next, an uncapper comes

down, a vacuum manifold, and lifts up the red tube caps. It holds onto them in rows of eight at a time. The tubes are lifted up on a rack and slid over under a pumping dispenser. The pumping dispenser has tubes that run back to large four to ten litre jugs of reagents. An appropriate volume of reagent is pumped into the tubes and then they are re-capped, transferred to the back of the robot and locked into a rotator where they are inverted. The machine can gently rock the tubes or vigorously vortex them. This is what I can see with my eyes. What is not visible is what is happening to the blood at the cellular level. The Autopure isolates the white cells because there are no nuclei, no DNA, in red blood cells. The nuclei of the white blood cells are ruptured and the DNA is released. The proteins are separated away from the DNA and then several washes in ethanol rid the DNA of any contamination. At this point, when the machine is doing the washes, the DNA in the tubes looks a little like cotton baton, white and fluffy. The DNA is “pelletted down” and put into a blue-capped tube, inverted so the ethanol evaporates off. The DNA has now been extracted but it still needs to be put in a hydration solution and rotated over night. The solution contains a buffer to protect the DNA from degradation. The samples are then stored at four degrees and every two weeks the lab technicians generate a “send out”. A technician pulls all the samples and checks that the DNA number, aliquot volume and concentrations match. The technician signs off on this and then puts the samples in a basket. At this point, Lisa from Laboratory X walks over and picks up the extracted DNA tubes.

Since the blood was taken from the child’s arm it has been given a patient number, a DNA number and a barcode number. Poured from one tube into another, white blood cells have been isolated from red, nuclei shattered, proteins separated from DNA. It has been washed in ethanol, dried and alluted into a buffer solution and stored in a refrigerator at four degrees. The blue-capped tube containing extracted DNA now sits in a basket, waiting to be

picked up and walked over to the Laboratory X.

5.3a Into Laboratory X

Lisa is a project coordinator in her mid-forties. She has a Bachelor's degree in microbiology and has been working at Laboratory X for fifteen years. She works four days a week here and one day a week at the autism clinic. When Lisa walks over to the DNA extraction lab to receive the tubes of blood they usually already have a unique identifier tag or label on them. Back at her own desk, she inputs these data into a database, which generates a spreadsheet. She double checks to make sure that all the data are correct (e.g., date of birth). The tube of extracted DNA is kept in storage until the coordinator of the academic section is ready to run experiments on it.

There are three main types of genetic experiments that occur in this lab, each associated with a different scale or resolution of detection. At one end of the spectrum there is cytogenetics, which focuses on microscopically visible cells. Karyotyping or FISH are examples of cytogenetic experiments. For autism cases, these experiments associated with cytogenetics are primarily reserved for validation of other findings. At the other end of the spectrum is Next Generation Sequencing (NGS). This technology is used to find single nucleotide polymorphism or SNPs (pronounced *snips*). NGS is able to detect a change in a single base (e.g., a T that is now a C). In between cytogenetics and NGS is a technology called microarrays. Microarrays, frequently referred to as arrays, are able to detect deletions or duplications in stretches of DNA. These deletions or duplications are called copy number variations or CNVs.

After arriving in Laboratory X, an autism DNA sample flows through these various experiments and technologies. The first line of investigation is a microarray followed by its associated cytogenetic validation experiments. Based on certain criteria, the sample might

then move through an NGS experiment. If an interesting mutation is found along the way, the case might be discussed at one of the laboratory meetings before being written up in a report to be given back to the clinician. What arrives in the laboratory in a little glass tube will leave the laboratory as words on a research report. Below, I will try to describe all the work, the activities, the ways of seeing, probing, investigating, the various and multiple conversions and representations that occur within the laboratory. I have pieced together a story that follows what happens to the DNA in a little glass tube: from microarray to NGS to computational analysis, until eventually it exits the laboratory as words on a research report.

5.4. The Microarray Process: From DNA to CNVs

Much of what I learned about the details of the microarray process came from a 5th-year PhD student named Ankit working under the supervision of Dr Lorenz, the director of Laboratory X. I interviewed him several times and interviews would often last for two to three hours. We also had lunch together on several occasions when I would learn about the more informal, behind-the-scenes operating of Laboratory X. During his undergraduate and Master's training in microbiology Ankit used to spend a lot of time in the laboratory but now his time is almost exclusively devoted to analysis and interpretation of results.

Consequently, he was able to talk me through the entire process. I was also able to interview the manager of the microarray facility and to observe the two technicians who run the Illumina array platform on several occasions. The entire experiment can take several days to complete with different activities occurring on different days of the week. Through these various observations and interviews I have pieced together below the microarray process.

5.4a Clinical vs. Research Microarrays

Before describing the microarray process, a distinction must be made between clinical

and research microarrays. The microarrays run at Laboratory X are research microarrays. They are high-resolution, meaning that they interrogate the human DNA strand at many points allowing for a more detailed view in more locations along the genome. In comparison, the clinical microarray probes the genome in only a few places. It targets only those areas in which genetic variation is already known to be associated with pathogenic outcomes. The linkage between the clinical array lab at the hospital and the research arrays at Laboratory X is a strong one. I frequently saw members of the clinical array laboratory at the Monday morning meetings at Laboratory X. Many of the cases that were discussed at these meetings were originally from the clinical lab. If the clinical lab is unable to find any CNVs on their clinical array platform but they still suspect a CNV to be involved, they will send the sample on to Laboratory X so it can be run on a higher resolution research array.

Significantly, just prior to the beginning of my field work, effective March 1st, 2011, the Ontario Ministry of Health and Long-Term Care began funding post-natal clinical microarrays for children with intellectual delays. The cost of the clinical array is now covered by OHIP, the Ontario Health Insurance Plan. Now, if a family doctor or paediatrician wants to refer a patient to a clinical geneticist because the individual has a developmental delay or autism, a clinical microarray must first be ordered before the referral can be made. There are two things that are important about this change. First, since March 2011, any physician can order a microarray (a family physician or paediatrician, for example) and not just a clinical geneticist. This also means that the results of the array are being sent back to and interpreted by the family physician or paediatrician. This is important for a discussion on knowledge translation as, according to the participants in this project, there is much concern over whether or not the referring physician will be able to interpret the results of a microarray. In particular, arrays with results of “unknown clinical significance” can be

confusing and tricky to interpret for even the savviest of clinical geneticists. Secondly, important for theoretical consideration, the clinical microarray has now been made a mandatory step in the referral process. The micro array is one of the criteria that must be fulfilled prior to being seen by a clinical geneticist. In the language of actor-network theory, the array has become a significant actor, an “obligatory passage point”.

5.4b Running a Research Microarray

We are at the far end of the laboratory. When you first take in the scene it is overwhelming, visually exhausting. There are so many things to take in at once; my eyes don't know where to land. There are bottles, boxes and machines crowding the rows of black benches. Every inch of space seems to be packed with labelled jugs of solutions with names that are unfamiliar, glass beakers, boxes of tubes, fridges, and many different machines. Two long, scratched up canisters stand at the end of the bench, for oxygen or some other gas I guess. They seem to me like they might be relics unearthed from a long ago submerged submarine, faintly reminiscent of a sepia-toned wartime photograph I might have seen. I have no reference for many of the items around me. For someone who has never stepped foot in a laboratory before, it feels as though I've stepped into another world. I recognize almost nothing. The only thing that looks familiar is a white fridge that appears very similar to the one that stands in my kitchen at home. The similarity stops there as the contents inside are alarmingly different. No milk jug or yogourt in here; instead, there are stacked up plates with rows and rows of tiny labelled tubes containing DNA extracted from hundreds of individuals. The air in the laboratory is warm from all of the heat given off by the machines. A constant, loud humming sound drones on in the background.

Today I am watched two different technicians, Mitsie and Chang. Mitsie tells me to set my backpack and coat on one of the chairs against the wall. She wears a long white lab

coat, her jeans and running shoes poking out the bottom. Light green plastic gloves are stretched over her hands. Her black shoulder-length hair hangs loosely around her neck. The aisle where she is working today is about three feet wide. On one side is an Illumina microarray machine. It is about three feet by three feet and two feet deep, essentially a big box sitting on the top of the black bench. It has a dark grey, opaque, plastic shell. There is a monitor attached at eye level and a keyboard sits in front. A large metallic arm is located to the side of the machine, the auto-loader which moves the plates carrying the prepared microarray chips inside the machine. Across the aisle sits another computer. Beside this is a large robot, about four feet long and three feet high and three feet deep. It too sits atop the bench. It has a glass front which can be raised up or down and a slit cut out along the bottom where the technician can reach her hands into the machine. There are other machines near by as well, a centrifuge for spinning samples, a hybridization oven, and more computers. There are a few spaces between machines and equipment so that I catch glimpses of the man working on the other side of the bench, bent over a computer. I see him glance at me quizzically a few times. Strangers are an anomaly in the laboratory where an intimacy develops amongst technicians over years of working side by side with each other. Hands and bodies seem to effortlessly slide into well-choreographed, predictable movements. Although I try to stand out of the way, try to be aware of the movements of the other scientists in the aisle, as I concentrate on capturing the details of the practices surrounding the microarray I am often encumbering somebody's pathway.

Before the array can be run, the lab technicians have to wait until there are enough samples collected because arrays are run in batches. Typically there are ninety-six samples on one plate. The tubes that Lisa picked up from the DNA extraction lab are sitting in the fridge. Mitsie takes them out and lets them sit so that they will be brought up to room

temperature before being loaded onto the microarray chip. There are several different machines and robots involved in the whole process of a microarray experiment. The first step is to scan the barcode numbers on each of the Illumina chips. The chips come in an orange box. Inside the box are maybe ten chips, each individually wrapped in a metallic package. On the front of each is a label with a barcode. Illumina makes each of its chips slightly different so that the probes on one chip are not identical to the probes on another. The barcode tells the robot where to look for the position of the probes along the genome. She scans each package into the computer using a little hand-held scanner. It reminds me of a price scanner at a department store. On the computer screen in front of Mitsie, there is an Excel spreadsheet open and every time a package is scanned a number appears in one of the boxes on the screen. She is meticulous about checking the order of the packages. The order she scans them in is telling the computer the order they will appear on the plate. There are specific loading patterns and each chip needs to be positioned in a specific place on the plate. Before scanning them she numbers the outside of the foil package. When I first observed I was not sure what she was doing and asked her a question. She ignored me for several minutes and answered later; I quickly learned that this was not the time to be asking questions. She joked that if she makes a mistake in the ordering of scans, a sample that is from a female may be switched with another and could come out as a male. "Then you know you've screwed up!" Each of these chips cost three thousand dollars. Today they are preparing twenty four chips. It takes her about twenty minutes to scan all of the chips. Inside each foil package is a small chip. It is about the size of my second ("peter pointer") finger. The barcode that was on the outside of the package is also on the bottom of the chip. As Mitsie explained, "every chip has a map of where the probes are". On this particular chip there are two and a half million probes. The chip she is using has eight different bands across it and each band will hold a different

sample. She calls these different bands “grids”. At this point, each chip only holds the probes, beads that were loaded on by the Illumina company. The patient sample has not been added yet, that comes next in the hybridization stage of the experiment.

Before the patient samples can be added to the chip, the samples first go through a stage called “amplification and digestion”. At this point, there is a clear plastic 6” square plate with 96 little wells in it, arranged in a grid. Each of the little wells holds a small amount of DNA, each a different sample from a different individual. Various reagents are added to each well and left for a twenty hour incubation. Then it is pelleted down during a purification step, leaving only the material that they want. The pellets are then dissolved into a solution again. Enzymes are added to the DNA to “de-nature” them. This was explained to me in the following way:

PhD Student: So what you do is they first chop up the patient’s DNA so it’s not 3.1 billion base pairs together. It’s sort of fragmented into different...I don’t know if you know about restriction enzymes?

Julia: No.

PhD Student: It’s not very important. Restriction enzymes, it’s a reaction mix that helps you slice up DNA.

Julia: It kind of loosens them up or something?

PhD Student: So it actually *slices* them. Slices a large chromosome into smaller fragments. So it slices it up into small pieces.

After the samples are “de-natured” (sliced up), they are hybridized. During hybridization, the probes on the Illumina chip are attached to the DNA sample from the patient. In the entire human genome there are approximately 3.1 billion base pairs. The array company designs chips so that they target specific areas of the genome. Each probe is twenty-five base pairs long. On the particular chip they are using today, the company has built two and a half

million probes. The more probes, the greater the resolution and the greater the ability to detect smaller deletions or duplications. If ten thousand probes are stretched across the human genome the variation has to be much larger in order to be detected. If 2.5 million probes are stretched across the genome the array has a greater ability to detect smaller CNVs.

For hybridization to occur, the sample of patient DNA has to be physically added to the chip. I observed as Mitsie did this for 192 samples one day. The technicians have to be extremely organized, knowing where each sample is being loaded. It takes two technicians working in tandem along with the hybridization robot to load the samples on the chips. First, Mitsie opened up the glass front door on the machine and fit in the first of two 96-well plastic plates containing the 96 DNA samples in eight rows of twelve. This plate was fit snugly in on the left of the machine. On the right side of the machine Mitsie places nine black containers, each holding a glass chip (each chip will hold eight samples). Dangling from the machine there is a little arm which holds eight thin needle-like prongs (called pipettes) pointing downward in a row. These pipettes are spaced apart so that they fit exactly into the wells of the sample plate. The arm moves back and forth a few times to orient itself and then lowers into the sample plate, dipping into the first eight wells and sucking up the DNA. (I looked in the plate later and saw that a small amount of DNA is left behind in each well as a back up in case there is a mistake and the hybridization needs to be repeated.) After the DNA is sucked up, the arm then moves up and over to the right so that it hovers above the top of the first chip. Two of the eight pipettes lower down and touch the chip at exactly the spot where two of the bands run across. Mitsie has reached her hand in through the slit in the glass front of the machine to help guide the pipettes, making sure that they drop the DNA sample at exactly the right place. The needles move up and the next two needles move down hitting the next two bands on the chip. Again, Mitsie guides the robot so that the DNA enters the band on the

chip at exactly the right place. This is repeated until the chip is filled. The robot arm then moves back to the left of the machine and dips the eight pipettes into an ethanol solution, cleaning them so that they can then be dipped into the next eight wells of DNA and the process can be repeated on the next chip.

While the robot cleans itself, Mitsie takes the black cartridge out of the machine and passes it to Chang. She takes the slide out of the black cartridge and places it in another black cartridge. Using a pipette, she adds a small bead of water to each band on the chip. This is to make sure that the DNA does not dry. If it dries, the DNA from the patient sample will not bind to the Illumina probes. I can see that the little bands have changed colour slightly now that they have DNA in them. At one point Chang told Mitsie they need to do one of the bands again; not enough DNA sample was added and it hasn't gone all the way across the band. They will manually add more of that particular sample at the end. A top cover is secured over the chip and from here it will be placed in the hybridization oven at 44 degrees Celsius for eighteen to twenty hours. While the chip sits in the oven over night, the Illumina probes align and bind to specific regions of the DNA sample.

I imagine the hybridization process is a bit like a grade six school dance. The oven doors are closed on the microarray chips. I imagine that Queen starts playing or perhaps in today's ovens it would be some sort of techno music with a booming bass. At first all of the rna probes are lined up against one wall while the sliced up fragments of patient DNA self-consciously chit-chat across the chip. With the heat of the oven, like the music in the gym, rna probes and DNA fragments begin to mix. Eventually, couples pair off and begin to dance. A frantic flurry of activity begins as DNA fragments try to bind with an rna probe. There are far more DNA fragments than rna probes. Anxiety sets in as more probes and fragments bind off together. Everyone is jostling and bumping around on the dance floor. A shorter fragment

is dwarfed by some of the other larger fragments. Suddenly, the shorter fragment bumps into a probe. They circle around one another first, checking each other out. They realize they fit together. They align! Their hydrogen molecules begin to bond. Eventually, all of the rna probes are aligned to the corresponding DNA fragments. The remaining DNA fragments bump around for a while, relentless in their search for a probe with whom they might bind. Eventually these remaining fragments settle down and enjoy the warm heat of the oven, perhaps chatting together in small groups and comparing stories about the previous ordeal of being extracted from their intra-cellular friends a few days or weeks earlier.

I came back to the laboratory the following day and watched as the chips were removed from the oven. At this point the chips need to be washed. The washing will get rid of all the bits of patient DNA that did not bind to a probe. The only thing that is left on the chip after washing is the segments of DNA that have bound to a probe. Below, are my notes describing the washing process:

Chang tells me to come closer and stand by her. She has placed several chips, horizontally, lying on their side, into a little wire basket and she is vigorously dipping it in and out of a clear buffer solution. She does this for a few minutes. Bubbles are forming at the top. At times one of the chips will become dislodged from the basket with the force of her moving the basket up and down. She stops and carefully puts it back into the basket and continues dunking it. The buffer is washing away all the non-binding DNA.

While Chang is doing this, Mitsie dumps the buffer out of a black container sitting on top of the bench in front of her where the four chips were resting that she has now moved aside. Chang pulls out the chips she has just been dunking and puts them into little black cartridges. Mitsie puts on a rubber strip around the perimeter of the chip. Chang pours in more buffer and Mitsie then puts on a glass slide. While Chang is dunking the next batch of

chips, Mitsie is taking scissors and trimming away the excess plastic strips that hang over the edge of the black metal cartridge. I can still see the little bar code on a white sticker sticking out from the bottom of the black cartridge. Once these are trimmed they are put into a container that holds four chips.

Chang and Mitsie are working silently, passing things back and forth without asking or signalling to one another. It is obvious that they have done this many, many times together and they have a carefully planned out rhythm and detailed choreography of their movements. While their legs are standing still, if you were to watch just their arms and hands it does almost seem like a duet or a dance of some sort that is being performed together.

At one point, when Chang is washing the next batch of chips, Mitsie walks over to the next aisle. I follow her. She is loading all the black cartridges into the glass-fronted “Freedom Evo” machine, the same machine that added the patient sample to the chips yesterday. This time, the chips are placed vertically in a large black metal box. This is the space in the machine to the right of the area where the hybridization took place yesterday. So the same robot is capable of doing different tasks in the different spaces within the machine. She closes the glass front. She walks over to the computer beside the machine and clicks the mouse on a window that has popped open on the screen. A green light turns on at the top of the machine. And immediately the little row of 8 needles/ pipettes goes down at the left and submerges in a clear solution. There are a few different plastic wells along the back. One of the wells is labelled RA1. The needles suck up some of the solution and then move up and over to the right of the machine above the vertically placed chips. At this point Mitsie shows me how each of the glass slides, which she had clipped on over the chips, has a little slant descending toward the chip. The pipettes drop the solution into this little divot and it slowly sinks down across the chip, moving across all 8 samples on the chip. Mitsie says she does not

have to use her hand to guide the robot pipettes for this washing stage as she did for the hybridization. This is because the divot in the slide is the entire width of the chip and as long as the pipette hits it somewhere in that little well it will be fine. She just has to be sure she has put the slides in the right way or the solution will just run over the top and not have a little well to sink into. The pipettes go back to the left of the machine and dip themselves into another solution. She shows me the different buffers it goes through and then says that the last two, on the right, are the stains. These stains are dropped into the chips in the same way as the buffers. The stains are what allow the DNA to become florescent when they are imaged in the microarray machine. After that, all the slides and clips are removed from the chips and they are washed once more and then a coating is put over top of the chip. They are dried and then they are ready for the array machine.

From here, the chips are loaded into the microarray machine. It takes about an hour and a half for each chip to run through the machine. Because there is an opaque plastic cover on the microarray machine, I can't actually see what is happening inside. To the side of the machine several chips are stacked up waiting to be put through the array. There is a coat on the top of them that Mitsie says she would not want to touch. She always wears gloves at this point. She says I should ask Chang to show me the image on the computer monitor. Chang is just putting out the garbage, a clear plastic bag filled with various empty bottles that they were using this morning for washing. She places the garbage just outside the door of the lab and comes back in. She nudges the mouse and the microarray screen lights up. The upper half of the screen is full of green and black dots. The lower half of the screen is full of red and black dots. Chang tells me that if a location is green and red it is heterozygous. If a position on the chip appears as only green or only red, then it is a homozygous call. A runner along the left edge of the screen displays a rectangle for each of the 8 samples that are

currently passing through the machine on one chip. A blue box sits on top of the sample that is currently being scanned. It is on the 4th sample right now. As the machine finishes a chip the rectangle on the left side of the screen becomes coloured. The top sample, that has already been scanned looks different from the others that have already been scanned. The others are all green. Each square, representing a sample, is divided into four horizontal bands. On the top sample rectangle, there are alternating red and green bands. Two of the bands that should be green are red. This means that something has gone wrong. Chang tells me that it could be the decode data that was downloaded. Sometimes they have to download the decode data again and it will be fine. Alternatively, it could be the sample. I talk with Mitsie about it later and she thinks it's not the decode data; it's the sample because all of the other sample rectangles seem to be coming up fine. Sometimes the sender gives them enough DNA to do a re-run, but sometimes they don't and they have to go back to the sender and ask them for more sample to trouble shoot.

Although I cannot see what is happening inside the microarray machine, the process was explained to me in this way:

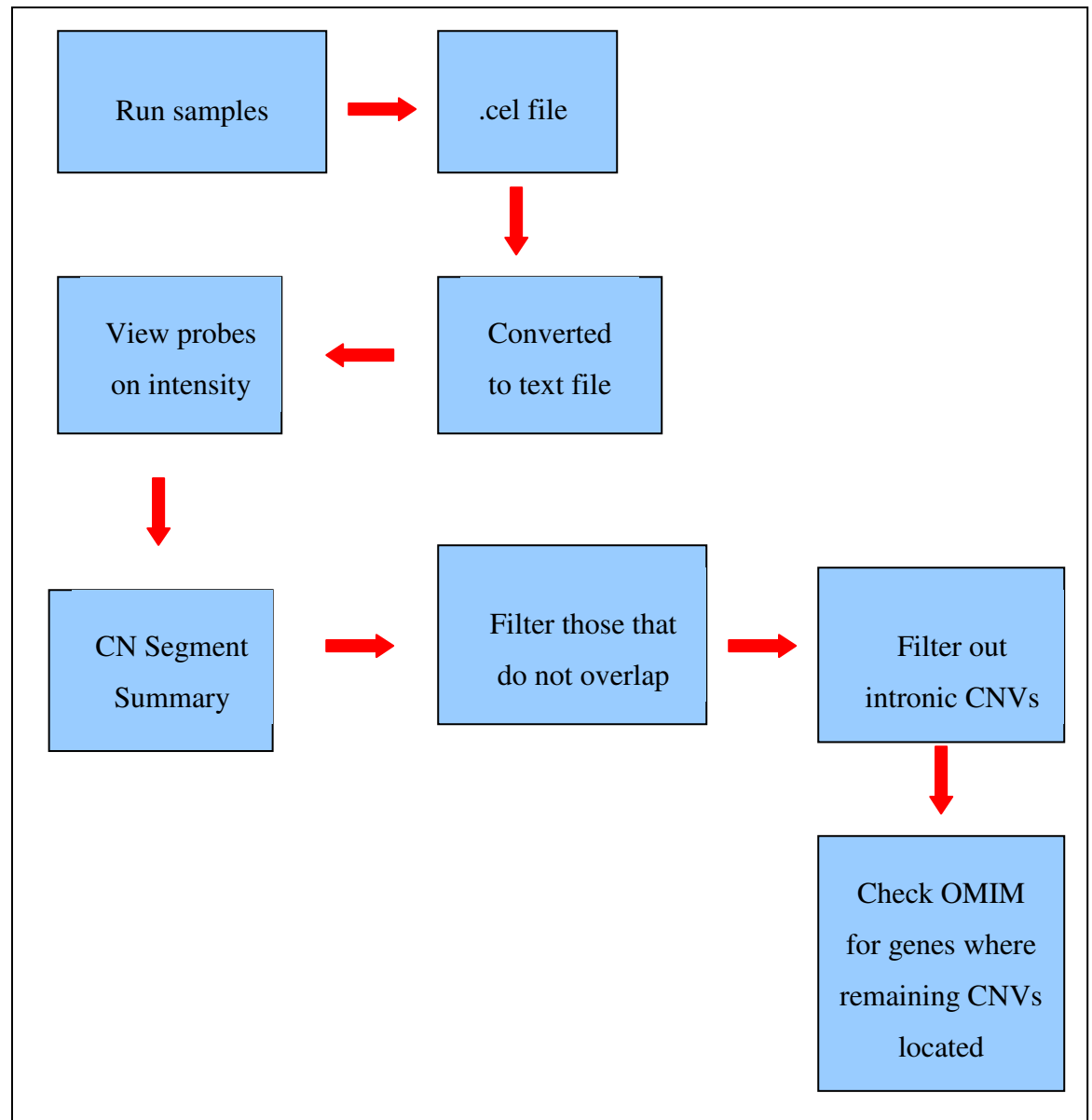
PhD Student: These probes are sort of fluorescent and when they bind to something they light up. So every probe that's bound to something, it lights up with a certain intensity. You take a picture through a fluorescent scanner and you get an idea of the intensity of each probe. So each probe will be a dot in this picture. The chip itself is very small but it has 1.8 million probes on it and you have data from 1.8 million points in this picture.

At this point the DNA has been converted to little green and red dots on an image. The computer file is then sent out of the lab to one of the post-docs or graduate students in the academic office. This is another significant conversion. The material being worked with from here on is no longer the physical substance of the human body. It is computer generated graphs and numbers that make their way out of the wet laboratory and into the research

office. Of course, these computer files are carefully linked to the DNA through patient identification numbers.

Although, for simplicity, I often describe this research as following DNA as it is translated between three locations (clinic, lab, home), each one of these locations is actually a complex arrangement of spaces and networks. What I call “the lab” could also be described as several distinct locations, spaces within spaces. For example, there is the “wet lab” where patient materials – DNA – is sliced, buffered, hybridized, warmed in an oven, washed, dried, and photographed. Gloves, goggles, lab coats, bottles, pipettes, tubes, and a lot of different chemicals are all integral to the network of this space. The academic office, or “dry lab”, however, contains none of these artefacts. Computer files, spreadsheets, mathematical algorithms, journal articles are the property of this space. There is movement between these spaces and their close proximity is important. People from the dry lab might periodically move into the wet lab, checking on a procedure if a result does not seem quite right. For the most part, technicians from the wet lab do not, however, move into the dry lab. In the wet lab patient materials are translated into computer files. In the dry lab, the computer files are interpreted, graphed, written up into reports. So while “the laboratory” may be described as a unified whole, a single place when it is discussed by clinicians, it is also a complex arrangement of distinct, highly differentiated but related spaces for those who work inside it.

Figure 5.2: Flow Chart Depicting CNV Interpretation Process



Once the microarray data is moved from the array machine in the laboratory to the computer of one of the academics, it is actually a binary code to a text file called a .cel file. This file contains the probe intensity information. The scientists take this binary information and load it into the company software, which then converts the information to text. There are different microarray companies (Illumina, Affymetrix, and CGH), and each company produces its own proprietary computational software. However, academic lab groups also develop their own open-source software for analyzing microarray data. The scientists I talked

to explained that they used multiple tools (software) in interpreting microarray data, combining the results to increase specificity. A PhD student explained:

If you used just one tool to identify CNVs on your microarray, you'll find that there's a false-positive rate, which can be as high as thirty or forty percent. So, for example, if you get an array from a lab for a patient and use a single tool, it tells you there are like a hundred CNVs. But if you actually went to the lab and tried validating them by quantitative PCR you would find that only 60 of them would be real and forty of them would be false. This would be a case for any tool. So if you take three different tools and you take only the CNVs that were detected by at least two of the three, those tend to be real. So the validation rate for those is like ninety percent. This is actually a big deal because we have too many patient samples to go and validate all of them together. So we just stick to the stuff that is more likely to be real.

There is another reason why combining results and increasing “true-positives” are important. It not only saves time by allowing lab techs to run validation experiments on fewer samples; it also is important because CNVs have to be reported back to the clinic. Ankit explained in an interview, “It reduces the chance of them being false, which is a big deal when you're reporting results to a patient. So, you need to make sure it's *true* before they make any clinical decisions or something based on that.”

The software provides a visually friendly format from which to analyze the data. The microarray information can be plotted on an intensity graph. The intensity of a probe is directly related to the amount of DNA that has bound to it. If more DNA binds to a probe, it lights up more. If no DNA binds to a probe it won't light up at all. If there is no light signal from it then it will show up black. This can all be captured on an intensity graph, which has an X-axis as the central line. Most probes cluster at this central line. This line corresponds to a copy number of two. Usually a person has two copies of every base, one inherited from the father and one from the mother. When the probes on this graph dip below the central line it means there is less genetic material binding to this probe and only a copy number of one. This means that there has been a deletion of genetic information. The microarray has “called”

a deletion.

Ankit clicked on the program and was able to zoom in and out on the chromosome, quickly changing scale and allowing him to analyze the data in different ways. With another click, the program showed him the “break points” for the deletion which told him the exact position of the deletion. It also showed him which genes were located there. This is the first indication that there might be a deletion in this region. However, the person interpreting the graph is not certain. The intensity graph cannot be trusted on its own. This is because sometimes probes fail because of technical problems. If a probe fails, it would look like a deletion on the graph, but it's *not real*. A PhD student explained:

PhD Student: So this is why you have to validate everything the array calls with something else before you report to patients or to clinicians. You've got to show that it exists. So this is why we use either FISH which I showed you before or we use something called quantitative PCR, qPCR, which is sort of the same thing. It's an independent experiment with confirmation of a deletion or a duplication.

Once the CNV has been validated with qPCR, the next step is to identify whether this deletion or duplication is in a region (usually a gene) that is already known to be associated with autism.

In addition to the graphical view of intensity information, the microarray software program produces something called a CN segment summary. This provides a list of all the CNVs that the software found for each sample run in a batch on a microarray. The segment summary shows several columns including: sample name, copy number state (whether it's a loss or a gain), chromosome number and coordinates within the genome. For each sample there will usually be about forty or fifty CNVs found. However, most of these are found in the general population. The scientists need to distinguish between those CNVs that are rare (and most likely contributing to the phenotype) and those that are common in the general

population. In order to do this, there is a comparison between patients (called cases) and controls.

When talking with me about the analysis process, Ankit switched on his laptop and brought up something called the DGV, the Database of Genomic Variants. It's a free on-line database, which I later looked at more closely at home. Throughout my fieldwork, this tool was repeatedly used in meetings to discuss variants. The DGV allows you to zoom in on any region of the human genome. There are various tracks that can be turned on or off. It distinguishes between exons and introns. An exon is the part of the genome that codes. It is made up of genes. An intron is a region of DNA that does not contain any genes, but sometimes it is important for regulating genes. It used to be called junk-DNA but scientists are realizing that it might actually have important epigenetic functions. On the DGV, the exons are represented as vertical bars and the introns are horizontal bars. So, for example, you could look at the NRXN gene on chromosome 2. The DGV will tell you that you are on Chromosome 2 and give you the coordinates. Chromosome 2 is approximately one hundred fifty megabases long. The position on the DGV might zoom in to display between fifty and fifty one. It will also show you the probe distribution in this region. The green bars show you that there are plenty of probes in this location. So if there is a CNV, it should be picked up. The DGV is also an amazing resource for interpreting CNVs. This is because the DGV also compiles all the information published in academic papers that report CNVs. For example, according to Ankit, in the last seven years there have been about one hundred studies of CNVs in the general population. One study might look at CNVs in a thousand Europeans and another might look at CNVs in a thousand Africans. The DGV builds up all this information. This is important because all people have CNVs and so the people looking at patient samples have to interpret whether or not these are rare in the general population, if they are primarily

seen in cases and not in controls. For every gene, the DGV tells you what deletions or duplications have been commonly found in the general population. A blue line would show you a duplication and a red line a deletion (the colours sometimes change). So if a deletion has been validated using qPCR the PhD student will then go to that exact region in the DGV to see if that same deletion is frequent in the general population. If there are very few deletions or duplications in that region amongst controls that information also supports the significance of that genetic variation as potentially related to the variation in phenotype.

Another way to determine if a particular CNV is found in the general population is to look at the CN segment summary. Here, there is a column titled “percentage overlap”. This column indicated how much of the sample CNV overlaps with CNVs already found in the DGV, which are found in the general population. Most CNVs that are called overlap 100% with the DGV, meaning they are common in the general population. So, you only investigate further the ones that say zero percent. These are the CNVs that are not found in the DGV and are therefore not found in the general population. This means that they are rare deletions or duplications. Roughly one CNV from each sample will not overlap with the DGV. At this point you can further filter out the CNVs that do not touch on genes; these ones are intronic and are less likely to be significant.

Ankit opens up PubMed and types in the name GPHN, the gene symbol for Gephyrin. Immediately, fifteen papers appear in which this gene has been described. Some of the papers describe a particular disorder in which GPHN is involved and other papers describe functional information, telling the reader what the particular protein does. This is useful for new genes. However, when a gene has been well described over time Ankit uses the OMIM database. OMIM stands for On-line Mendelian Inheritance in Man. He stated:

So, there are twenty thousand genes in the human genome, give or take a few thousand. A certain fraction of those have been reported in disease before. If you run a genetic test on somebody and certain genes come up you want to know if the genes that you found have been reported with a particular phenotype before. So, essentially they compile papers together and they come up with lists of genes that have been reported as mutated in specific disorders.

Thus far in the process of detecting CNVs, a microarray was run and a deletion was found by looking at an intensity graph. Then this was validated using qPCR. Following this, the region was compared to the DGV and found to have no similar mutations in this region in controls. At this point, the PhD student needs to learn more about this CNV. Was it inherited or *de novo*? *De novo* CNVs are deletions or duplications that are not inherited. They arise spontaneously in individuals and often seem to be more likely to be associated with phenotypic variations indicative of autism. If the laboratory already has DNA collected from the mother and father of the case (called the proband) then a micro array can be run on them separately. The PhD student told me that autism was particularly successful at getting trios (mother, father and child DNA) because diagnosis tends to happen early on and the child is accompanied by his or her parents at clinic visits. (In comparison, in schizophrenia it is much more difficult to acquire complete trios because patients are often in their thirties or forties and sometimes their parents are no longer alive.) Once you have all three samples plotted on an intensity graph you can easily see if the mutation is *de novo*. If the probes on the mother and father's graphs are all clustered along the central axis, then they both have a copy number of 2. The dip in probes below the axis on the proband's graph is not inherited from either mother or father.

There are other ways that CNV data are interpreted and analyzed. The PhD student explained:

PhD Student: So they run the microarrays and they give us the data, like, the fluorescence data. So obviously the CNV data is computational because you can't go through probes individually. So the array that they are currently running is from this company called Illumina. So they give us this software called Genome Studio. So it sort of streamlines the whole analysis procedure. So the arrays are fed into this software, like the information on the arrays, like the intensity information.

He showed me how Genome Studio worked. He was able to change chromosomes in the

browser and to zoom in and out. Here is another excerpt from one of our conversations:

PhD Student: So that's SNP data. This is intensity data. Now how does this CNV look? A NRXN1. So this is zoomed in [moving the mouse around], Chromosome two, zoomed in. [Clicking with the mouse] So if you want to see the [clicking] so this is the whole of chromosome two. Like it's generally along this baseline. But you'll see at some of the positions, some of the probes are lower. These could be deletions. In fact, the NRXN1 is here. So if you zoom into this position, it looks like this. So this is just the NRXN1 locus, it shows you where the gene is. And here is your baseline which corresponds to copy number 2. So you see that they always cluster around the baseline. So most of the regions of chromosome two, the person has two copies. This is what you'd expect. Except here you suddenly see these probes fall off a cliff.

Julia: Right.

PhD Student: So that is where your deletion is expected to be. And the interesting thing, you can sort of see a pattern in the genotypes as well. So if two copies are present, of DNA, you'd expect there to be three combinations, right. Homozygous for one base, homozygous for the other base or heterozygous. So you can see that the heterozygous was present when there was two. It can be homozygous, heterozygous or homozygous. But in the deletion region there's no heterozygosity possible. So it calls it homozygous so this sort of supports the intensity information.

At this point, after examining the CNV through the DGV and the Genome Studio software, the case might be discussed at an upcoming Monday morning meeting as an interesting finding.

5.5. Validation – From CNVs to *Real* CNVs

Several times in my field work I heard people talking about FISH or qPCR. These are

techniques that are used to validate microarray results. fISH stands for fluorescent *in situ* hybridization. When a technician finds an unbalanced rearrangement of genetic material (a deletion or duplication) they cannot be sure that it is real. Microarray results can be “a bit noisy”. Investigators need to add another layer of evidence, another independent test to confirm the variation. Ankit explained it this way:

You’ve got to show that it exists. So this is why we use either FISH which I showed you before or we use something called quantitative PCR. qPCR. Which is sort of the same thing. It’s an independent experiment with confirmation of a deletion or a duplication.

With an array, you put the DNA on a slide and see right across the human genome. With fISH or qPCR, you have to know the specific region you’re testing. For example, an array showed that there was a segment on Chromosome 16 that was duplicated in an individual diagnosed with autism and Ankit needed to have that verified.

5.5a fISH

fISH is within the purview of cytogenetics. The cytogenetics office sits off to the side from the main lab, a small room, perhaps ten feet square in area. The walls are circumscribed by lab benches with a few work stations (designated by stools or chairs) in various places. There are two microscopes in the room. One day, when I was interviewing the manager of the cytogenetics lab she showed me around. A more junior cytogeneticist sat perched on a stool, clad in a white lab coat, bent over a microscope. Around the perimeter of the room, are a series of “chromosome paints” in bright colours. They’re quite beautiful actually, like modern abstract art. The manager of the cytogenetics lab explained to me that the work carried out in her lab is considered quite obsolete compared to most of the newer technologies. The objects that are worked on in this lab, chromosomes, are microscopically visible. The scientists who work in this lab are tuned to or oriented toward an entirely different object.

The landscape of the cell, interrogated through a microscope, is comprised of completely different components than the landscape of extracted DNA which is probed through microarrays or sequencing. There is very different work going on here in this small laboratory by these few scientists, sequestered off from the large main laboratory room.

FISH was first developed in the 1990's as a technique in which fluorescently labelled probes are hybridized to a patient's chromosomes (George et al., 2011). If a fluorescent signal is detected, it indicates the presence and copy number of that region in the patient's genome. To conduct a FISH experiment, the scientist needs to have live, growing cells. They cannot be frozen or prefixed. Depending on where they stop the cell growth, cytogeneticists can do different things. At interphase the chromosome fibres are more loosely packed than at metaphase. If there is a segment of DNA that is duplicated close by to the original segment you can see it better in interphase than in metaphase. The resolution is higher. If you want chromosomal positional information, however, cytogeneticists arrest the cell growth in metaphase. When checking for a duplication, the cytogeneticist will use interphase nuclei but will also use metaphase nuclei to check that the probe was in the correct position. The manager of the cytogenetics facility, a clinical cytogeneticist whom I will call Gloria, explained the FISH process as follows:

So you have your slide with your chromosomes on it and then you denature your chromosomes so that the DNA goes apart, like, separates. And then you have your probe which is your sequence of DNA with your little fluorescent tag. You denature that and then you put it onto the slide. So both of them are denatured and you leave them to renature and it will go to the targeted region, yeah.

Once the probe has hybridized to the patient DNA the cytogeneticists can arrest cell growth in various stages of development and count the copy numbers of the fluorescent probe. Gloria showed me an example of a 22p11.2 deletion in an autism case. She opened up her laptop and found the image depicting the fluorescent signals. "So you see two reds and two greens.

And here you see two reds and two greens. And then, yes...see, over here, there is only one signal being picked up.” The green signals are from the control probe while the red is from the test probe targeting the 22q11.2 region. While the green control probe is consistently there, the red test probe is absent.

5.5b Polymerase Chain Reaction (PCR)

Rabinow’s book (1996), *Making PCR*, describes the development of PCR in detail.

The story goes that Kary Mullis, the man awarded the Nobel Prize for his idea of PCR, while driving in his car to his cabin, starting thinking about DNA polymerases and DNA sequencing. Polymerases are enzymes that repair and replicate DNA. The first step in this process is to separate the double strands of DNA. While this is a normal part of cell division, it can be mimicked in the laboratory through heating. By adding a primer (a section of DNA that acts as a starting point) the polymerase builds on the primer along the template, following the principle of base-pair complementarity. Mullis realized that by iterative cycles of heating and cooling, a chain reaction could be started in which a defined and specific target of DNA sequence could be exponentially reproduced. The products would be of a defined length, the length between the outside ends of the two primers. This was Mullis’ “eureka” moment.

Mullis and other scientists at the Cetus Corporation where Mullis worked had stumbled on a technique, PCR, which completely altered the practice of microbiology. As Rabinow asserted in the mid-1990’s, “it is no exaggeration to claim that PCR is a fundamental tool that makes feasible such magaprojects as the Human Genome Initiative” (Rabinow, 1996). PCR was a ubiquitous component within many of the experiments I observed in Laboratory X. What follows is a brief description of one of the PCR experiments I observed in the summer of 2011.

I observed as Heather did a PCR this morning. She microwaved a liquid in a container, adding ethidium bromide (a carcinogenic substance) to the mix. After microwaving the liquid for a couple of minutes she took it out and brought it back to her bench space. The substance had turned into a kind of viscous gel. There are several small wells or indents along one edge of the rectangular container that holds the gel. With really tiny fragments of DNA, you need a very firm gel. Our DNA fragments today are fairly long so the gel does not have to be quite so firm. Heather told me to think of it like a sieve. She said, "So imagine you've got a big bag of frozen peas that are all different sizes. Some of them are really tiny and some of them are really big. So it's like a sieve to sort out the different sizes of peas that you've got". She's not sure how large her DNA fragments are because she doesn't know the break points. She guesses the fragments are between two and ten kilobases. She's trying to amplify across a deletion of unknown size and she's not actually positive it is actually deleted.

To run the PCR she needs to put a dye in the gel. It's coloured and lets her see. The dye is also heavy and pulls the DNA down into the wells so it doesn't float around. At this point there is no DNA in the wells yet. The DNA is still in a row of little plastic tubes. The tops of the little plastic tubes, each filled with sample DNA, are bent over from melting a little in the heating cycles of the PCR machine. Heather shows the guy sitting at the bench beside her and says she will not use these tubes again. It's tricky to fit the end of the pipette in them. There is a little dial on the pipette that changes the amount of liquid that will be sucked up. She rotates this with her thumb. There is a tiny amount of liquid in the tubes, about five microliters. We put the gel in the fridge to wait for it to set. After ten minutes we take it out of the fridge and load the DNA sample. Alongside the sample DNA there is something called a ladder. It contains many DNA fragments, all of known sizes. So you can

compare your samples and the ladder. Each of the little wells or holes in the gel along one side has a buffer solution. When the DNA is added it sinks into the well. Heather sets her timer for thirty minutes. A current runs through it on an electrophoresis, a small machine that sits beside her on her bench. Heather tells me that because DNA is charged, it will separate. The small fragments will move through the sieve faster than the big ones. After the gel and DNA has sat in the electrophoresis for about half an hour, we come back. Taking the rectangular container with us, we walk to the end of the aisle and toward the wall by the door of the laboratory. Here there is a UV light box called a UV transilluminator. Heather puts the container into the box and waits while it takes a picture. The ethidium bromide that she added to the gel makes the DNA glow. After a minute a black and white photograph is spit out of the machine. It shows the ladder along the side, basically a line of vertical bands going down the photograph. There are other rows of vertical bands beside the ladder. These are running down from the wells where the sample DNA was dropped. With the photograph in hand, we walk out of the laboratory and back to Heather's desk in the research office. Several black-covered lab books are lined up at the back of her desk. They look much like the black notebook I carry around and scribble in during fieldwork. Heather is involved in so many different projects; she juggles between five lab books. She describes her lab books as a "historical recipe book with everything I've cooked". Each of the pages is filled with detailed notes of all the steps of each experiment she has done, along with taped in print-outs generated along the way. She opens one of the books to the last used page and tapes in the black and white photograph of the PCR.

I asked Heather what the next step would be. At this point, she would repeat the experiment. She said, "in the words of my old supervisor – anything real will happen twice".

5.5c PCR to real-time quantitative Polymerase Chain Reaction (qPCR)

The description above is about the PCR process. The PCR process is not used for validation but it led to another technology, real time quantitative PCR or qPCR that is used in validating microarray results. While a cytogenetic experiment called fluorescent in situ hybridization (fISH) can be used to detect and verify microdeletions and duplications, fISH is usually only used when the region in which the CNV is located is already known. Moreover, fISH is time-consuming, costly and sometimes does not have the resolution to detect small CNVs (Weksberg et al., 2005). PCR is used to amplify DNA fragments, with 20 cycles producing a million-fold increase in DNA. This amplification, however, introduced the potential for a lot of error, as all fragments may not amplify with the same efficiency. Eventually, the PCR cycles no longer produce an exponential increase in DNA fragments, with some cycles generating more than others. This is called the “plateau phase”. Real-time PCR, (VanGuilder, Vrana, & Freeman, 2008) first described in the mid 1990’s, plots the gain in fluorescence against time (the number of PCR amplification cycles). Real-time qPCR allows one to measure the PCR products as they are accumulating. Therefore, the scientists can determine the amount of fluorescence while the experiment is still in the exponential range. It is only during this exponential phase of the PCR experiment that the scientists can extrapolate back to calculate DNA copy number measurements of the starting sample.

After the microarray and qPCR validation, the little tubes of extracted DNA frequently move on to another place in the laboratory, continuing on their journey, to be used for sequencing. Not all samples continue, however. There is a prioritization that occurs. An academic project coordinator explained the prioritization to me, with the caveat that as prices start to come down all samples will be run on Next Generation Sequencing in the future. For now, samples are sequenced if they have:

- 1) high resolution array data
- 2) a known CNV of interest (to see if other variants were detected)
- 3) high quality DNA from blood
- 4) good phenotype information with family members available for follow up

He explained that the second point is a bit counter-intuitive but they want to find out if other variants could explain or at least contribute to the phenotype. What follows is a description of the sequencing experiments that I observed and talked about with scientists in Laboratory X.

5.6. From CNVs to SNPs - Next Generation Sequencing

Next Generation Sequencing (NGS) is a technology that can detect all types of variation in the genome but is most often used to find a variant called a single nucleotide polymorphism or SNP (pronounced ‘snip’). Compared to CNVs, SNPs are much smaller. They might be only one or two base pairs in length. For example, if a length of DNA in the human reference genome reads A, C, G, T, C and a length of DNA in a sample of DNA reads A, C, T, T, C, then this could indicate a SNP at the third base. Where there is a G in the reference there is a T in the case sample. In order to detect SNPs, an entirely different technology is used. Whereas microarrays were used to detect CNVs, sequencing is used to detect SNPs. Traditionally, sequencing was carried out using Sanger biochemistry and was limited to smaller, targeted investigations. Recent Next-Generation platforms are able to sequence whole genomes. There are three different NGS sequencing platforms used in Laboratory X (454 sequencing, Solexa, and SOLiD platform); each has specific uses depending on a customer’s budget and the size and quantity of the samples being processed. Each of the platforms has specific advantages and disadvantages (i.e., read length, types of error, and cost). According to Shendure and Hanlee (2008), “Although these platforms are quite diverse in sequencing biochemistry as well as in how the array is generated, their work

flows are conceptually similar”. During my fieldwork the SOLiD 4 machine was updated to a SOLiD 5500. My observations are based on experiments using the SOLiD platform.

There are several steps involved in a NGS sequencing experiment. In the lab where I conducted my fieldwork, the scientists were involved in exome sequencing rather than whole genome sequencing. In exome sequencing, only the exonic parts of the genome are captured and explored with the intronic stretches of nucleotide bases being washed off in the process. The first step is to prepare the library. The second step is called hybridization where the DNA is captured. The final step involves adding barcodes and doing an emulsion PCR. The barcodes are added if DNA is being pooled during the experiment. In this section, I will describe the NGS process for an exome sequencing experiment. This description has been pieced together based on five different interviews with two post-docs and a manager, as well as three different observations of sequencing in the laboratory.

The first step for Heather to do is to prepare the DNA. Other people have already extracted the DNA from a blood sample. What matters is the quality of the DNA. All she needs is the extracted DNA. She reaches into her fridge and pulls out a tube containing clear liquid. This is DNA in solution. I'm quite fascinated and ask her if she can tell that this is DNA in here. She says, “It's just a tube. It's not very exciting. If you know what you're looking for you can tell. If it's really high concentrations you can tell because it's gloopy.” She lets me pick up a tube and look more closely at it. At the bottom is a tiny bit of clear liquid. I gently wiggle the tube but the liquid doesn't slosh around at all. She says this is because the tube has been stored at such a cool temperature. So she takes her DNA in a tube and does an enzymic reaction to purify it. The next step is the hybridization. This is important because they are not doing whole genome sequencing for the Autism Genetics Study; they are doing exome sequencing. This means that they only want to capture the

exome, the genes, and not all of the intronic bits. So she needs to capture the exome and wash away all the rest of the genome. This is called hybridization. This step is done early in the morning, while the lab is quiet and nobody is there to interrupt her. She explained the process like this:

So, what we have is a little sequence, little RNA baits basically that correspond to the exons and so we attach these to the DNA in our sample. We shatter our sample into tiny fragments, prepare those and repair them and stuff. And then we bind those with the RNA bait that corresponds to the exon so they stick. And then capture the RNA bait using magnets. So then with the magnet we can pull out the DNA fragment and wash off everything that hasn't stuck to a fragment.

The fragments are very small, approximately 200 bases long. The RNA baits are about 120 bases long. She adds the RNA baits to the extracted DNA sample and leaves them at 65 degrees Celsius for about twenty four hours. Hydrogen bonding occurs between the corresponding fragments during this time. After this, the washing process takes about five hours of adding solutions (like ethanol), mixing it, pulling the beads to the side with a magnet, sucking out the solution and putting in another solution. Over and over.

In the first part of this step the RNA baits bind to the DNA sample. A fishing analogy is often used in the lab to talk about this process of capturing regions of the genome. Heather explained,

I need baits because in some of my experiments I'm only interested in some of the genome. So if you imagine a fishing experiment, I go in and fish out the bits of genome that I'm interested in. So to carry on this kind of fishing analogy, they call them baits. So the baits represent a complementary sequence to the sequence I'm interested in. So you use the baits to fish out the bits you want.

Then the rest of the DNA is washed away with various solutions. So all she is left with are the exons.

The next step is to give each sample of extracted DNA a bar code. This is because she

runs six samples at the same time and needs to mix them together. The barcode on each sample will enable her to figure out which fragments belong to which sample at the end of the sequencing. The barcode is a short stretch of sequence included within a primer. A primer is a sequence of base pairs that is unique to a very specific region of the human genome. Most of the primer is the same for each of the samples but at the end of each one is a little sequence tag. This is attached to each fragment. So the first thing that is sequenced is the little tag which tells the scientist who the fragment belongs to.

Below is an excerpt from my field notes when I observed the hybridization and adding the barcodes:

Heather holds onto a long magnet with red handles at either end. Hanging over the length of the magnet are eight tubes. The lids of the tubes have tiny patient ID numbers handwritten in green marker. Each of the tubes is quite small, about half the length of my baby finger. They each contain a clear liquid. At the side of the tubes resting along the magnet there is a small brown line. Heather explains that these are actually tiny magnetic beads being pulled over to the magnet. The DNA fragments are attached to these beads. She spins the tubes on a round centrifuge and the liquid turns brown as the beads become dispersed or resuspended in the solution. Then when she puts them on the magnet they are pulled to the side and the solution becomes clear again. This way she can fill the tubes with different solutions and then take her pipette and suck the liquid out again without sucking up the beads. She does this several times with different solutions. The pipette seems to be almost an extension of her gloved hand, as she quickly presses a button at the top of the pipette with her thumb to draw up the solution. A self-proclaimed “techno-nerd”, she explains that she has been doing this for over ten years. She thought it was funny that I didn’t know what a pipette was because she has worked with them almost every day of her adult life.

She is adding the barcode tag. She sets the timer which is stuck to her workbench at eye level when sitting. There are lots of plates in front of her on the work bench. After a while the timer beeps as she is adding primer to each sample. She has lots of tricks to make sure that she doesn't make a mistake when adding the primer. Finally, she takes a pipette and draws liquid out of one tube and drops it into another plate which contains several small holes. The holes in the plate are numbered along the top from 1 to 12 and there are letters going down the side from A to H. She is removing the water and DNA and leaving the beads behind and then adding the DNA to the primer that is already in the holes in the plate.

She is using rows C-F and columns 3 -10 on the plate. These are tiny amounts of liquid that she is moving around, only 50 microliters. She can't talk to me right now. It is very important for her to concentrate and make sure that she doesn't add two different samples of DNA to the same hole in the plate. She has lots of little tricks to remind her which of the holes she has already added the DNA. Each of these experiments costs several thousand dollars to complete. Once all of the holes in the plate are filled she presses on a clear, thin plastic sheet which looks like a big square sticker, to prevent any of the liquid from spilling or evaporating during the PCR. We walk over to the end of the aisle and open the lid of the PCR machine and lay the plate inside. She pushes several buttons on the display at the front and the machine starts. She says it will take about an hour.

Once the samples are in the SOLiD machine, it takes about two weeks to run. The SOLiD machine is basically a robot. She describes the machine in this way, "They're like children. They have tantrums like children. The one I'm running at the moment, you can't touch it. It crashes as soon as you touch it." When she took me on a tour of the lab she showed me a few of their NGS machines and there was a hand written sign on a piece of paper saying 'do not touch!' on one of the sequencers. Once the samples are put into the

SOLiD machine for sequencing a light is emitted for each base and the machine then photographs each one of these lights. Each base pair has a different colour light. The absolute raw data from these machines are the millions of photographs taken of each of these lights. This is called “colour-space”. This then gets converted to nucleotide letters. After this the nucleotide letters are aligned to the reference genome.

What actually happens is you get reads that look like someone’s thrown some Smarties on them because there are so many errors. Most reads, or a lot of reads, have an error in them. So you’ll get a load of position that match to the reference and then on nearly all the reads there’ll be one base scattered around and different. But basically you get a pile of reads that all correspond to your region. (Heather, post-doc)

These Next Generation Sequencers are “high through-put” meaning they can process a lot of data. However, they are also very error-prone. According to Shendure & Hanlee (2008, p.1137) “base-calls generated by the new platforms are at least tenfold less accurate than base-calls generated by Sanger sequencing”. If she finds any mutations that she thinks are interesting she has to validate using a second method of sequencing. This second method is called Sanger sequencing. She explained, “This is just traditional Sanger sequencing. This is how sequencing was done before Next Generation Sequencing and we use it for validation of NGS because it’s cheap and cheerful and you can do a small targeted region for not much money very quickly.” Sanger sequencing does the same thing as Next Generation Sequencing except that it does a very small, targeted region. If she finds a variant in a particular exon in the NGS data, she will only Sanger sequence that particular exon. It might be about 300 base pairs in size. It takes about four days to do the Sanga validation and at the end “you get very nice, clean data”. She went on to describe the data that she gets from the Sanger,

So you know exactly what it is; you know exactly where it’s coming from.

It's very simple to interpret and it doesn't require massive amounts of bioinformatics and huge quantities of data storage and stuff like that. It's all just really simple.

5.6a The Computer Pipeline

The NGS machine produces several spreadsheets. All of the data runs through a computational pipeline. Intense interest and concern over the quality scoring of the generated sequences gave way to lively discussions at weekly lab meetings. There are a variety of different software and data analysis tools available for processing and interpreting data. Different software have different functions in the data analysis process, such as aligning the sequence reads to a reference genome, base-calling or polymorphism detection, *de novo* assembly from paired or unpaired reads, and genome browsing and annotation (Shendure and Hadlee 2008). SHRiMP, for example, is an algorithm used for alignment of SOLiD data. At one point in my fieldwork, I interviewed the bioinformatician who developed the pipeline. I also observed an exome sequencing meeting in which she delivered a one-hour presentation about the pipeline. A young Asian-Canadian woman in her late twenties, she had a calm, quiet voice and smiled easily. When she began to speak about her work on the computer pipeline it was like she was speaking another language. *Despite, or perhaps in spite, of my father making my siblings and I work through computer programming books in Quick Basic when I was seven and eight years old, I have not taken an interest in computer languages or taken any computer science classes in University. The description of the pipeline process is limited by my lack of familiarity with computer science.*

The NGS data in its most raw form is actually a huge series of photographs. These take up three to four terabytes of disc space for each run and are almost immediately converted into colour space. Once the bases are "called" in colour space, the image files are erased. Each

colour corresponds to a different nucleotide and along with the colour the SOLID machine will also give a quality score, indicating how confident the machine was in calling each colour. So the colour space is actually based on numbers from 1 to 4. If the machine is unable to make a call about a base it will insert a dot. Colour space is then quickly converted into nucleotide space (e.g., T, C, G, A). All of this data is taken off the sequencer and put on the computer cluster, where the bioinformaticians access it and analyze it. Once it has been converted into nucleotide space, the data is then put into the “Pipeline”. There are several steps to the pipeline process. The first step is to align the nucleotides to the human reference genome. When there are differences between the sample and the reference genome it could indicate a SNP or it could mean there is an error. If there is a “true SNP” there will be two colour changes. If there is only one colour change, it is most likely a sequencing error. In this case, the pipeline will insert a base from the reference genome at this point. This, however, introduces something called “reference bias”.

The next step is to remove duplicates or PCR “artifacts”. The problem is that if one allele has an artifact and the other has a true SNP, they both get thrown out. There are various complicated algorithms that recalibrate the sequence. For example, if a reference base was inserted in an earlier step, it gets recalibrated to N at a later step. The whole pipeline is designed to try to increase the number of true SNPs and decrease the number of false positives. There are all sorts of scores and statistics used to estimate the probability that when a SNP is called it is true. They want to be sure that if they are “calling” a SNP that it is really *real*. For example, during a meeting someone suggested that they could adjust one of the computer filters to give Tyler more SNPs and Tyler responded, “We don’t want more SNPs, we want more *real* ones!” The entire pipeline is very complicated and involves a lot of computer science to understand. However, as the NGS facility manager stated, “Basically

what's important for people is two types of data. One would be the sequences themselves. And the quality scores associated with those sequences". Sequencing technologies are changing quickly and were described by several people in both the laboratory and autism clinic as a "constant moving target". What seems clear is that the challenges likely to face this area of research in the coming years are those associated with how to interpret and make clinically relevant all of the masses of data that are generated by these high through-put technologies. As Shendure & Hanlee stated,

Analogous to microarrays, we also expect that the challenges will quickly shift from mastering of the technologies themselves to the question of how best to go about extracting biologically meaningful or clinically useful insights from a very large amount of data" (2008, p.1143).

I feel I should briefly interject in the description here to make a point about agency. In Chapter 2 I discussed the notion of agency and how it is problematized within practice theories and actor-network theory. Particularly relevant here is the idea of the dialectic between the social structure and the individual or the actor and the network. Each constructs the other. Through my research in Laboratory X, this post-humanist, dynamic relationship between different agencies is witnessed in surprising places, even at the very core of how science itself is practiced. The human genome, micro array testing, PCR and all the tools, robots, protocols and material entities that are implicated in these technologies are in fact pushing back on the scientists. The scientists are not only involved in their creation but are also created by them. For example, since the human genome and technologies such as the micro array which have been developed to probe the human genome, the way in which scientists conduct research in the field of molecular genetics has been completely altered. Whereas research used to be hypothesis-driven, the paradigm has shifted to a discovery-driven model. Hypothesis driven research is no longer realistic or productive with the unruly multitude of actors now opened up by these new technologies for mapping and probing the genome. As one scientist explained to me:

PhD Student: But now we have access to pretty much the whole genome so that helps a great deal in finding disease genes. So previously before the sequence of the genome was known, say you wanted to find a gene for a disorder, you were restricted to a handful of genes for which function is known. And so you go and look at only those genes, any sequence with those ten genes and then see if they have any mutations. So this is what's called a candidate gene approach. So you are obviously restricted by what you know. Because there is no other way to approach that. But now that you have sequence from the Human Genome you can sort of look at everything in one go and you might find a mutation in an unknown gene and it could be interesting, it could not be interesting; it's hard to interpret, especially if the gene is of unknown function. But it's opened the door to a whole other level of detection. Now we're not restricted by what we know anymore. We're sort of moving from hypothesis driven research into discovery driven research. So they are sort of two different approaches. Like, hypothesis driven would be like if you took a single gene and you think it's involved in a certain disorder because it has a known function and say my hypothesis is that this is involved and we want to look at this. That's hypothesis driven. Discovery driven is, you're just going to take a patient's DNA and put this on a whole genome micro array and see what's going to fall out. (interview)

So scientists are influenced by, constructed through, the technologies which they create. They developed the human genome, microarray, and sequencing machines and in turn these technologies are forcing scientists to completely alter how science is ordered, organized, practiced. Scientists do science differently because of the agency of these technologies; hypothesis-driven research is no longer always manageable or desirable. The scientific method, at the core of science, is changing as technologies change. The world is approached differently now because of these new technologies. Agency is shared in a dialectical dance among human and non-human actors.

5.6b Monday Morning Meeting

The door is locked to the conference room. I'm early as usual. A few minutes later,

Tyler comes along and opens the door, propping it open with a chair he's pulled from along the wall. He's wearing blue jeans and a black long-sleeved shirt. His dark hair is starting to grey at the temples. He must be about forty. We talk for a few minutes while he sets up the laptop and projector. After a few minutes, others start to walk into the room, finding seats and quietly chatting. Some wear coats, indicating they've made the trek here from other buildings. Others have already shed their jackets and instead carry coffee. Felicia, Claudia, and Loren walk in, arriving from the Autism Clinic. They sit down beside each other at chairs near the head of the table.

The Monday morning meetings are held every second Monday in the conference room of Laboratory X. The conference room is large, at least 25 feet long, with one big wooden table running the length of the room. There is a white board at one end of the room and windows at the other end. There are two doors through which one can enter the room, both automatically locking. Black chairs hug the edge of the table and a second ring of chairs flank the outer walls of the room. I have been to meetings with as many as forty people are crammed into this space. Monday meetings begin at 9:30 and run for an hour. An agenda is circulated by email ahead of time and electronic PowerPoint slides are distributed early on Monday morning. The meeting is organized and chaired by Tyler, the main project coordinator in the academic lab. Dr Lorenz often attends but the meeting is not cancelled if he is going to be absent. Only academics attend this meeting. Technicians are not invited. From Laboratory X, there are post doctoral fellows, PhD students, bioinformaticians, and other lab directors involved in autism genomics. From the Autism Clinic, the director who is a developmental paediatrician, the genetics project coordinator, and one of the psychologists are present. There are also clinical geneticists and genetic counsellors present, although they sometimes have their own clinics to run and can not always attend the Monday morning

meetings. As well, there are often a few people from the clinical laboratory at Hospital X who attend this meeting. Typically, there are about twenty people in the room, although the numbers were sometimes fewer over the summer months.

Since the Autism Genetics Study is a large, multi-site project, there are always people who phone into the meeting. From the other geographically dispersed groups who are involved in the Autism Genetics Study are project coordinators, psychologists, clinical geneticists and co-principal investigators.

Tyler opens the meeting by going over the agenda, which appears in point form on the large screen behind him. He reviews the minutes from the last meeting and then passes it off to the first person to present. Presenters at these meetings are almost always from Laboratory X. In other words, the PowerPoint slides primarily convey information about genetic experiments and findings. The clinicians in the room tend to be observers, sometime interjecting to add phenotypic information pertaining to a specific case. (In the eight months that I observed these meetings, only two presentations were made by someone who did not work at Laboratory X – my own presentation to recruit them into my project and presentation by a woman from the federal Ministry of Health who was setting up an autism surveillance program.) I was told that occasionally, in the past, a clinical geneticist has presented cases. Usually, however, it was the scientists who presented genotype information and then asked the clinicians for more phenotype information from which to interpret the genetic results.

Typically, the agenda would contain three or four cases to be discussed. Some might be results from the micro array and others from Next Generation Sequencing. There might also be informal discussion about a conference or discussion about a research ethics board (REB) application. Often they discussed the protocol that was being developed for a newly funded project, which was really just another way of acquiring samples for the Autism

Genetics Study.

At the beginning of the meeting, the case studies to be presented would be listed by patient number. For example, one Monday meeting contained the following list:

H1243/H5204 (NRXN1 nonsense mutation) – report sent

H3980 (IL1RAPL1 maternally inherited intronic deletion) – 5M analysis?

H5763 (NRXN1 intronic deletion) – Ankit to get report

H1376-03 – 19p12 and 4q32.1 gains (report sent)

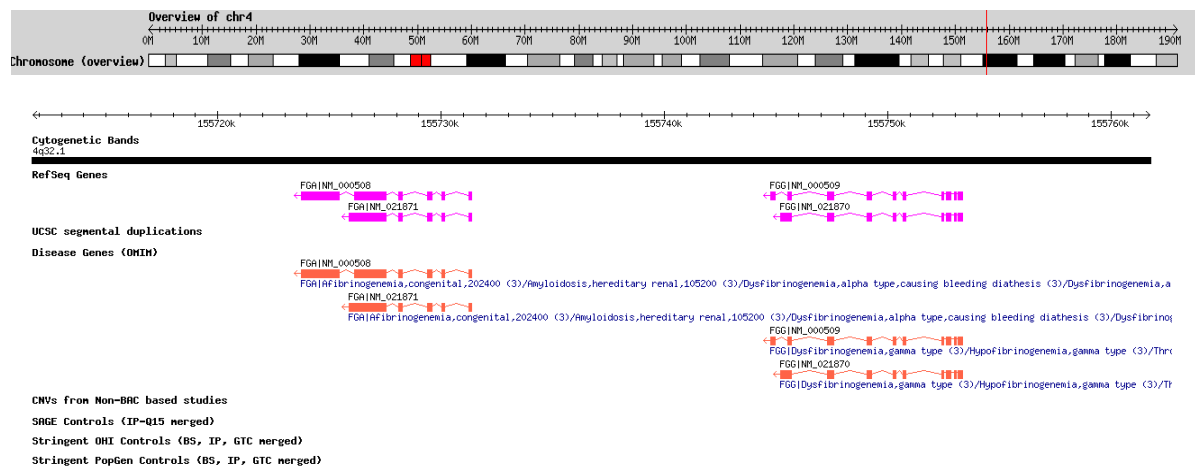
As the presenter introduces the case, I can hear the clinicians whispering to each other, conjuring up the people represented by the patient number. “Is this the Fuller kid? The boy from [Y]?” Loren asks in hushed tones. “No, this is the Stevens family. His sister was diagnosed first and he is part of the sib study.” Claudia has brought a stack of patient charts with her. The email from Tyler the previous day has given her time to pull the relevant charts, ready to offer more detailed information if asked by a presenter.

The presenter, usually a post doc or grad student, first describes the type of mutation found and offers a brief description of the function of the particular gene in which the mutation was found. Here they might show a slide with a list of scientific articles that have already published about this gene. Then they indicate which type of experiment was used to find the mutation and how it was validated. If the mutation is a CNV found with a microarray then the next slide is often a screen shot from the Database of Genomic Variants.

A slide from the Monday meeting on October 17th was laid out in the following manner. At the very top of the slide is a chromosome overview which looks like a striped ruler. It is divided into segments. Each segment denotes ten megabases (ten million bases) of the human genome. At one point a red line crosses the ruler perpendicularly. Under this is says, for example, “4q32.1 - 14kb gain”. This tells the audience the location of the mutation

and the size of the mutation and whether it was a loss or gain (deletion or duplication) of genetic material. Under this there is a second line that runs across the width of the screen. This line is divided at regular intervals so that it looks like a ruler. This is illustrating a particular region of the chromosome. It is at a different scale than the top line above, showing just the portion of the chromosome where the perpendicular red line intersected the first line. This zoomed-in ruler, for example, might increase by ten thousand base pairs with every notch, spanning a total of fifty thousand base pairs across the slide. Under this line are various blocks of coloured lines that indicate where particular genes are located in the human genome relation to the ruler across the top. These are called RefSeq Genes. Under this are another set of coloured lines which indicate where OMIM genes are. OMIM is a database which contains all of the known disease-causing genes. Directly under the coloured OMIM lines there is also a brief description. For example it could say, “FGA Afibrinogenemia, congenital, 202400, (3) Amyloidosis, hereditary renal, 105200...” In this way, the slide allows you to compare the location of the CNV found with the location of other known disease genes. (See Figure 5.3 for an example)

Figure 5.3: Example of a DGV slide



Following this screen shot, the presenter would often then show a slide with a pedigree. The pedigree is a particular type of family tree. At the top of the pedigree is the family identification according to the patient number. Different levels of the pedigree correspond to different generations, just as with a family tree. A circle is used to depict a female and a square is used to illustrate a male. On the pedigree, if the circle or square is coloured in black, this means they have been given a diagnosis of ASD. If the circle or square is coloured in grey it means they have been diagnosed with another neurodevelopmental disorder. The pedigree also gives information about any deletions or duplications associated with a particular circle or square. For example, it might say “de novo NRXN1 deletion”. Sometimes there are several deletions or duplications listed under a single circle or square. Some circles and squares have deletions or duplications listed under them but they are not coloured in black, meaning they do not have a diagnosis of autism.

Some pedigrees are small, containing just two levels or generations. A trio (mother, father, and proband) is a frequent pedigree that appears. Others are large and expanded pedigrees. The pedigree shows visually who has autism, who carries a CNV, whose blood has not yet been collected and it can also indicate other phenotypic traits that are not standardized. For example, some pedigrees contain information yielded through conversations with the parents of the proband. One pedigree contained information below a square that stated “very shy when younger” another square stated “quiet and reserved, keeps to himself”; several other circles had the word “scoliosis” written underneath them. One pedigree went so far as to indicate below a square “organizational difficulties, recites Shakespeare”. There was some discussion about this particular inclusion on the pedigree, with the director of the Laboratory X stating with exasperation, “but maybe he was a high school English teacher! I can recite the 1984 statistics from the Montreal Canadians hockey

team but that doesn't mean I have autism".

Needless to say, the pedigree is a site where information from the laboratory is joined with phenotypic information gleaned from the clinic. (Sometimes the junior members of the laboratory are not clear on which phenotypic information is appropriate for a pedigree.) Indeed, very frequently the presentation of the pedigree segued into a discussion in which the scientists would ask the clinicians present at the meeting if they had or if they could obtain any other phenotypic information about members of the family. This information could help the scientists further interpret their data, determining if the phenotype segregated with the same distribution of the genotype.

In addition, the pedigree was often followed up with a discussion about whether or not there was a need to try to contact the family to get more blood from other relatives. If more blood samples were needed a research report would first have to be written and given to the clinical geneticist to explain that there had been a new finding. From there a feedback session would be booked with the family to explain the finding and to ask if they would be willing to contact extended family members for purposes of obtaining a blood sample. The decision of whether or not to write up a research report is a common outcome of these Monday morning meetings. Minutes from these meetings commonly contained statements about which reports were to be written and by whom.

5.7. From Data to the Report

Reports are written by several different people at the Laboratory X. For one of the post-docs, this seemed to be one of her main duties. A PhD student who was heavily involved in microarray analysis was also responsible for writing research reports. At the top of the report is the date, the physician's name and the sample ID number. The CNVs are then categorized into four different classes. The following excerpt details a particular report that

the PhD student named Ankit showed me:

PhD Student: So class four is CNVs that are in controls as well, Class three is CNVs that are not in controls but don't overlap any genes, Class 2 are not in controls and they overlap some genes but we're not sure what they mean. Like, they could be significant or they might not be. And class 1 is it's a known syndrome or a known pathogenic locus. So for this particular patient the array computational analysis programs spat out a list, in this case, there were 37 copy number variants. So they are listed in this table. So we give the physician the position, the start position and the stop position, size of the variant. The type, loss or gain, and each of them is given a class.

Julia: Wow.

PhD student: So you'll see that of the 37 copy number variants [scrolling with his mouse], 31 are class 4. They were seen in controls. So two of them are class three which don't overlap any genes. We don't know what they mean. Two are class two. They overlap some genes but for these particular genes there is not much functional evidence in the literature. Not much is known about their function. So they call it class 2. And there are another 2 which are class one. So, one of these is the NRXN deletion. So we say that 'one class one deletion overlaps NRXN1 and there is evidence in the literature for the [?] of exonic deletions.' And we also say "this deletion was detected in samples from the dad and sister but not in the mom by qPCR". So it sort of summarizes.

The report then leaves the laboratory and moves the genetic information back into the clinic.

This report speaks for all the work that was done in the laboratory. Since arriving in the laboratory in a little glass tube, the DNA has been sliced, put on a slide, washed, photographed with a florescent scanner, magnified, plotted on graphs, turned into pedigree diagrams in power point presentations, and now categorized into four different classes. What came into the laboratory in a tube has been converted and transformed many times and now leaves the laboratory on a research report. All of the work that took place in the laboratory is behind the scenes, or backstage. For the clinician, it is the report that matters. Just as the tube of blood seemed somehow significant for me so too did the report. In the same way that a tube of blood "stands for" a person, a report is made to "stand for" all the work of testing,

discussions, conversions and representations that are done in the laboratory. Weeks and months of work are summarized in a few typed paragraphs on a page.

During my fieldwork I witnessed a lot of discussion concerning whether or not a report should be written and if so, the precise wording of the report. Several times, a research report would be written up to the frustration of the clinical geneticists who would remind the scientists that if a report is written there has to be a feedback session with the family. This is because once a report is written it becomes part of the patient chart and the patient needs to be properly informed about the information. The clinical geneticists indicated that it would be best if reports were only written for cases that had “clinically significant” findings.

The issue of the wording of reports is exemplified in another interaction that I observed. I was sitting in on a monthly meeting between two post-docs from the laboratory, two clinical geneticists, a genetics counsellor, and the main research coordinator for the genetics research at the Autism Clinic. The conversation was not recorded but I captured the discussion in detailed notes. The conversation unfolded something like this:

Research Coordinator: *Normally we don't give the research report to the parents at the feedback session. But these parents have requested a copy of it. They want to leave with it in their hands at the end of the feedback.*

Clinical Geneticist: *You can give them a service report but not the research report.*

Genetic Counsellor: *Why can't they have the research report?*

Clinical Geneticist: *It's too complicated for them.*

Genetic Counsellor: *But the wording is appropriate.*

Clinical Geneticist: *Alright, but we need a statement at the bottom of the report that says it's a snapshot at this date. It needs to be explicit that the interpretation and the technologies could change over time.*

The biggest difficulties arise when clinical significance is uncertain. These are sometimes

termed “fence cases”. These are difficult to communicate to families in feedback sessions because they are so complicated and often much of the information is not there. The literature is inconclusive. The interpretation of the data is uncertain and couched in several modifying hedge words when discussed in meetings. There is a tug-of-war between not wanting to cause the individual undue anxiety and frustration and wanting to make sure that the individual has all the relevant information with which to make clinical decisions.

The issue of ambiguity is a growing concern among the clinicians. In a meeting at the autism clinic I listened as Dr. Morten explained how previous versions of their consent forms stated that the genetic testing would help to reduce ambiguity and uncertainty. They have now taken this statement out of the consent forms because they find that genetic testing actually increases uncertainty and ambiguity; it opens up more questions than answers as the technology continues to change.

This issue of ambiguity is well described in the science studies literature. Hedgecoe & Martin have described the impact of genomics on the reclassification of disease, for example. Even cystic fibrosis, one of the most simple, monogenetic disorders, has endured complex expansion into neighbouring conditions (Kerr 2000; 2005; Hedgecoe 2003). Genetic classification of disease is messy, unpredictable, and can lead to increased ambiguity rather than clarity.

When results are clearly clinically significant the research report is then written up and sent to Dr Morten at the autism clinic. The project coordinator phones the parents and schedules an appointment for a feedback session. Often, it has been several years since the individual gave blood. Then, out of the blue, the telephone rings and the parents are told they need to meet with a genetic counsellor as there is new information about their DNA that could be contributing to their child’s autistic behaviours.

5.8. Exit the Laboratory: The Feedback Session

Once a report has been written and sent back to Dr. Morten at the Autism Clinic, the family is contacted and asked if they would come in as there have been clinically significant findings from the genetic testing. Dr. Morten or Claudia usually makes the phone call. For some families, it has been years since they've had contact with the Autism Clinic. The phone call takes them by surprise. "We'd like to make an appointment to talk with you. We have some interesting genetic findings about your son and we'd like to update you." An appointment is made; a date and time are set. At the meeting there will be a genetic counsellor and often either a clinical geneticist or Dr Morten, a developmental paediatrician. During my fieldwork, I was able to observe several feedback sessions. In addition, I interviewed six parents about their experiences in receiving genetic feedback. The story that follows is an amalgamation of stories based on the various feedback sessions I observed and my interview conversations with parents. The story is told from the point of view of a mother as most of my interview participants, within families of children with ASD, were mothers.

They weren't sure what to expect after receiving the phone call. Dr. Morten didn't go into any detail about what the "interesting findings" were or how they might impact the life of this family. The mother lay awake all night. She was excited to finally have an answer. It's been nine years since their blood was collected. Could there be a major breakthrough, some new findings with therapeutic implications? Technology has changed a lot in that time. So has this family. When they first brought little Davey into the clinic he was just two years old. Despite already suspecting there was some sort of developmental delay, the diagnosis of autism was still an overwhelming shock for the mother and father. Their imagined lives that lay ahead, talked about with excitement, suddenly crumbled before them. Since then, they

have adjusted their expectations. They have learned to go on in their daily life with their son, whom they love dearly and whom they can not imagine living their life without. There have been difficulties along the way but routines were established and a new normality quietly settled around them long ago. The phone call has stirred it all up again. While she has been content and enjoyed her life these past years since her son was diagnosed, the mother can't help but feel her heart beat faster when she thinks about the news they might receive. She tries not to let herself get too excited or hope for too much. Still, lying in bed on the night before the meeting, in the quite minutes before sleep finds her, she imagines how their son's life might change with the news they are about to receive.

They left home with plenty of time to get to the Autism Clinic, but traffic was unusually slow and they find themselves walking off the elevator only a few minutes before their scheduled appointment. They have both taken the day off work, he a sales manager and she a dental hygienist. On most days off work they dress in casual comfortable jeans and sweatshirts. Not today. She looks at her husband. He's wearing freshly ironed Dockers and a dress shirt and tie. The tie is what gives it away, the importance of the day. She wears her dark green skirt and cashmere sweater, a silk scarf hanging loosely over her shoulders. They approach the reception desk and give their name. "I'll let her know you're here", the friendly receptionist smiles and tells them to take a seat before she disappears down the hall. A few minutes later a diminutive, middle-aged woman approaches them, a younger woman following behind. The first woman extends her hand toward them, "Hello, I'm Donna", a genetic counsellor. She introduces the young woman who stands slightly behind them. The mother and father are told that she's a student who would like to observe the meeting. Glancing at each other, they nod in acceptance. The student pulls out a piece of paper which describes her study. They quickly read it over and sign the consent form. They follow Donna

down the hallway and into a conference room.

The conference room is fairly small with two couches and two chairs placed in a circle around a small central coffee table. Along one wall is a large window which looks out onto a busy street six floors below. It is grey outside today but the sun keeps trying to break through the clouds and for a moment sunlight beams through the window, spilling across the dark grey carpet. A brightly coloured painted canvas depicts a part of the large mural that adorns the walls of the waiting room. The woman and her husband sit down beside one another on one of the small couches and the genetic counsellor, Donna, sits across from them. The younger student sits off to the side. Donna starts by telling them that there has been an explosion of research in the last five to ten years. Their son's sample has been in the laboratory a long time, as it was collected almost ten years ago. There have been recent advances in the technologies used to explore genetics and that is why we are here today. She asks how much background they have in genetics. The couple respond that it has been a while, since high school biology probably. Donna pulls out a thick, white, three-ringed binder. "We have over thirty thousand genes. As you know", she says, "our genes are like a blueprint of instructions. Genes are everywhere in our bodies and we can get at them through a blood test to look at chromosome structure". She flips the binder open to a page with several little black and white worm-like squiggles on it. "Our genes are on chromosomes. You can think of these chromosomes like a necklace and the genes are like the beads". She explains that in previous technology scientists could look at a blood sample under a microscope and see each of the chromosomes. She shows them that there are 23 chromosomes and that there are two copies of each chromosome. One copy is from your mother and one copy is from your father. "With new technologies, we are able to look for subtle changes. We can detect missing or extra pieces that are very small". She says you can

imagine that the chromosomes are like a map and the new technologies are like the little blown up insert on the map that shows one area in more detail. With your son's blood sample, we blew up each chromosome to look for missing or extra pieces. Donna then takes out a sheet of blank white paper and begins to draw. First she draws two vertical lines and marks a small x on one of them. She then writes "16" underneath the lines. Donna explains, when looking at your son's chromosomes with this new technology we have found that there is a small piece that is missing on chromosome 16. She writes the word "DELETION" in capital letters on the piece of paper. "When we look at the literature to see what other scientists have found in this region of chromosome 16 we find that there are two different sizes of deletions here, one larger and one smaller." She then draws two horizontal bars, one smaller and one larger. She explains that there are about 50 people reported and described in the literature with the larger deletion in this region but the smaller deletion is not as well understood. It seems to be more variable. There have not been any other reports in the literature with individuals with this deletion who are on the autism spectrum. However, some individuals have been described as having learning or behavioural difficulties. Donna draws another line and above it writes "range of difficulties". She explains that some genes are cause and effect and you can almost be sure that they will be on the spectrum if these genes are interrupted. Other genes, however, seem to be risk factors but are not totally responsible. At this point Donna stops and asks if the mother and father have any questions. The woman asks, "What does this mean for us?" Donna responds, "At this point in time we cannot give a more effective intervention. It is just information. But knowledge is power and we felt that it is important for you to know what we have found so far. There will be lots of new information in the next few years as technology continues to advance".

The meeting continues with Donna collecting information about both the mother and

father's family history. She asks if there have been others in the family diagnosed on the spectrum or with any other neurodevelopmental diagnoses. She creates a kind of family tree with circles and squares, writing in all the information about grandparents, aunts, uncles, cousins, and siblings. She also asks if there were any learning difficulties, speech problems or quirky behaviours in any of the extended family members. After several minutes, Donna explains that they would like to get a blood sample from the mother and father to understand if the deletion on this chromosome was passed down or if it arose spontaneously in their son. The woman and her husband look at each other and nod, saying they would be interested and willing to participate in this. From the stack of papers in the binder Donna produces two consent forms and leaves the room while they read through them. Donna and the younger student return about ten minutes later and Donna asks if there are any questions about the consent forms. The woman and her husband do not have any questions and they have already signed their names at the bottom. With this in hand, Donna leads them out of the office and directs them to the blood lab on the first floor of the hospital.

The couple walk silently out of the office. Waiting at the elevator in the hallway the father says he is a little disappointed that all they received was information, that it doesn't really change anything for their son Davey at this point. The mother agrees and says she had been hoping for more. "But" she says, "it is really interesting and hopefully some day it will make a difference, maybe not for Davey, but for some other family in the future". The elevator door dings as it opens and the couple walk in, heading down to the blood lab below.

5.9. Back into the Clinic

5.9a Diagnoses: Clinical and Research

When a family first arrives at the autism clinic to give blood for genetic testing, they

arrive with a previously given clinical diagnosis of ASD. This diagnosis will have been given by a paediatrician or family physician or perhaps even a neurologist. It is usually based on brief examinations of the individual and information gleaned from parents about the medical history and development of the individual. This clinical diagnosis is a criterion for being in the genetics study in the first place. When the family returns to the autism clinic for deep phenotyping sometimes years after their initial visit, following the genetic testing in the laboratory and the feedback session, they are involved in much more rigorous assessments. When the assessments are completed the individual will get a research diagnosis, which *usually* confirms the clinical diagnosis of ASD.

As I stated earlier, the protocol for the genetics study had recently been changed prior to my fieldwork. Previously, everyone received the rigorous deep-phenotyping assessments before the genetic work-up. According to the clinicians at the Autism Clinic, many of the participants wanted to participate in the genetic research because these diagnostic assessments are so difficult to obtain otherwise. There are long wait lists for these gold-standard tests. Children often remain for up to a year on waiting lists of educational psychologists to be tested. If a family is wealthy, these tests can be paid for and obtained privately. For many families this cost of private testing is out of reach and so they must wait. Participating in this genetic research, with its accompanying battery of clinical assessments included, was a means of obtaining assessments and was a big incentive for families to become involved. As the research coordinator stated, “I have never had to go out and actively recruit patients. In the nine years that I’ve been working here, there has always been a waiting list of people wanting to be in our study.” There was some concern, therefore, that the change in protocol would see a marked decline in families willing to participate in this research. During the following year, while I conducted my field work, they did not see a

decline in participants on the waiting list. There must be other motivations for people to be involved in this research, as the deep clinical assessments are no longer guaranteed, given only to those found to have clinically significant genetic variants.

After the family has received the genetic feedback another appointment is made to come back to the autism clinic at a later date in order to do all of the clinical testing or “deep phenotyping”. The purpose of these clinical assessments is to help interpret the genetic information by developing a more detailed picture of the physical and behavioural characteristics of the individuals in the family. Here I will discuss three important types of formal assessment along with informal conversations, which contribute to the phenotype information. These three assessments include the Stanford-Binet Intelligence Test (5th Edition), the Autism Diagnosis Observation Schedule (ADOS) and the Autism Diagnostic Interview Revised (ADI-R). These are gold-standard assessments for the diagnosis of ASD. These are primarily conducted by a practicing psychologist or psychology PhD students. In addition to these assessments, a digital photograph is taken of the patient and the parents in order to be used for a dismorphology exam, performed by a trained clinical geneticist. All of the deep-phenotyping takes place at the autism clinic.

5.10 Setting the Stage: The Autism Clinic

The large foyer of the grey office building contains a glass-covered desk with a list of all the offices and their floor numbers. Within the list, there are government offices, lawyers, and several offices and clinics associated with the hospital. A coffee shop bustles with activity as professionally-dressed people line up for coffee or muffins. The building is tall with twenty-four floors. As I step on the elevator several other people squeeze in beside me. Some are wearing hospital name tags around their necks but many are not. I step off the

elevator at the sixth floor. To the right is a law firm. I head to the left. A sign on the wall indicates that this is the Autism Clinic. An arrow below the sign directs me to continue down a smaller hallway to the right to find the door to the waiting room. I follow the arrow.

Stepping through the door to the waiting room, the florescent lights shine brightly. The room is about eight feet by twelve feet in area. There are green, vinyl padded benches pushed against two of the walls for people to sit down. On the wall opposite the entrance is a large sliding glass window. Small Smurf figurines and a little wild-haired troll are poised on the ledge of the window, inviting little hands to reach up and play with them. The friendly administrative assistant sits at her computer behind this window. The walls are light blue. There is a bulletin board reserved for articles and notices that pertain to ASD in adolescence and adulthood. On the far wall, there is a large bookshelf containing binders and pamphlets as well as videos. Some of the pamphlets are several years old. A shelf with several small, labelled cubby holes holds various toys and puzzles. A child-size table and two small chairs are placed in the centre of the room. Artwork drawn by children hangs in black frames along one wall. One frame hangs askew on the wall, empty. There is a recess in the wall beside the reception window where another locked door is located, always closed. On the back of the door are posters advertizing various research studies inviting individuals with autism to participate.

The administrative assistant has seen me and opens the locked inner door to let me through to the back. I'm here to observe some assessments today. The inner door opens and to the right is the administrative office. The carpeted hallway is narrow and leads past a few offices on the right. The first office is where Mary sits. She is a psychology PhD candidate and she does a lot of the testing for the infant sibling study as well as for the genetics study. She shares her office with another psychologist who is currently on a maternity leave. The

next office on the right is Dr. Morten's. It is much larger and holds a large desk as well as a round table and chairs. There is a window that runs across the length of the office. Filing cabinets and book shelves are crammed in against the walls. Across from these two offices, on the left side of the hallway are two other rooms. One room is used for testing and contains a small table and chairs as well as a brightly coloured play mat and lots of different toys. The adjacent room is very small and is used for observations.

Continuing down the hallway, there is a section with dividers. Claudia and Don sit to the right of the hallway (Don is a summer student in microbiology and hopes to go to medical school one day) and Florence often sits in one of the cubicles to the left. Florence is a research coordinator for one of the non-genetic studies but during my fieldwork she started working on phenotypic assessments for the genetic study. There are large beige coloured filing cabinets lining the walls. I've seen them being pulled open, the heavy drawers holding tightly packed patient files. There are well over two thousand patient files in this office. Further down the hall is another office on the right. This is where Loren sits. Finally, at the end of the hall is the large kitchen area with a large square table. This room also serves as the conference or meeting room. In addition to fridge, tea pot, toaster and microwave, this room has a white board and projector screen at one end. Windows at the far wall let in natural light. At lunchtime employees come in this room to sit and eat together.

Compared to the Laboratory X, the autism clinic space occupies a much smaller footprint. There are also far fewer employees here. At most, there are ten people who work here. I sit down at the table and wait until they are ready to do the ADOS testing that I will observe today.

5.10a Assessments: ADOS, ADI-R, and Intelligence Test

There are numerous assessments, both standardized and non-standardized as well as questionnaires that are filled out during the process of the deep-phenotyping individuals who have been involved in the genetics study. The three assessments I will present here are hallmarks of a research diagnosis of ASD and are considered by the clinicians I talked with to be gold-standard assessments.

i) Autism Diagnostic Observation Schedule (ADOS)

I am sitting in a very small room. With me are two other women. One is a PhD psychology student and the other is a project coordinator who has a Master's degree in psychology. There are three chairs in the room on which we sit down. Around me in this room are another desk and three other computer monitors and a recycling bin. Several boxes are piled up. At the end of the room, the wall is lined with a floor to ceiling bank of blue filing cabinets. In front of us, perched atop a desk is a video monitor, a panel with buttons and what looks like a joy stick. We are watching the interactions between the developmental paediatrician and a young three-year old boy in the room beside us. They hand me two paper booklets, two versions of the ADOS assessment. They are each holding these forms in their hands and writing on them every time the boy on the screen engages in any type of social interaction. At first, they are not sure which ADOS forms to use. There are different forms that correspond to different levels of child development (preverbal, early verbal, or later). The development paediatrician has never met this little boy before and has to determine through his interactions which of the measures she should use. She is "blinded" as to whether he has been previously diagnosed with autism. She will initiate a different set of interaction and play activities depending on where she thinks the child is positioned developmentally at

this point in time. At first the child is alone in the room with the paediatrician. The first part of the observation is called “free play”. The paediatrician sits in a small chair at the table while the young boy explores the various toys on a brightly coloured mat on the floor. He picks up some blocks. The paediatrician watches him and asks if he can build a tower. He ignores her, drops the block and moves onto a different toy. The paediatrician writes something down in her ADOS form at the little table. He flits around from toy to toy for a few minutes, picking them up, looking at them and then dropping them again. The paediatrician is trying to engage the boy and get his attention. She calls his name but he doesn't look or respond. The boy finds a figurine that he seems particularly interested in and holds it up for the paediatrician to see. She writes in her ADOS form again. The paediatrician gets down on the mat too. She shows him a bubble machine. It blows bubbles out and the little boy loves it. He is squealing with delight and chasing the bubbles. He wants to try it too. He says the word “bubbles” and everyone in the room with me, hovering around the video monitor, quickly writes this down. The boy is making eye contact and interacting a little more now with the paediatrician. She is laughing with him.

The child's mother enters the room and sits on a chair at the far wall. The boy runs to her and she gives him a hug. “Come see bubbles” he says. He is speaking a little more now that his mother has arrived. Everyone in the little room writes this down and they all seem to be switching to a different ADOS form, one that is targeted toward children who use phrase speech rather than the pre-verbal/ single word module. The boy comes back to the paediatrician while the mother sits on a bench against the wall. The paediatrician asks the boy to come sit at the table with her. They sit across from each other in small child-sized chairs. The table is not very wide and their hands can easily touch. The paediatrician asks him to pretend he is getting ready for bed and brushing his teeth. She asks what he usually

does. The boy is having difficulty sitting in his seat. He wants to use the bubble machine again. He ignores her when she asks about brushing his teeth before bed. He gets out of his chair and walks around to where she has placed the bubble machine. He wants it. The paediatrician says he can use it in a minute as a treat once they have played a little more at the table. The boy sits back in his seat, reluctantly. The paediatrician brings out a picture and puts it on the table. She asks him what the picture is about. From the little observation room, we cannot see what the picture depicts. The boy sits rocking in his chair and says something quietly. The paediatrician asks him if he likes horses. (It must be a picture of a horse that she is showing him.) She asks him what else he likes. He doesn't say anything. She gets out a picture book. She opens it up and asks him what is going on. He reaches up and turns the pages. He briefly describes what is in each picture. Again, he gets out of his chair and tries to reach the bubble machine. She lets him use it briefly. He is laughing and chasing the bubbles around the room. The paediatrician directs his attention

“Here's one. Try to pop it!” The boy follows her gaze and runs over to pop the bubble. His mother is laughing too and the boy is clearly enjoying himself. After a few minutes he is directed back to the table and the paediatrician takes out a small doll. She says it is the doll's birthday party! She has little plates on the table. The boy is uninterested. He says something about blowing out the candles on her cake. He sits back in his chair and doesn't seem to want to play. She asks if he wants to take a break and have a snack. No, he is not ready for a snack.

Once the ADOS is finished, the boy and his mother leave the room. This boy has participated in the ADOS as part of the infant sibling study, another study being conducted out of the Autism Clinic. He has siblings who have been diagnosed with autism and so he has been monitored closely at intervals since birth. Now they are going into the hospital to have their blood drawn for the genetics study. This is quite common at the Autism Clinic; a single

family participates in several on-going research studies and the researchers share tests across studies. It reduces duplication and saves time and money. If a child has an ADOS performed through the infant sibling study the genetics study can use this clinical (phenotypic) information to later help interpret genetics results.

We say goodbye to the little boy and his mother and then we all head down the hallway toward the kitchen at the back. We sit around a large table and compare our notes and scoring in the ADOS booklets. The coding is organized into five groups: language and communication, reciprocal social interaction, play, stereotyped behaviours and restricted interests, and other abnormal behaviours. The child is scored on several items in each category. He can receive a zero, one, two, or three for each item. For example, one item under the Language and Communication section is Overall level of non-echoed language. A zero is given if the child uses three or more words per utterance and some grammatical marking such as plurals or tense. A score of three is given if the child uses single words only or no spoken language. I listened as they talked about what tenses the boy used, pointing, looking, visual referencing. They said that vocally he would not get a zero. He whispers a lot. They went through the list of different items for each of the groups to be scored, comparing what they heard and saw and then giving a score. At one point one of the students who was in the room said she was having difficulty deciding between a score of one or two for some of the items. The developmental paediatrician who had experience doing the ADOS said that the way she decides between a score of one or two is she mentally tries to think through the list of things that the patient did well and then a list of things that are off. She then compares these mental lists and it gives her the distinction between a score of 1 or 2. A score of 1 has a longer list of good things and a score of 2 has a longer list of things that are off.

ii) Autism Diagnostic Interview – Revised (ADI-R)

The ADI-R is a detailed interview with the parents, which often takes about two or three hours to complete. The interview is historical in nature, asking intimate and involved questions about everything from the pregnancy, birth, early development and into school experiences, depending on the age of the child being clinically investigated. On three occasions I planned to attend and observe an ADI. I would make the 2 and a half hour journey to the Autism Clinic, however, each time the parent cancelled or did not show up to the appointment. Consequently, my description of the ADI is based on interviews with a psychologist and a psychology PhD student who conduct the ADIs at the Autism Clinic, as well as document analysis of the ADI-R questionnaire guide.

The ADI questions are divided into several topic areas: background, early development, acquisition and loss of language/ other skills, language and communication functioning, social development and play, interests and behaviours, and general behaviours. The background questions are designed to give the person doing the assessment an overall picture of what the “subject” is like. For example, questions are asked about family composition, past playgroups and schooling, or any current concerns. Early development questions deal with the onset of symptoms. For example, the examiner asks “how old was [subject] when you first wondered if there might be something not quite right with his/her development?” This section also contains questions related to motor milestones, toilet training and bladder control. The acquisition and loss of language/ other skills section contains questions such as: “How old was s/he when s/he first used words meaningfully, apart from ‘mama’ and ‘dada’? What were her/his first words? How did s/he show that s/he knew their meaning? [Get Examples]” Other questions try to understand whether the “subject” experienced a regression, losing a skill that he/she once had. For example, ‘Was

there ever a time that s/he stopped speaking for some months after having learned to talk?

The next set of questions relates to language and communication functioning and contains questions such as: “How much speech does [subject] have now?” Other questions are designed to illicit information on stereotyped speech patterns, social chat (small talk), reciprocal conversation, intonation, volume, rhythm, rate, pointing, nodding, imitation, and imaginative play. Social development and play questions ask the parent to describe the “subject’s” use of direct gaze, social smiling, directing attention, sharing, sharing enjoyment, offering comfort, facial expressions, favourite activities and toys, group play with peers, friendships. The interests and behaviours questions ask about unusual preoccupations, repetitive use of objects, compulsions, unusual sensory interests. For example, “Does s/he seem particularly interested in the sight, feel, sound, taste or smell of things or people? For example, does s/he tend to sniff toys or people inappropriately?” This section also asks questions about negative responses to specific sensory stimuli, difficulties with minor changes in routines or personal environment, hand and finger mannerisms. The section about general behaviours includes questions related to gait, aggression toward care takers or family members, self-injury, hyperventilation, and special, isolated skills. Special isolated skills include abilities that the subject has such as visuospatial ability (puzzles, patterns), memory skills, musical ability, drawing skills, reading ability, or computational ability.

The ADI is 85 pages long. On the top of each page is a brief summary of the purpose of the question or in some cases an operational definition will be given here to clarify what is meant by the question. For example, item 51 on page 45 is about social smiling. At the top of the page it says “defined as spontaneous smiling directed at a variety of people, including smiling back at someone smiling at her/him, smiling during an approach, and smiling as a response to what someone does or says to her/him”. On each page, below the purpose of the

question and operational definitions, are the question and a few probes that can be used to further specify behaviour. To the right hand side there is a scoring system. The interviewer scores each question in real-time, as s/he is going through the interview questions with the parent. Question 58, for example, is about inappropriate facial expressions. The scoring system is listed as follows:

0 = facial expressions almost always appropriate to mood, situation and context

1 = facial expressions slightly or occasionally inappropriate or odd

2 = facial expressions obviously inappropriate in several different situations

(SPECIFY)

8 = N/A (almost no variation in facial expression, appropriate or inappropriate)

9 = N/K or not asked

At the far right side of the page are two tick-boxes, labelled “current” and “ever”, used to determine if the behaviour being described is current or has ever occurred in the past.

Included in the ADI interview protocol is also an ADI-R Comprehensive Algorithm Form. A PhD student in psychology who conducted many of the ADI-R interviews explained the scoring system in one of our interviews:

Julia: How does the algorithm work for the ADI? Is there a scoring system?

P: There’s a scoring system and you have to be trained and get reliability on that. And the scores go from 0 where there’s nothing that indicates autism or any kind of developmental issue, to a score of one or two. Two or three are usually the highest you can get. So the diagnostic algorithm only uses scores of 0, one and two. So, a three turns into a two. There are other, in certain questions, in language or motor movement where if a kid has a severe physical disability or has a different type, like a stutter or something then you would put a different type of score. So each question indicates which number you should be putting in... They do give descriptions about what each score would mean and then

you're supposed to be scoring as you go along with the parent. So if there's anything that you're not sure about you have to really probe deeper.

On the Algorithm Form, the interviewer copies down the score given for specific questions. These scores are added up for each section and a total is arrived at. For example, section A is called Qualitative Abnormalities in Reciprocal Social Interaction. It is comprised of four sections with each section drawing on various questions from the ADI-R interview protocol. Different questions pertain to different subject ages, so that the questions involved in the algorithm for a two-year old are different than those included in the algorithm for a five year old. On the front page of the Algorithm Form there is a space for the score summary. The interviewer writes in the sum of all the scores corresponding to the questions in section A, for example. There is a diagnostic cut-off given for each section's total score. For example, section A has a cut-off of 10. If a "subject's" scores were above the cut-off scores for each of the sections, then the ADI-R would be interpreted as indicating ASD. This ADI information would be compared with scores for the ADOS and other questionnaires as well. Moreover, the clinician meets with the patient to get an overall impression. Several of the psychologists I interviewed suggested that clinical judgement is an important component of diagnosis.

iii) Intelligence Testing – Stanford-Binet 5th Edition

Another standard assessment that is conducted at the Autism Clinic is Intelligence Testing. The same PhD student who did many of the ADI's was also responsible for much of the intelligence testing at the Autism Clinic. I observed him conduct the testing and interviewed him about the process. In addition, several of the other people I observed and interviewed in the Autism Clinic described various aspects of the intelligence testing.

The first functional intelligence test was developed in France in 1905 by Binet and Simon. Initially, the test was not well received. Lewis Terman, from Stanford University bought the publishing rights from Binet for the sum of one dollar and in 1916 the first Stanford-Binet Intelligence Scale was published, translated and adapted from its original form (Viney & King, 2003). The Stanford-Binet Intelligence Scale, 5th Edition, was released in 2003. It is a one-on-one, individually administered test in which an examiner uses various cognitive tasks to assess the intelligence of an individual. The test is used on a broad range of ages (from two years to 85+ years) and can be used to test a wide variety of disabilities and exceptionalities. Intelligence is broken down into five categories or factors underpinning cognitive ability: fluid reasoning, knowledge, quantitative processing, visual-spatial processing, and working memory. Some of the advantages of the 5th edition over earlier editions are its game-like qualities with more colourful artwork, toys and manipulatives and its balance of verbal and nonverbal content. The game-like qualities of this newest edition are especially important considering the pervasive concern for examinee fatigue. Indeed, the testing that I observed at the Autism Clinic was often punctuated by several breaks as young examinees would often begin squirming in their seat after a little while.

As with the ADOS testing, I watched the Intelligence testing from an adjacent room through a video monitor. The intelligence testing room was quite different compared to the room set up for the ADOS testing. Two chairs were arranged on either side of a small table pushed up against one wall of the room. A round clock was mounted on the wall. The room was painted in a neutral colour and was, with the exception of the table and chairs, empty with no stimuli to distract the examinee from concentrating on the tasks presented to him or her. The testing consisted of various cognitive tasks that were worked through across three different booklets. The various factors (ie., working memory) contained different items or

tasks for the examinee to respond to or perform. The items would begin more simply and increase in difficulty. The books were set up like a tent on the table between the examiner and the examinee, with one page facing the examinee and the backside of the previous page containing scoring information and instructions facing the examiner. As the testing was in progress, the examiner recorded the scores for each item. In the exams that I observed, the child being tested was alone with the examiner while his or her parents waited in the waiting room. Once each of the three testing booklets had been worked through the psychologist would apply an algorithm to interpret the scores gleaned from the testing process. This information is then combined with scoring from other assessments and taken together they form the basis of a research diagnosis.

At this point, I have followed DNA as it has moved through many different places and spaces within the laboratory and clinic, being translated and transformed many times along the way. From blood, to extracted DNA it moved into the laboratory. Here it was sliced, washed, photographed, amplified, plotted on intensity graphs, compared to reference genomes, compared to other findings in the literature, displayed in PowerPoint presentations, run through a sequencing experiment, tagged with a barcode, validated through PCR, and written up in a research report. Out of the lab, the DNA was discussed in a feedback session with parents, represented in photographs of chromosomes, through metaphors of necklaces and beads, and blueprints. Moving into the clinic, the DNA is combined with phenotypic data gathered through standardized observations, interviews, and intelligence testing. A clinical report is written and given to the parents.

There have been several different humans involved in translating and transforming the products that have moved through these spaces: the patient and his or her family members, the developmental paediatrician, and project coordinator, the nurses in the blood

lab, the laboratory technicians in the DNA extraction lab, PhD students, post docs, technicians, and a wide variety of scientists at the Monday-morning meetings, genetic counsellors and medical geneticists in the feedback sessions, psychologists and paediatricians in the clinical testing.

There have also been a large number and variety of non-human actors that have connected to the DNA along the way as it has moved through the laboratory and clinic. Arms, hands, numbing cream, needles, blood, tubes, robots, slides, chips, ovens, pipettes, magnets, buffers, computers, mathematical algorithms, statistical pipelines, intensity graphs, research reports, clinical reports, diagrams and doodles, PowerPoint presentations, peer-reviewed manuscripts, consent forms, standardized observation schedules, scoring sheets, video monitors, toys, bubble machines and databases are but a few.

Thus far, I have not described what DNA or autism means to individuals but rather have focused on describing how autism is *done* through the interaction of human and non-human actors.

5.11 Entrance: Into the Family Home

Unlike the story I have recounted from the laboratory and the autism clinic, the story that I want to tell about the families involved in genetic research are based on interview conversations only. I was not able to observe these families as they went about their daily routines. I could not see with my eyes how autism was *done* in the family home. Through interview conversations, however, I was given glimpses of how autism and the genetic information these families have received is enacted in everyday life. I have tried to unfold the different ways that autism is materially enacted by these families. I wanted to at least offer a glimpse of how the genetics of autism is reassembled beyond the walls of the hospital.

5.11a Demographic Information of Parents

The people interviewed included parents from six families who had participated in genetic testing and received genetic feedback about autism. The interviews were conducted at least 8 weeks after the families received the genetic feedback. Five mothers and one father were interviewed. Four of the mothers who were interviewed described themselves as single parents. All of the participants had completed at least some college or university. When asked about ethnic background each participant described his/herself as Canadian. The current age of the child diagnosed with autism in each family ranged from eleven to twenty one. The age of the child at the time of the original diagnosis of autism ranged from three to eleven. Three of the six families had more than one child diagnosed on the autism spectrum. The specific genetic findings varied with each family, such that across the families a number of genes had been identified as associated with autism including: NRXN, SHANK, PTCHD1, and SH2B1. Some parents were not sure of the gene involved but were aware of the location, for example chromosome 16. All of the genetic findings involved copy number variations (deletions or duplications) found through microarray testing. In the following section I would like to discuss how autism is constructed in relation to daily routines and the process of diagnosis. After exploring how autism is enacted or done through daily routines and the process of diagnosis, I will then be able to describe how genetic information becomes entangled with the enactment of autism in the daily life of families.

During the feedback session, genetic information about autism is given to parents. At this point, this information enters entirely new networks as it becomes entangled with all kinds of human and non-human actors that make up the daily life of the family. The networks into which genetic information enters are elucidated by exploring the daily routines of children and families living with autism. All of the families described the importance of

keeping a routine. In the description that follows, I have cobbled together the daily routines gathered from each of the parents and presented them in one short account of a day in the life of “Bobby”. I have created an amalgamation of the stories, condensed into a single character named “Bobby” because I am concerned with the anonymity of participants and their family members. Bobbie’s routine is recounted in the third person, from a mother’s perspective.

5.11b Bobbie’s Daily Routine as Told by His Mom

Bobbie has always had a strict routine. From the time he was a tiny baby I became a single mother and so I always had to work to financially support our family. I had to get up and go to work every morning so the kids always had to get up early too. Bobby wakes up in the morning around 7:00 am. He is often in a bad mood and swears at me or picks on his brother or sister. I do my best to make a nutritious breakfast: pancakes or French toast, fruit, and milk or something like that. I make milkshakes with berries a lot because I think the berries are good for Bobby’s brain. I want to know that I’ve done my best to start him off on his day in the best way I can. Often, when I’m racing to get breakfast ready for everyone and to get myself ready for work Bobby will have a meltdown about something. This morning, for example, he demanded that I come to his room at once because he did not like the particular socks I had laid out for him to wear. “I don’t care what you’re doing mom; I hate these socks and I want you to get me new ones, now!” Eventually, we all scarf down some breakfast and I drive Bobby to school. My two older children take the bus to their school but I’ve always been nervous about putting Bobby on the bus. He can get taken advantage of easily. So I drop him off at his school. He is in an LD (learning disabilities) class but it is partially integrated. So he does take some of the usual subjects that other kids take, like drama or computers. I usually get called by the school, most days. Bobby spends a lot of time in the principal’s office and sometimes they let him practice being the secretary to give him

something to do. Sometimes Bobby gets sent home from school because he is acting out. So I've had to change my job, rearrange my work life so that I can have the flexibility to come home and be with him if I need to. Even though Bobby acts out and gets in trouble at school, I know he really enjoys it. It is the only place he has any real friends. He doesn't have any friends anywhere else. He goes to an amazing school with an army of people taking care of him.

So at the end of the school day I pick him up. School ends at 3:00 but I pick him up at 2:30 so he can avoid the commotion of the hallways when all the students get out of class. As soon as we get home he immediately goes onto his computer in his room. He likes Facebook and has thousands of "friends". My other two kids try to track him on Facebook; they're worried someone might try to take advantage of him. Around 4:00 he starts to talk about food. We have dinner. Then it's time for a shower. At 7:00 pm we watch *Wheel of Fortune*. At 7:30 we watch *The Simpsons*. At 8:00 he goes up to bed. He doesn't go to sleep then but he always went to bed at 8:00 and he can't get over that. He has to be in bed by 8:00 then even if he's not tired yet. That's how it goes, over and over, Monday to Friday.

In this short description about Bobby's routine, a slew of new actors are introduced that are not part of the actors of the genetics laboratory or the autism clinic. The description is very shallow and does not relay the kind of thick description gained from participant observation. Even so, one is introduced to socks, fruit milkshakes, school buses, principal's offices, Facebook, *Wheel of Fortune*, parents, siblings, teachers, and friends. The networks of the family home are further elucidated when the diagnostic process is considered.

5.11c Becoming Diagnosed on the Autism Spectrum

Although my research was not focused on constructions of ASD within the diagnostic

process, the diagnostic process was referred to by several parents in relation to their motivation for participating in genomic research. Two of the parents described getting a diagnosis quite quickly, by the time their child was three years old. For these children, early intervention was a possibility. For four of the parents I interviewed, the process of getting their child diagnosed with ASD was a long and arduous journey which was fraught with challenging encounters with physicians and school boards as well as misdiagnoses along the way. For these children, early intervention was not possible. Several of the parents knew very soon after their child was born that something was wrong. Severe colic and non-stop crying for hours at a time was described by some. Difficulty talking or walking was described by others. In these stories of diagnosis the binary opposition of either being on or off the spectrum began to crumble and fragment into particular sub-classifications within ASD. One parent retold the story of her son's diagnosis with Asperger's in the following way:

Mother: So he was eventually diagnosed in grade eight. So what happened was we had suspected it in grade four. He was identified as gifted, LD in grade four. And then a doctor, a paediatrician gave me a book about autism and I read it and it fit [my son]. You see he was very eccentric since he was little and he was brilliant, absolutely brilliant. At two and a half he could recite the Night Before Christmas. And he would tell me when to turn the page and it was word-for-word. So we knew. And he always had difficulty socially and sensory and then in grade four when he got identified gifted LD, like I said, the doctor gave us this book. But he didn't suspect it. You see we're both into sports and music. Well, I was into the arts. So our son was always involved in sports when he was little. So his gross motor was a little bit more developed. But he still had, he was still a bit of an awkward walker. But he was still very good at sports, especially football. So then, as the years went on, we found out more about him. Like in grade six I knew that he had a writing disability. He had difficulty doing things. But no one did anything about it so I finally took it upon myself in grade six to find out that he did have a writing disability. I had him tested. And then in grade eight they had 'Toonies for Autism' at his school. So they had somebody from the autism foundation come in and talk about autism. And he came home to me and he said, 'You know what mom, I have a lot of those traits'.

Julia: So he identified it himself!

Mother: Yeah. So then there were huge sensory difficulties and social difficulties in grade eight and his grade eight teacher didn't pay attention to his IEP. So he literally shut down before Christmas. So that's when we phoned a specialist, a child psychiatrist, and we got him in and he was diagnosed.

Another mother recounted the long and frustrating route to a diagnosis of Autism for her son in this way:

Mother: It was a long road. Right after he was born, everybody knew there was something different but nobody could put their finger on it. Of course, it took us eleven years to figure out it was the chromosome 16 deletion, right. But we noticed issues in his development, issues with tolerating formula when he was an infant and once he was around a year or so there were some issues with some milestones... But when I went to the doctor he opened up my file and said, 'you had post-partum depression after he was born, right.' And I said are you kidding me? Like he was telling me that I was crazy! So we continued to see developmental milestones not being met and we really started to see the stickiness, like he couldn't handle change. Change the colour of his socks and he'd freak out. He had this hat he had to wear. A hundred degrees and he still had to wear a wool hat.

I really had to kick down our family doctor's door to get a paediatrician involved. So we went to the paediatrician sometime between two and three, closer to three. And I had done my own research and I went in there and said I think he has autism. And the paediatrician gets out a list and he goes through and he checks them off and he goes, 'well the problem is he only has fifteen out of sixteen characteristics'. And I looked at him and said are you kidding me? And I asked what one is he missing and he said, 'well according to your statements he seems to sleep through the night'. And I said he screams for eighteen hours a day, of course he's going to sleep! ...So I had to fight the whole hospital board and this took another year and finally they came back and said they would do it. But by this time early intervention had also got us a referral to [Hospital X]. And I said I feel more comfortable going to [Hospital X] because other parents at our local hospital would go in for an assessment and they said we'd be in the waiting room and the staff would be arguing and then they'd compromise; one thought it was autism and one didn't so they'd call him Asperger's. It was a compromise. So I said, I feel better going to [hospital X]. I'm so glad we did. So we didn't actually get in there [hospital X] until [my son] was six and he was seen and given a diagnosis of autism.

5.11d How Does Genetic Knowledge about Autism Relate to the Daily Routines and Experiences of the Diagnosis Process?

In practice, the genetic knowledge that parents learn in the feedback session at the autism clinic does not change the routines of these families at all. As one mother said:

I found during that process, where you're all excited, like, 'wow, we have an answer' and it's like, nothing's different. Okay, we know what's causing it but it's going to be years before they can figure out if there's any treatment or anything else.

For all of the participants interviewed the genetic knowledge was practiced in an orientation toward the future. Some of the parents had difficulty getting their child diagnosed with autism and it is this experience that they hope to prevent for future generations through advancements in genetic testing.

I think the thing for me is you absolutely feel helpless. All you want to do is help your child and they sit there going we don't know what to tell you. Everything is a mystery. And I think at that point my hope was that some day they would be able to have some answers for parents.

These families who participated in the genetics of autism research are aware that the benefit of the research will primarily be felt by future generations of families. One mother stated:

How I feel is I know there is probably nothing that is going to help with my family but in future generations, putting my genes together with the others that they found had something in common. We could be part of the cure for the future. Finding out where this is happening in and what's going on and maybe there could be a test in the future to say hey, if you are breeding with this person, there is a high chance that you could have a child with autism or you have the gene. And you might decide who you're marrying. You would at least have the chance to say, hey I have the autism gene, we might not want to have kids. I don't know.

The ways in which the future is mobilized in expectations and motivations for engaging in medical technologies has previously been explored by Brown et al (2000). The genetic knowledge that the families received in the feedback session was also described as important

and beneficial in relation to family planning for siblings of individuals with autism. One of the mothers whom I interviewed had two sons with autism and a daughter who was not diagnosed on the spectrum. She said she planned on telling her daughter about the genetic results when her daughter was older. She said:

So if I said to my daughter, be careful [daughter] because you'll probably have a child with autism. It would be helpful for anyone to know that, right, at a certain age. I don't think they should know that before a certain age. I think if you knew that before a certain time in your life it could be very depressing.

During one feedback session that I observed two “unaffected” siblings were present. Both of these siblings were over 18 years old. They told the genetic counselor that they wanted to have their own DNA tested. Specifically, they wanted to know if they also had the copy number variation as their diagnosed brother. They wanted to know if they might pass this on to their own children some day. This idea of family planning was also a concern for some participants. One mother described her son's concerns about the possible implications of genetic testing:

But one of his concerns, he voiced it with [Dr. Morten], was that he was worried that the information taken with the research, that he was worried, I think it was [the genetic counselor] had mentioned something about possibilities for down the line for interventions. And he was concerned that it would be a negative intervention. In that if somebody knew they were going to have a child with autism would they abort the child? So he was concerned about the moral implications of that.

Participants talked about other benefits of receiving genetic information. For example, one mother described always wondering if she had done something wrong when she was pregnant or when her son was a baby. Receiving genetic information enabled her to stop blaming herself for her son's condition. She found out that her son's genetic variation was *de novo*, in other words it was a spontaneous mutation and was not inherited from either his mother or father. She stated:

I think in some sense, you know, before we had this piece, you always have this sense of did I do something wrong? Is this my fault? You're dealing with this child and you're going to all these places and in the back of your head you're wondering, what are they thinking? What did you do wrong? But, to realize the genetics of it all, you know, when you think back fifty years ago it was blame the mother, blame the mother. Those poor women.

Another mother described feeling a similar anxiety about what had caused her child to have autism. She stated:

I always often wondered what factors may have influenced it. If it was something in the environment, something I had done, blah, blah, blah. And then when you hear finally, ok, there is a genetic component you think, well, OK. You know, so they've discovered something. I mean, I had always wondered how it had come to be and always thought there could have been some genes involved. I didn't know. I had to figure out what it could have been. So I thought it could be environmental, did something happen in the womb? You know.

Another woman whom I interviewed found out in the feedback session that her son had inherited the clinically significant genetic variant from her. She too carried this variant and passed it down to him. During the interview she talked about the complicated feelings she had about learning the genetic information, a sense of relief as well as feeling guilt:

OK, I think at that point I felt bad in a sense, a certain amount of guilt. But I think also a certain amount of relief because now I could talk to my daughter and we need to really, and knowing now that there was something, it wasn't just something that happened during pregnancy. There was some sense of relief, you know, there was mixed emotions. But at the same time you've lived with it for so long that you know you're, whatever, this is the way it is.

Genetic information was also expressed by some parents as giving them a long awaited answer to questions they had been asking for years. One mother in particular described the difficulties of getting a diagnosis and how she had felt belittled by family physicians and paediatricians. She recalled getting a call from the autism clinic at 10:30 at night. She was dozing off watching TV in bed. Dr. Morten told her about their findings:

She said that it turned out that [my son] was one of the children with the deletion. I remember she said, 'so it's official. You're not crazy!' All the issues

with his walking and his speech, they're all related to that deletion on the sixteenth chromosome. I remember when she said it's official I wasn't crazy I asked if I could have it in writing. (laughing) ... I didn't sleep all night. It was kind of like all of a sudden the answer to everything. Like poof there it was. It was one simple thing that could explain everything.

For others, genetic information opened up more questions:

So my point is that I have more questions. So that's something I'd be interested in pursuing is finding out more questions about the gene, answers to the questions and what does the gene, what does NRXN3 mean compared to NRXN1? So I did have the meeting with [the genetic counselor] and then my husband had the meeting with [the genetic counselor] but with one meeting you still have lots of questions.

Thus, for families participating in autism genomics research, autism is, in part, constructed in relation to everyday routines and in relation to the experience of getting a diagnosis.

Participating in genomic research and receiving genetic information, the parents who participated in interviews with me describe a variety of experiences. Some parents felt genetic information gave them long-awaited answers, while others felt the information opened up more questions. For some mothers, the genetic results relieved them of guilt, while for others feelings of guilt were sustained and reaffirmed. All of the six participants who were interviewed described an orientation to the future, hoping that the genomic research of today would change the diagnostic process, opportunities for early intervention, and possibilities for family planning for people in the future.

5.12 Summary

In this chapter I have attempted to follow DNA as it moves around the laboratory, clinic, and family home in the process of genomic testing in autism. Starting with blood collection and DNA extraction I then moved into the laboratory. From here DNA was sliced, amplified or “denatured”, aligned to probes and primers, tagged with barcodes, scanned, and photographed. Intensity graphs are made along with comparisons with a reference genome.

Described in the language of CNVs and SNPs, DNA is talked about via PowerPoint presentations at meetings and classifications are later made as research reports are written up; a genotype is established. Here the DNA has exited the laboratory and enters into another network of actors in the Autism Clinic. Children played with bubble machines, toys; they made eye contact or they do not. Talked or remained silent. Gestures were scrutinized by clinicians in a tiny room watching through a video monitor. Parents were interviewed about pregnancy, infancy, breastfeeding, toilet training, friendships, school and other intimate details of family life. Psychometric tests designed to measure intelligence were administered; questions were asked and answered. Assessments were scored. A phenotype was established. Through the Laboratory and Clinic, genotype and phenotype data were brought together, a phone call was made to parents. Here, the DNA entered another network in the family home. Routines, socks, school buses, siblings, friends, bedtimes were the actors found here. DNA became entangled in new associations with guilt, futures, diagnoses, divorce, relief, questions and answers.

I have tried to illustrate, by following the translations of DNA, some of the different practices of the laboratory, the clinic, and the home. Through the practices enacted in each of these spaces, DNA is constructed in relation to very different networks of human and nonhuman actors. Knowledges that are produced within these spaces are intimately tied to materially heterogeneous actors. For the most part, this chapter has pushed down explicit discussion of the theoretical and philosophical ideas that informed my interpretations. I have, except for a few comments, attempted to describe events, activities, people and technologies in their own terms. The following chapters, however, will attend more explicitly to practice, constructionism and actor-network theory.

Chapter 6: From Problematization to Mobilization: An Actor-Network Theory Account of Translation

- 6.1. Overview of Callon's Framework for Translation
- 6.2. Problematization in Autism Genomics Research
- 6.3. Interestment in Autism Genomics Research
- 6.4. Enrolment in Autism Genomics Research
- 6.5. Mobilization in Autism Genomics Research
- 6.6. Conclusion

In the previous chapter, I laid out a story following the production of genetic knowledge about autism as it moves between the family, the laboratory and the clinic. As I traced the route through which genetic knowledge flows, I described some of the most important actors (both human and non-human) along the way. As I re-read this last sentence, something strikes me as not quite right, not really reflective of what I experienced in my observations and conversations during field work. It occurs to me that the word *flow* is what bothers me. Does knowledge flow through a route? What is concealed by this verb, *to flow*? This is what the next section must elucidate, the work, the tensions, the non-coherence and the strategies for bringing disparate networks of actors together in order to make knowledge appear to *flow*.

When I first thought through the layout of this dissertation, I imagined a general overview of the route through which genetic knowledge is produced in the first section and a deeper, more focused analysis in the second section. I realize, however, that it is not just a

matter of looking more closely, zooming in. Instead, I need to unfold an entirely different story altogether. One that if layered on top of the first story will align in some places and not in others. There are points of connection as well as areas that will not cohere. In Chapter four, the story is recounted in a linear, chronological fashion. The blood is collected from a child diagnosed with ASD, DNA is extracted, an array is run, the DNA is sequenced, it is discussed in meetings, written about in reports, and then conveyed through different charts, graphs, and diagrams in a feedback session with clinicians and parents. However, much of my data is not captured within this linear story. In order to convey more of what I experienced during my field work, I need to tell another type of story, introducing a few new actors along the way. I need to add another narrative layer by describing what happens to knowledge as a story of *translation*.

Translation, as it is captured in this chapter, has a very particular meaning, a historicity. It is situated within a specific place and time: 1980's French science studies. Nestled within actor-network theory, translation was first unveiled by Callon in 1986 as a story of scallops, fishermen and scientists. Translation, in this specific instance draws on Actor-Network theory and describes an ongoing process in which one actor becomes the spokesperson for several other actors. When an actor (human or nonhuman) becomes translated it becomes black-boxed, represented, and fronted by another actor. For example, when a scientist presents a Power Point slide that lists recently found candidate genes for ASD, there are several actors being translated within this slide, including: patients, DNA, microarray and sequencing technologies, journal publications, and distant laboratories and scientists involved in conducting experiments that discovered and validated each of the candidate genes. By invoking this specific notion of translation I am introducing a specific way of breaking translation down into four distinct phases: problematization, interessement,

enrolment and mobilization. Unlike the previous chapter, the story of translation is not necessarily chronological. Each of the four components of translation requires constant ongoing work in order for the network to be upheld.

6.1. Overview of Callon's Framework

One of the most often cited papers on the issue of translation in the science studies literature was written by Callon (1986). In this paper the authors outlined four components or 'moments' of translation: problematization, interessement, enrolment, and mobilisation. This framework for translation is grounded in three basic principles: agnosticism (impartiality between actors in a controversy), generalized symmetry (which explains conflicting viewpoints in the same terms), and free association (abandoning distinctions between the natural and the social). Callon tells a story in which fishermen and scientists came together in an attempt to increase the production of scallops. The scientists came with a technique for cultivating scallops they had learned from the Japanese. Neither fishermen nor scientists knew much about the relationship between larvae and adult scallops. The fishermen were worrying about dwindling stock in St Brieuc Bay. Callon captured the interdynamics between these actors (scientists, fishermen, and scallops) with his four moments of translation.

The first moment, *problematization*, refers to the process by which a particular actor attempts to define the nature of a problem and thereby rendering itself an obligatory passage point for its resolution. Translation involves the imposition of a particular way of defining a situation for others. The scientists in Callon's story set themselves up as an obligatory passage point by defining the problem; they want to know if the techniques used in Japan for cultivating scallops can be applied in France. Through this problem a network of alliances between actors is assembled: fishermen, scientist colleagues, and scallops themselves.

Interessement describes how one attempts to capture others in particular roles. In order to address the problem that they have identified as important, the scientists must convince the other actors to adopt certain roles and identities. The tools (towline) that the scientists put into the water in order to capture the scallops are an example of interessement. The scallop larvae are taken from their context and protected from predators. In order to convince the fishermen, the scientists hold meetings in which they show graphs representing the decline in stock in the Bay.

Enrolment depicts the scenario in which actors accept the roles assigned to them. Any of the actors may refuse. For example, the scallop larvae may not attach themselves to the towline device or the fishermen may decide to fish and capture all the scallops being preserved by the scientists. Enrolment highlights the negotiations that take place in order for actors to accept their identities.

Mobilization encompasses the methods used to ensure that the spokesperson for related collectives are not betrayed by the collectives or thwarted by competing spokespeople (Callon 1986). For example, it is not the fisherman themselves but their official representatives that sanction the research project proposed by the scientists. If all the actors are enrolled, the scientists are able to speak on behalf of all the fishermen and scallops. The scientists may go to a conference and present graphs and figures with numbers to a small group of experts. These diagrams and tables represent different populations of silent actors - scallops and fishermen - who have been mobilized, displaced, and translated into a graph. A host of alliances have been built up in order for the graph to exist. At any point the alliances may fall apart; the scientists may fail to enrol actors with their particular definition of the problem.

Callon's (1986) framework emphasizes the work that is needed to keep disparate

actors together in a group or network. Put in the context of the day-to-day activities of autism genetics research this framework highlights the negotiations and the trials that a research project must survive in order to be translated. In the remainder of this chapter I will address each of Callon's four moments of translation as they pertain to the various networks (laboratory, clinic and family) brought together in the autism genomics project. At the end of the chapter I will highlight how this framework might contribute to a discussion of knowledge translation.

6.2. Problematization in Autism Genomics Research

Problematization is a way of identifying and framing matters of concern so that the envisioned path to follow appears inevitable (Callon, 1986). Problematization does not only indicate the matters of concern but also sets up a particular network of actors as integral to the solution of the problem. There are always, however, other ways of framing a particular problem, alternative courses of action that could be pursued. Each way of framing a problem rests on differing sets of values and assumptions.

There are several examples of Problematization that I observed and recorded in my field notes. The most prominent of these was an advertising campaign distributed by a major Canadian newspaper. This campaign was sponsored by Autism Speaks, a parent-driven NGO whose aim is to fund genomic research related to autism. Through this campaign, autism was problematized in a particular way such that the genetic research conducted at Laboratory X became a natural, obligatory passage point for a solution to be achieved. I will first describe the campaign and how a particular problematization was presented.

On a large four foot by four foot bulletin board on one of the walls at the entrance to the research office of the Laboratory X hang several full-page newspaper advertisements. The advertisements are dated from the summer of 2010. Along side some Christmas cards

from participants in the genetics project, these newspaper clippings have hung on this board throughout my field work. They are an example of a highly visible public articulation of a particular way to problematize autism. For several weeks, between May 2010 and July 2010, a national newspaper displayed full-page advertisements, sponsored by Autism Speaks. The advertisements depicted a jigsaw puzzle, almost fully completed. A final piece was missing and remained to be filled in. Across the puzzle was a photograph of a famous person's face. Don Cherry, a legendary Canadian hockey commentator, for example, was presented in one of these campaign advertisements. On one day, the advertisement displayed a photograph of Dr. Lorenz (pseudonym), from Laboratory X, as the face in the puzzle. Along with his photograph was a quote, "I will not stop until a cure for autism is found". Within the ad some information about Dr. Lorenz was given. By having his photograph and that quote appear in this ad, Dr. Lorenz and his research were (likely non-intentionally) aligned with a particular way of problematizing autism.

In this problematization, autism is a disorder that needs to be *cured*. Genetic research and in particular research on copy number variations are offered as a means through which the problem might be solved in the future. Autism is described as the problem and a cure as the solution with Dr. Lorenz and the Laboratory X as an obligatory passage point between problem and cure. A large network of actors are implicated in this problematization: individuals diagnosed with autism, genes, award-winning scientists, all the equipment and robots in the laboratory, the human reference genome, technicians, project coordinators recruiting patients, the list goes on. The challenge is to get all of these actors to align themselves with this particular articulation of the problem.

6.3. Interestment in Autism Genomics Research

In order to address the problem as it has been identified, each actor in the network

must be given a specific role to play. This designation of roles is called interestment, according to Callon's (1986) framework of translation. Among the scientists, clinicians, and families I observed, interestment took many forms, perhaps the most visible of which was the letter of information and consent form, written by the research investigators and handed to potential research participants.

Early on in my field work, I observed a situation that highlighted some of the difficulties in getting actors to accept their defined roles. In this situation, a project coordinator was talking with a parent of a child on the autism spectrum. The parent was initially interested in becoming involved in the genetics research. She was eager to participate and had previously phoned the project coordinator several times in an attempt to get her child moved up on the waiting list. Claudia (pseudonym), the project coordinator, responded and a date was set for the child to come in and have blood drawn. Prior to this date, Claudia had sent the mother the letter of information and consent form for the research, so that the mother would have ample time to read over and consider the project. I attended the autism clinic on the day of the scheduled blood draw so that I could observe. When I arrived, Claudia explained that she had been on the phone with the mother all morning. After reading the consent form the mother was no longer interested in participating in the genetic research. She was concerned about the section in the letter of information that described implications for her or her child being able to get insurance. According to the project coordinator, this was a fairly typical concern:

It's one of those things that has to be in there to protect the hospital. And we don't know that, even the mom today asked something about putting that in their medical records. I told her, right now I don't have anything to put in your medical record, but if we find something that's clinically significant then we'll have to write a report and that possibly will go in your medical records. We've had families that have refused because of that. They don't want to be involved because they don't want it to affect their insurance. And we can't guarantee

because we don't know what's going to happen.

Each actor is involved in many different networks. In the scenario described above, the mother and her child are asked to play the role of patient. As part of this role they would be accompanied by another actor, the patient medical chart. The mother, however, is already potentially enmeshed in a separate network, one set up by her insurance company. She refused to accept her role as patient in the autism genetics research because the potential findings, if included in her patient medical record, could adversely affect her or her child's future insurance coverage.

Several examples of interestment take place in the laboratory. Here, attempts are made to capture a non-human actor, the DNA, in a particular role. First, blood or saliva are collected in a tube. The little glass tube is one way in which scientists try to physically capture DNA. Later on, microarray machines are brought into the lab, at great expense. The scientists try to make these machines play particular roles. For example, the hybridization machine must play the role of mixing genetic samples with Illumina probes. The array machine must be captured into the role of making florescent images. The human genome reference must be captured to play the role of representing the "standard" human.

6.4. Enrolment in Autism Genomics Research

Enrolment describes the negotiation process through which actors are convinced to play their allotted role (Callon 1986). Actors may refuse. A complex and dynamic dance occurs amongst the actors in order to get all the actors to accept their role and continue to play that role over time. If enough actors refuse to enrol, the network will fall apart. In Callon's article, the fishermen had to be enrolled in the network, agreeing to refrain from fishing the scallops in the bay during the experiment. The fishermen had been convinced by the problematization laid out by the scientists and had agreed to leave the scallop larvae

alone in order that they be further studied. The graphs and charts depicting dwindling scallop numbers had been presented to them by the scientists and had temporarily convinced the fishermen to suspend fishing. One night, however, the fishermen dissented and drugged the bay with their nets within the towline. The network set up by the scientists failed to capture the fishermen as actors and as a result the scallops could not be captured either. The network crumbled.

There are parallel examples of failed enrolment in the autism genome story as well. One of the crucial actors in the autism genome network is the proband (an individual diagnosed with ASD). Without probands the network could collapse. In the clinic, there are many tools used to assess and confirm a diagnosis of ASD. The ADOS is one of those tools. In the ADOS assessment, children are asked to play with various toys and engage in conversation with the examiner. As one psychology student at the Autism Clinic explained, however, sometimes the ADOS fails to capture individuals in a diagnosis of autism. She explained:

A lot of times, especially for the higher functioning kids, and especially girls, like girls with Aspergers, the ADOS does not capture autism very well. So, most of the time they will actually come out not autistic. They won't meet the criteria. But that doesn't mean they don't have autism. So we have to figure out ways to support our decision in giving them a diagnosis...[O]n the ADOS you score for things like if they don't talk a lot, but they're very chatty. But those things aren't what you score on the ADOS. They don't score for that but that is social impairment. So the ADOS itself doesn't capture those individuals very well.

Other means of capturing particular social impairments are needed in order to enrol these individuals in the autism genome network. The phenotyping visit is a two-day affair, during which time several assessments and discussions take place. If the individual is not captured as a patient in the ADOS, there are other assessments, such as the ADI-R, which will help to include and enrol more people in the role of patient. Moreover, several participants described

the crucial role of clinical judgement. Built up over time, with increased experience, clinical judgement is what allows a psychologist to make diagnoses when the ADOS does not. In this way, through multiple tools, the individual who eludes a diagnosis through the ADOS might still become enrolled in the network as patient.

Part of the work of enrolment is to ensure that individual actors remain committed to a particular problematization. In the context of the autism genetic research, autism had been problematized as something that required a cure, a cure which could be reached through genomic research. During my interviews with some of the participants, it slowly emerged that some of the participants whom I interviewed were not entirely comfortable with this particular way of problematizing autism. Some were concerned that when autism was problematized as needing a cure, with the obligatory passage point of genetic research, future outcomes could include solutions that were, in their eyes, undesirable. One participant who worked in the autism clinic stated,

Because you don't really know because the technology keeps changing, which scares me a little bit too. I'm worried that I'm going to be old and grey and then realize this study I've been doing my whole life is doing prenatal tests on people and aborting kids because of this. It's really going to bother me if that's what it comes to. But I feel like it could come to that. But it's going to be hard because it's not going to be one gene and you don't know. In one family two kids could have the same rare CNV, they don't look anything alike. One could solve some crazy thing and be a genius.

This research involves problematizing autism as something that needs to be cured through genetic research. The concern of the individual quoted above was the ambiguity of what the results of genetic research might lead to or be used for. In particular, she was concerned that genetic information might be used for prenatal diagnosis in order to prevent individuals with genes associated with autism from being born. (In deed, this participant's concerns are similarly discussed elsewhere in a burgeoning literature that has grown up around the

concept of geneticization (Lippman, 1992; Lippman, 1998; Nelkin & Lindee, 1995) and the ethics of prenatal genetic testing (Lippman, 1994)(Asch, 1999).

Another participant described her concern over the problematization of autism and specifically mentioned the newspaper campaign with the puzzle pieces. She stated:

Participant: The main concern obviously adults with autism have is what is the implication for this. What are you really . . . What is the purpose? Is it better intervention or is this going to go the way of Down's Syndrome? And are you really saying that you want to understand the genetics for what purpose? Why are we doing this research? I am also very mindful about who funds research. Like genetics and their taglines of their organizations. So when I hear someone say Cure Autism Now by the leading scientists here at [the hospital], what does that mean, what does he mean by that?

Julia: Is this the [newspaper] thing?

Participant: Exactly. That is a very Autism Speaks driven mandate and Autism Speaks believes in that I think.

She continued by explaining how she is involved in recruiting adults with autism to participate in the annual research conferences. She felt that they would no longer participate because they did not agree with this particular problematization of autism. She stated,

I've always been in charge of bringing adults on the spectrum to talk and I don't know if they'll do it. Once [Laboratory X director] came out with that 'cure' thing, I know many of my adult contacts wouldn't be comfortable now.

Thus, competing problematizations can pull actors out of one network and into another. The quotes above indicate that this participant was simultaneously engaged in a different network, one that was sceptical of the word "cure". Advocates of disability rights do not problematize autism, but instead problematize a society that does not offer resources and opportunities to support families living with autism (www.neurodiversity.com). Asch (2000; 2005), has put forth a social paradigm of disability, questioning whether disease and disability are the problem or whether the challenges associated with disability stem from

particular social arrangements that are amendable to change. This alternative problematization, brings together a very different network of actors: accommodation resources, educational resources, respite care, employment opportunities, etc. In the problematization of autism disability rights advocates genetic research is not an obligatory passage point in the network.

My research suggests that keeping a network of actors together requires constant work at every stage. Over the course of my field work, there were several instances in which the members of the autism genetics research at the Hospital publically articulated a particular problematization. Newspaper ad campaigns, radio and television interviews each contained a representation of the problem such that genetic research became an obligatory passage point, defining particular roles for various actors to play.

Another actor, integral to the autism genome network, is DNA. DNA must consistently be enrolled in order to be captured in the network. At any point along the way, through multiple experiments, DNA can refuse to be enrolled in the network. There are many examples throughout my field notes and interview transcripts that describe instances where DNA is not being captured and the scientists have to respond. For example, in order to acquire the DNA, a blood or saliva sample needs to arrive safely in the laboratory for extraction. I listened to a project coordinator describe in a Monday morning meeting an instance in which obstacles were met when trying to transport a sample. The lid had not been properly screwed on and the saliva leaked. The courier would not accept the package and refused to deliver it to the laboratory. In response, the scientists found a company that developed padded packaging specifically designed for carrying genetic samples. If the sample leaked, the package soaked up the sample and a cell line could still be established from this in the laboratory; the DNA could still be extracted and captured in the network.

Almost all meetings were, at least in part, devoted to enrolling DNA as an actor within the autism genome network. There were so many places in which the DNA could fail to be captured along the experimental pathway. One example that repeatedly arose in discussions between scientists was the issue of GC-rich areas on the genome. These are stretches of the genome that have a disproportionate number of G-C base pairs and fewer A-T pairs. These areas are very difficult to capture in Next Generation Sequencing. Unfortunately, one of the gene families recently found to be associated with autism, the SHANK family, is highly G-C rich. When I asked one of the molecular biology post docs to tell me more about the G-C problem I kept hearing about, this is what she said:

Post doc: SHANK 1, 2 and 3. So they have a really high GC content which means that a lot of the bases are G and C, not A and T. I don't know how much genetics you have...

Julia: I understand that part.

Post doc: So A and T, when they bind together, they only have two hydrogen bonds. G and C have three hydrogen bonds. So a GC bond is stronger. If you have a high GC content that region of the genome will be more tightly bound than an A-T rich region. Um, and that can make sequencing really difficult because it's harder to separate your DNA and it's just harder to use, well, it's hard to use data that's AT rich or GC rich but for different reasons. So if you want something easy to do you want a good mixture of bases and you want them all mixed up as well. So even if it's say 50-50 G and C but it's all GGGG, CCCC, AAAAA, that makes it difficult as well. So easy things are all kind of mixed and balanced. But the SHANK family have got a really high GC content so just doing any of the steps with them is more difficult. So, for a lot of the samples we've sequenced so far, we've got really bad data.

The post-doc continued by explaining that she spends a lot of time tinkering with the experiments to overcome problems like the GC coverage issue. She calls herself a “techno-nerd” because while other post-docs prefer to analyze the data, she enjoys figuring out ways of capturing more data and making sure it's real. The GC problem is just one issue that can

affect coverage of the genome. There are some areas of the genome that are repeat-rich. All of these issues can result in “dirty” data. The qPCR experiment, used to validate microarray results was described as being “dirty”. One day while walking through the lab, I saw a handwritten note taped to some machine (I’m not sure what the machine was for) that read, “This is a clean machine. Please, no pcr products!” I asked a participant why PCR and qPCR were considered “dirty” and this is how he responded:

It’s quick, it’s fairly cheap, and it can give you an idea but it can be very ambiguous. Like some I was looking at yesterday for example, the results are half way between deleted and not deleted. So how do you interpret that? My control samples look beautifully not deleted. My actual samples are kind of half way between a deletion and a no deletion and I’ve done it three times and I’ve got the same result three times. So what does that mean? And that comes up time and time again. Because a lot of experiments are kind of specific to a region and if that region just doesn’t, it’s just riddled with problems. So sometimes it can be great, it can take a couple of days, you get a really clean result, you think ‘great, my deletion is beautiful. It’s inherited from dad and it’s in the unaffected sib or it’s not in the unaffected sib. Beautiful’. The next day you do qPCR and you think, well what does that mean?

Thus, DNA has to be captured at several steps in several places within the laboratory. Even if it is captured by the microarray, it could still refuse to be captured in the qPCR, refuse to be validated. Certain regions of the genome are more difficult to capture than others. This has quite significant implications. At one Monday morning meeting, the scientists had just returned from a large international genome conference held in Montreal, attended by over 8000 people. On this Monday morning the scientists took turns around the table describing interesting talks or posters they had observed. One post doc complained that she felt there wasn’t anything new being presented at the conference, no new and exciting areas of the genome showing up. Another post doc responded. As usual, I was madly writing notes through this meeting and this is what I have captured about her response:

Heather says that some genes just sequence really well compared to others - so genes they

[at conference] are talking about are found in these regions for technological reasons. She's not convinced it is not highly dependent on the technological limitations. Other genes don't sequence very well so people are not finding mutations there.

In other words, some stretches of DNA are not being captured at various places in the laboratory. This DNA is failing to be enrolled, not only in the small, immediate network I observed at the Laboratory X, but these regions of the genome are not being captured by hundreds of other laboratory networks represented by posters and talks at the conference either.

As I stated earlier, much of the work being done in the laboratory can be thought about in Callon's terms as "enrolling" the actors. It is a continuous, on-going process that needs to be managed across several steps and stages in each experiment. One particular way of measuring the quality of "enrolment" is through computational analysis. An entire team of computer scientists is employed in order to measure and ultimately increase the quality of what is being captured by the various technologies in the laboratory. In Next Generation Sequencing, for example, all of the data is taken directly off the machine and run through the Exome Pipeline. Each indel (insertion or deletion) is given a quality score which indicates the confidence in calling that mutation. When the sequencer fails to "read" a nucleotide base from the sample, the pipeline will insert a dot and this later becomes replaced with a base from the human reference genome. The concern is that the scientists don't want data dumped because of one missing base in a read. Equally of concern, scientists also want to ensure that the SNPs they are reporting are *real*, that they are not artefacts of the technology. Complicated algorithms are applied in order to capture the most data, while still minimizing 'false positives'.

Callon's (1986) framework describes the many trials that a network is put through

and the constant work that is done in order to maintain the enrolment of all of the actors along the way. In the network he described, the towline did not initially successfully capture the scallops. Many alterations had to be made in order to get the scallops to play the role they were supposed to play in the scientist's network. Likewise, the fisherman had to be convinced and cajoled into accepting their role in order for the network to be maintained. Similarly, the autism genome network requires several actors to be enrolled. The proband and DNA, described above, are two of these important actors. The ongoing work of keeping actors enrolled was visible at every meeting and in each interview I conducted.

6.5. Mobilization in Autism Genomics Research

According to Callon's framework, mobilization refers to the process by which actors are displaced and represented in some other form by a spokesperson (1986). All of the trials and work that has ensured the enrolment of the actors are bracketed off. In the case of the autism genome network, mobilization is frequently achieved in the form of the research paper, published in a peer-reviewed journal. The patients, the DNA, the machines, consent forms, assessments, blood, saliva, technicians, pipettes, glass slides, glass tubes, coloured caps, classification scales, protocols, and robots – all of these come to be subsumed within the article. The authors of the article speak for these actors, as long as the network has been maintained. There are other examples of mobilization: a conference talk, a poster presentation, a PowerPoint slideshow. What carries the most weight, however, what mobilizes these silent actors and makes them travel farthest is the journal publication. Once mobilized in the form of a journal article, these silent actors as represented on a graph or a table will be drawn into hundreds of other laboratory networks around the world, if even for a short time as competing or collaborating scientists read the article.

All of these forms of mobilization, the journal article, poster presentation,

PowerPoint, are highly transportable, easily taken up and communicated. All of the work and effort done in the laboratory is represented in these mobilized forms. It is extremely time-consuming (it takes decades to develop a laboratory on the scale of the Laboratory X) and expensive to hold together a network of actors such as the one in the autism genetics project. This is why these mobilized representations are so coveted, so valuable. There is often a race to publication between competing laboratories so that all of the effort, the work of keeping a network held together, is not wasted. Talking to some of the post-docs and PhD students in the laboratory, I learned about the scavenger-like behaviour of the drug companies who attend the scientific conferences. One post-doc described the drug companies as “predatory”. They run around between posters at poster sessions taking notes about any new gene that might be implicated in a disease, peppering the presenter with questions about the details of the genomic location. In one meeting, I heard the director of the lab state that conference presentations are precisely where you’re not going to describe your most interesting findings, exactly for that reason.

Journal publications are more likely the first place where new experimental results are announced. As I learned from one of the assistant directors at Laboratory X, the journal publication is also important because the number of articles produced by a laboratory is ultimately what gets measured by funding agencies, and thus journal articles become an important form of mobilization for the laboratory and the genetic research reported in each article. More articles will result in more funding, which in turn enables further future research.

The importance of mobilization in the form of journal publications was visible in several instances in my field work. Often, PowerPoint presentations would include a slide with screenshots depicting several journal titles. For example, when trying to convey the

importance of the NRXN gene in autism research, one presenter flipped to a slide with the names of published articles that contained “NRXN” in their titles. The presenter could have just said, “I’m exploring this region of the genome where the NRXN gene is located because it is known to be associated with autism”. But, what if an audience member were to disagree and argue that NRXN is not where this presenter should be focusing? Calling up all the titles of the related articles, however, gives weight to what he is saying. Each of the titles represents an interesting experimental finding from a laboratory. Subsumed within each title is a huge network of silent actors. By listing the titles, the presenter is calling up all of these actors that were brought together and maintained in a network through all the stages of various experiments in all of these different laboratories. By including this list of articles in the PowerPoint, it is as if the presenter is saying to the audience, ‘go ahead, challenge me. But you’ll have to challenge all of these networks and the hundreds of silent actors that have been mobilized behind me and represented in these titles’. Thus, publication is an effective way to mobilize diverse actors within the genetics network.

The genetics group on whom my research is based are proving to be very successful at problematizing, enrolling and mobilizing actors. With enormous grant funding, high-tech, cutting-edge technology, an ever-flowing line-up of patient samples to be processed - this network appears to be durable with strong associations amongst human and non-human actors. The framework provided by Callon provides a way of examining the work that is needed in order for a network of actors to be maintained. Future improvements in technology, for example, will be a vital means of enrolling non-human actors, such as particular G-C rich genes that are associated with autism.

While an exploration of competing, alternative problematizations of autism is beyond the scope of my research, some participants suggest some ambivalence toward the current

problematization of autism in the genetics research project. Positioning genetics as an obligatory passage point is not what worries the individuals I interviewed. One could imagine a problematization in which genetic research is set up as the obligatory passage point to enable earlier interventions for children with autism. In deed, this was the problematization I often heard in the autism clinic. There seemed to be a flexibility in the way that autism was problematized within the different spaces of the laboratory-clinic network. It was only when the director of Laboratory X made a very public articulation about finding a cure for autism that a few participants became concerned about enrolment.

6.6. Conclusion

The four stages outlined by Callon apply equally to human and nonhuman actors. This framework allows for an account of translation in which agency is shared. In this way, it resonates with Pickering's dialectical mangle of practice. I am, in part, uneasy about including this chapter in this dissertation. In many ways, Callon's (1986) framework underscores the *political* nature of the translation process, drawing attention to all of the enrolling, convincing, and ongoing negotiations that are necessary to keep disparate actors playing their allotted roles. Indeed, Callon (1986, p.199) described his article as providing "a better understanding of the establishment and the evolution of power relationships...the capacity of certain actors to get other actors – whether they be human beings, institutions or natural entities- to comply with them". Doing fieldwork is itself a political process in which alliances were made between me, my supervisor, and the director of the laboratory field site, among other actors. In writing about the on-going work and negotiations that take place throughout the process of translation I have not conveyed the personal animosities between competing laboratories or competing scientists. While that may well be a part of the process of knowledge production, and this has been attended to elsewhere (e.g., (Latour & Woolgar,

1986)), I have tried to illustrate how the political transcends human-to-human interactions. The politics of translation is embedded in the non-human technologies, tools, protocols, DNA, probes, and reference genomes as well as the human actors assembled in the autism genetics network.

I have included this chapter because it is this political nature of translation that is noticeably absent in the KT literature. For example, “identifying a problem” is one of the key components in the CIHR’s Knowledge to Action (KTA) model. (This model will be discussed in detail in the final chapter of this dissertation.) In the KTA model the political dynamics of identifying a problem is not described. Similarly, the KTA model proposes stages such as “adapt knowledge to local context” and “select, tailor, and implement interventions”. In contrast, the notions of interestment, enrolment, and mobilization provide a new language and a novel entry point from which to critically approach the neutral representation of translation in the various components of the CIHR’s KTA cycle. The framework proposed by Callon (1986), which highlights translation as an inherently political process, may contribute to and enrich current understandings of the KT process in which the political is rarely addressed.

Chapter 7: Translations Amidst Difference and Multiplicity

Medicine is not a coherent whole. It is not a unity. It is, rather, an amalgam of thoughts, a mixture of habits, an assemblage of techniques. Medicine is a heterogeneous coalition of ways of handling bodies, studying pictures, making numbers, conducting conversations (Berg & Mol, 1998).

[M]edicine does not merely describe a pre-existing biological reality, but instead creates its own objects of analysis (Lock & Gordon, 1988).

7.1 Overview of Key Concepts

- a) Difference
- b) Multiplicity
- c) Coordination

7.2 The Practiced Individual with Autism

- a) The Clinically Practiced Individual with Autism
- b) Laboratory Practices of the Individual with Autism
- c) The Individual with Autism Practiced at Home
- d) Strategies of Coordinating the Multiply Practiced Individual

7.3 Autism(s) in Practice(s)

- a) Practicing Autism in the Clinic
- b) Practicing Autism in the Laboratory
- c) Autism in the Family Home
- d) Non-Coherence in the Practices of Autism
- e) Strategies of Coordination

7.4 Conclusion

In this chapter I explore the idea that medicine is not a unity, that a phenomenon can be practiced quite differently within the same hospital. Through the concepts of multiplicity and

coordination, I explore the tensions that arise when practices shape a phenomenon in divergent ways and examine what happens when these practices rub up against one another. In doing this I aim to explore the concepts of difference, multiplicity and coordination. The subsequent chapter will then consider how the concepts of difference, multiplicity and coordination might inform the notion of knowledge translation.

In order to consider these ideas I will examine two specific phenomena as they are practiced in the clinic, laboratory and home. The first phenomenon is the individual diagnosed with ASD. This may seem an unoriginal and over-worked choice. Social scientists have been complaining for years that medicine reduces the human body in different ways, that the unified person becomes dehumanized and fragmented as various parts are sequestered off, counted, imaged, scanned (Casper, 1998; Lock & Nguyen, 2010; Martin, 1987; Rapp, 1988). “Tsk, tsk” we might say as we read about the doctor who refers to a patient as the coronary in room B or the hysterectomy in the OR. This criticism, however, takes for granted the idea that there exists a patient as a whole. A unified person becomes the normative standard to which the reductions of medicine are compared. My research, influenced by scholars in the social study of science (Latour, 1992; J. Law, 2000; J. Law & Mol, 2002; J. Law, 2002; J. Law, 2003; J. Law & Mol, 2008; J. Law & Singleton, 2000; J. Law, 2007; Mol & Berg, 1994; Mol & Law, 1994; Mol, 2002; Mol & Law, 2003), starts from a different place. Following Berg and Mol (1998), I want to suspend the notion that the unified patient body exists as self-evident in the beginning, preceding the practices of medicine and instead focus on the practices that shape what counts as the individual with ASD. Through this examination the notion of a single unified patient body gives way to an image of a complex pastiche of bodies that are reduced in innumerable ways with various measurements, practices, habits, conversations, spaces and instruments. To say that the body

is reduced becomes uninteresting. What becomes important is to understand how these inevitable reductions that multiply with varying practices relate to one another, contradict one another, and coexist side-by-side one another. Understood in this way, the unity of the individual is an effect, a consequence of much effort and work to make differences cohere.

The second phenomenon through which the notion of difference will be explored is “autism”. Here, I want to compare how autism is enacted in the clinic, home, and the laboratory. This is a complex task as the multiplicity of practices that are found in the laboratory and clinic are layered with the complexity in the diagnosis of autism, a complex and heterogeneous diagnosis with a broad spectrum of clinical manifestations (Freitag, 2007). In the practice of autism genomics, however, the complexity of this diagnosis may be reduced. As I discussed in previous chapters, in practice, the complexity of the spectrum is often reduced to a binary opposition: patients, siblings, parents, family members in an extended pedigree were either on or off the spectrum. Diagnosed with autism or not.

Thus, in my analysis I will allow the binary reduction of the complexity and specificity within the spectrum to remain reduced and unproblematized, as that is how it was most often practiced by the participants in this study. Instead, I will focus on how autism (taken as a unified phenomenon) is practiced in the clinic, laboratory and home.

7.1. Overview of Key Concepts

Before attending to 1) the individual diagnosed with autism and 2) autism, as they are practiced in the context of autism genetics, I will first introduce a few ideas and texts that have influenced my analyses and interpretations presented in this chapter. Much of what I want to introduce here is intimately related to actor-network theory, previously explored in Chapter 2. Many of these concepts are rooted within and often extend actor-network theory

into new territory. In particular, I bring to the foreground the ideas of difference, multiplicity and coordination.

7.1a Difference

While the idea of difference is at the heart of much of what I have been reading and writing pertaining to actor-network theory and knowledge translation, difference is often an unspoken assumption subsumed within other concepts or ideas. I did not come across a formal analysis that focused squarely on the notion of difference until I had already begun collecting data for this project. The idea of difference is so simple, so obvious, that it had escaped my attention. It was an assumption that was always already there, just beneath the words I was reading and writing. When I came across a book by Berg and Mol (1998) titled *Differences in Medicine: Unravelling Practices, Techniques, and Bodies*, it struck me that this was a fundamental concept underpinning what I was exploring. In some ways, *difference* is at the very core of this dissertation. Knowledge translation is needed because there are differences amongst those who inhabit the laboratory, the clinic and the homes of individuals with autism.

With the notion of difference, scholars have begun to tease apart the assumptions of unity in a variety of contexts. Berg and Mol (1998) explain how the unity of Western medicine, for example, unravels when one considers the various techniques, measurements, technologies, tools, and specialized vocabularies found within various fields of medicine. Likewise the unity of the patient dissolves when approached in this manner. Finally the unity of the present, as a time that breaks from the past, becomes problematic when approached from the notion of difference. The present often contains traces of the past. Moreover, there are differences in the times that make up the present such as the beginning and end of a consultation. Thus, with a focus on differences, what was once taken for granted as a unified

whole can be re-imagined as containing diversity. This diversity, state Berg and Mol (1998) is a feature of any complex practice and is neither inherently good nor bad. We can attend to the generative places where different practices are creatively coordinated as well as to the sites of conflict and tension. Diversity and difference are not something to overcome.

Willems' (1998) work offers an example of how differences might be explored. He described and compared two cases of asthma. Willems suggested that the different treatment practices engaged in each case enacted different asthmas. Asthma is made different in the practices of Carl and Steven. Steven takes salbutamol, a bronchodilator which combats airway obstruction. Carl takes steroids which act against inflammation. Conventional wisdom might attribute these differences in treatments as reflecting different aspects of the same disease, distinctions between mild and severe asthma or differences in prescribing habits of the physician. Willems, instead, sets out to illustrate how drugs produce different asthmas and different lungs. At times, a single patient may have to engage in two different treatment regimes. Willems (1998, p.17) asked "how is this to be imagined? Do people indeed switch from one disease to another, from one body to the other? Do their airways consist of muscular tubes in one moment and of inflamed mucous membranes the next?" Through this research Willems illustrates how lungs and diseases may be practiced differently as the patient enters into multiple treatments which imply different geographies of the diseased body.

7.1b Multiplicity

Multiplicity is related to the idea of difference. An object multiplies as it is practiced differently in different contexts. Mol's work (2002), for example highlights the differences in atherosclerosis by comparing the practices of the clinical consultation and the pathology lab. In the clinical consultation, patients complain that their legs hurt when they walk and the pain

stops when they rest. A doctor might ask questions about where it hurts and how long the patient can walk. She might hold a patient's feet in her hands to feel and compare the temperature. She might feel the pulsing of the arteries in different places along the legs. Down the hall, through the closed doors of the pathology lab, however, atherosclerosis is practiced quite differently. A leg has been amputated and refrigerated, a cross-section of an artery is made, and cells are stained. The lumen of the vessel wall is measured. Under a microscope, the pathologist sees arteries with thick intemas. This is what atherosclerosis is in the pathology lab. The objects of the clinic and the pathology laboratory might coincide. The patient with pain on walking and a weak pulse in the clinic might also be found to have a thick intema in the pathology lab. This is not always the case, however. In some instances, a post-mortem reveals extreme atherosclerosis in a patient who never complained.

Through these examples of difference, Mol suggests that atherosclerosis, the disease, is not found within the body. Instead, it is performed through practices. As practices multiply, in different areas of the hospital, so too does a disease. According to Mol, it is not just that there are multiple perspectives of a single object. For her, more than that is going on. She is not interested in understanding the meanings or interpretations of atherosclerosis. When we focus on participants' perspectives, the observers multiply but the object is left alone.

A crowd of silent faces assembles around it. They seem to get to know the object by their eyes only. Maybe they have ears that listen. But no one ever touches the object. In a strange way that doesn't make it recede and fade away, but makes it very solid. Intangibly strong (Mol, 2002, p.12).

By foregrounding practices and all of the materials and activities involved, the disease itself is examined as something that is *done* or *enacted*, in practice. Thus for Mol, an object (whether it is a disease or a body) is allowed to multiply when we shift our attention from

differences in interpretations to differences in localized practices.

Mol and others have gone to great lengths to describe how differences are made to relate to one another, how they are sometimes coordinated and made commensurable. Cussins (1996), for example, offered a thoughtful account of how women seeking services of infertility clinics actively participate in constructing themselves in multiple ways. She refers to a kind of “ontological choreography” which takes place when the body is constructed in relation to technologies. She stated “the subject is dependent on the constant ontological dance between ourselves and our environments that changes how many descriptions we fall under, of how many parts we are built, and how integrated we are or need to be” (Cussins, 1998). The physical exam with the technology of the metal speculum brings into view the woman’s vagina, cervix, ovaries and uterus. The ultrasound allows follicles in the ovaries to be measured and counted. During a treatment cycle the woman is “rendered into multiple body parts” (Cussins, 1998). The patient actively orients herself in relation to the part of the body that is under scrutiny. If IVF treatment is successful the synecdochal relationship between objectified body parts and long-range subjectivity are maintained. Conversely, a metaphysical rupture ensues when treatments fail. In a single cycle a woman moves “from one to many and back again” (1998, p.193). Thus, the body multiple is, as Mol suggests, “more than one but less than many”.

It should be stressed, however, that this notion of multiplicity does not necessarily pose a problem for medicine. Different practices are distributed in different spaces and an object is transformed as it moves among sites of practice. Mol suggests, “that the ontology enacted in medical practice is an amalgam of variants-in-tension is more likely to contribute to the rich, adaptable, and yet tenacious character of medical practice” (Mol, 2002, p.115).

7.1c Coordination

There are many ways in which differences and multiplicity are made to relate. Law and Mol (2002) describe what they call “fractional coherence”, in which things are drawn together but not centred. Law draws on this metaphor of mathematical fractals which are lines that occupy more than one dimension but less than two. For Law, single, coherent objects are the *effects* or products. Focusing on the TSR2, Law (2002) begins with a thought experiment in which the reader of a brochure is to assume a naïve position. The reader learns that the TSR2 is an aircraft on one page. That the TSR2 is a weapons machine on another page, a map-making navigational machine on still another page. A naïve reader who does not take the TSR2 as a priori a single object will learn from the brochure that there are many different objects held by the name TSR2. Law then outlines several strategies of coordination used in the brochure to connect and coordinate the various TSR2s described. The brochure itself wraps up all these different objects into one physically bounded place; the brochure has a table of contents which hierarchically relates different elements together, and 3-dimensional perspectival drawings hold various elements together at different angles. Rather than starting with the assumption that an object is singular, Law suggests that we explore how various objects are made to relate and cohere. The singularity of an object is “precarious, uncertain, and reversible” (2002, p.36).

7.2. The Practiced Individual with Autism

In this section I explore how the individual diagnosed with autism is practiced differently in the clinic, the laboratory, and the home. I illustrate how the body multiplies when one focuses on different practices which draw together different networks of human and non-human actors. As such, I will recount many of the activities that take place within the different spaces in which autism genomics is carried out as they pertain to the individual

with autism. I also want to comment on the ways in which the body(ies) is/ are made to cohere and relate to one another. What I hope will become clear is that various technologies and non-human actors are integral to the differentiation of objects and to their coherence and coordination. The individual diagnosed with autism multiplies because s/he is practiced within different assemblages of actors that are brought together in various spaces and places.

Before continuing with my analysis of the various practices of 1) the individual with autism, and 2) autism, I would like to make a brief comment about the experience of treating these two epistemic objects as separate. That is, treating the individual as separate from a diagnosis. During the process of acquiring ethics approval from the Hospital X ethics review board, I first had to pass an internal scientific review in the autism clinic. For this internal review I had to present a research proposal. At one point in my proposal I used the phrase “autistic individual”. This was immediately jumped on by all four of the reviewers sitting around the meeting room table. No, no. The correct way to phrase this was “individuals with autism”. Intrigued by the importance of this wording I asked if they could tell me more about the preference for this particular phrasing. I learned that the clinicians felt the phrase “autistic individual” carried a meaning that the person *is* autistic, that autism is part of who they are. Conversely, they felt the phrase “individuals with autism” conveyed the meaning that autism is just something the person *has* but it is not who that individual *is*. Since the separation of individual and autism was clearly important to the clinicians, I have attempted to keep these two objects of analysis separate. In practice, these two objects of analysis were not as cleanly separable, or distinct as the clinicians suggested. The individual and autism are intimately entangled, with different practices of autism implicated in the different practices of the individual/ patient body. Autism and the individual are often co-constructed in relation to one another.

7.2a The Clinically Practiced Individual with Autism

What I call the clinic is actually a research unit inhabited by various clinicians who perform clinical testing, monitoring and surveillance. The activities, technologies, and recordings that take place in the spaces that form the clinic perform the individual with autism in particular ways. Even within the clinic, a single human is performed in several different and sometimes conflicting ways.

i) Practicing the Individual as a Social Being

As has been described in Chapter 5, the clinical testing carried out in the autism clinic is highly standardized. These tests are conducted in relation to schedules or scales that are considered the “gold-standard” for autism diagnosis. In all of the observations, the paper documents were being closely followed and written on by the participating clinicians. In this way, the patient was being constructed or performed in relation to very specific guidelines in each of the different testing scenarios. These testing situations were highly controlled environments, such that the size, colour, objects and people found in the room would be similar in any testing situation. One of the first tests I came to observe in the unit was called the Autism Diagnostic Observation Schedule (ADOS). Clinicians must be trained (disciplined) in the ADOS to ensure that the test is being carried out and scored properly. In this test the child is placed in a room with toys. There are various versions of the ADOS, tailored for the developmental stage of the person being tested (pre-verbal, phrase speech, etc.). While the clinician is interacting with the child, s/he is also writing on the ADOS document, which is about 15 pages in length. Simultaneous to this, in another room connected via video monitor, other clinicians are marking in the ADOS schedule. On several occasions I was also given the schedule and expected to write in it as I observed.

The ADOS for Phase II (phrase speech) consists of 14 different tasks including: 1.

construction task; 2. response to name; 3. make-believe play; 4. Joint interactive play; 5. conversation; 6. response to joint attention; 7. demonstration task; 8. description of a picture; 9. telling a story from a book; 10. free play; 11. birthday party; 12. snack; 13. anticipation of a routine with objects; 14. bubble play. On the first page of the ADOS there is a box containing the child's information including their ID, date of birth, gender, chronological age, the examiner, and the date of the evaluation. Subsequent pages are set up such that the tasks appear on the left hand side with a brief description and the right hand side is an empty space in which notes are to be written. All of the tasks afford a different way of evaluating the child's social interactions. Specifically, the ADOS rates five different areas: language and communication, reciprocal social interaction, play, stereotyped behaviours and restricted interests, and other abnormal behaviours.

While watching the interaction on the video monitor the other people in the room with me were silent so that they could hear what the child was saying. The little camera lens could be moved by a joy-stick in order to orient our view to the movements of the child-clinician interaction. In this little room we followed along the ADOS schedule, marking in examples of language use or play as they pertained to each task. Occasionally, someone would whisper, "what did he say?" At times one's gaze would be directed at the schedule, writing in an example, instead of at the monitor observing the interaction. The room was often intense with concentration as the raters did not want to miss any interactions. The observers in the little room would write down examples of the child showing shared enjoyment (this was common in the bubble blowing exercise) or using facial expressions to communicate feelings, pointing, or engaging in imaginative play with figurines or dolls.

Through the ADOS the clinician is oriented to the patient as a more or less "social" being. The patient is practiced as a social entity, one who navigates social interactions. The

patient is quite literally performed in this way, as an audience of evaluators observes the contrived interactions, the props of play things are placed on the stage, and the script of the ADOS is closely followed.

ii) Practicing the Individual as the Thinker/ Knower/ Puzzle Solver

Another test in the clinical unit, the Stanford Binet Intelligence test, was routinely practiced. Through this test the patient was performed as a cognitive being, a thinker/ knower/ puzzle solver. Unlike the ADOS test, in the Intelligence test the eye contact or experiences of shared enjoyment for example, were not of relevance. The patient as a social being was bracketed off. The multitude of play objects included in the ADOS to provoke play and interaction between the patient and the clinician administering the test were noticeably absent in the physical context of the Intelligence test. In this scenario the room was bare except for a table and two chairs and the little flip charts that sat on the table between the clinician and patient. Whether the child whispered, yelled, or sang the answers was not important; with eye contact or without; in this context what mattered was whether the child answered the question correctly or not.

As with the ADOS, the Stanford-Binet Intelligence test is highly standardized. The examiner wrote down the verbal answers given by the patient while following along with the various components of the test. The test would sometimes take hours with the examiner allowing the patient to stop for breaks and snacks along the way. The test is divided up into different booklets, each focusing on a different task.

During one session I observed, for example, the clinician asked a boy who looked to be about ten years old, “which letter is missing from the picture?” Later he asked “what’s happening in this picture?” following this he said, “Tell me what each word is: apple, dress,

dog, hat, parrot, puddle, factory, allow, lend, eyelash, curiosity, skill”. The boy was not sure how to define curiosity. He sat in his chair wiping away tears, clearly upset that he doesn’t know the answer. When the clinician reassured the boy that he was not supposed to know all the answers and that the same sets of words are used for adults the clinician was responding to the boy as a social being. The boy was communicating, through tears and in his verbal responses that he was feeling upset. This would be a highly informative interaction in the ADOS test; I imagine the observers in the little room would be madly writing notes in the margins of the schedule trying to capture all the verbal and nonverbal details of this social interaction. In the intelligence test situation, however, the clinician did not write any of this down. All that is captured are the boy’s words that he has spoken in trying to define ‘curiosity’. This is because the intelligence test practices the patient as a thinker/ knower/ puzzle solver. The social interaction in which affect is communicated is not relevant to the specific incarnation of the individual that is practiced through the intelligence test.

iii) Practicing the Diachronic Individual through the ADI

A third way in which the individual is practiced in the autism clinic was through the autistic diagnostic interview (ADI-Revised). This was a standardized interview that takes place between a clinician and the parents of a child on the spectrum, designed to elicit a detailed historical picture of the child. Through this interview, the individual is practiced as a temporally located being. The interview asks questions about when the individual achieved various developmental milestones (such as walking and talking); it also asks about school performance and friendships. In some ways, the ADI-R captures similar information as the ADOS and the intelligence testing, but it does so in a way that is diachronic. The individual with autism is performed as a changing, growing person who has inhabited different places

and situations over time. The ADI seeks to understand a more global historical overview of the individual from the parents' perspective(s).

There are many other ways in which the individual with autism is practiced in the clinic. For example, the consent form practices the individual with autism as a voluntary research subject. The photograph taken of a individual's face practices him/ her as a unique constellation of physical traits. The appearance of the patient's photographed face is later interpreted and labeled by a trained clinical geneticist as dismorphic or not. Moreover, in the clinic patients come to be known as members of families. Clinicians may become aware when families are going through difficult periods, such as divorce. Personality traits of family members may be recalled when a patient is discussed. As such, in the clinic patients also often come to be practiced as members of an extended family.

7.2 b Laboratory Practices of the Individual with Autism

I would like to turn now to some of the ways in which the individual with autism is practiced in the laboratory. In the spaces of the laboratory, through a variety of technologies, the individual with autism is translated many times. Each of the technologies goes about ordering the individual in different ways. At various points these orderings are brought together and made to cohere or relate to one another.

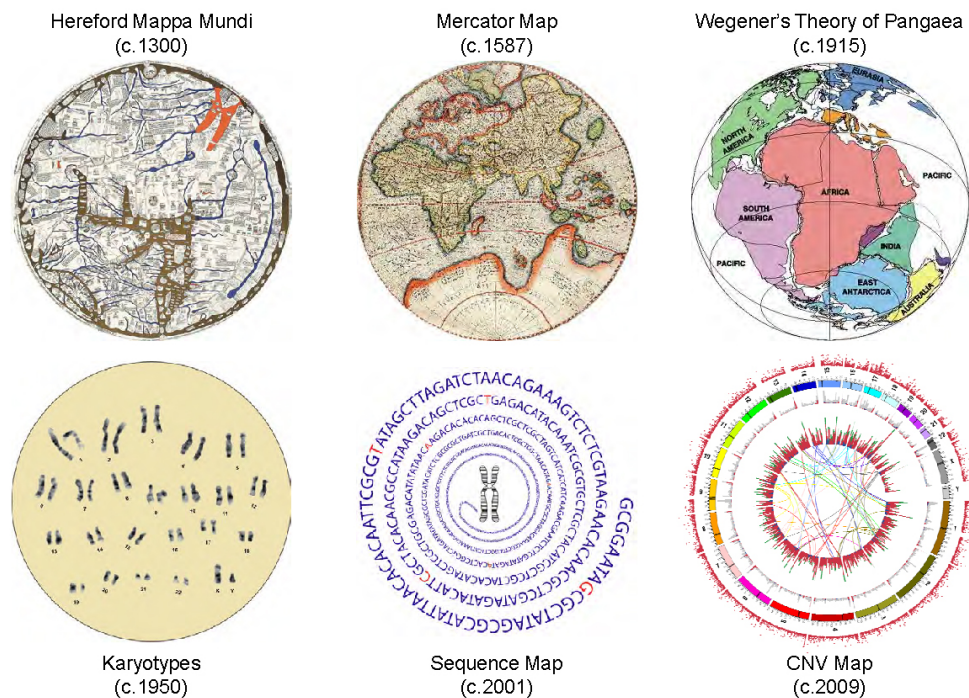
i) Practicing the Individual with Autism as a Geographic Entity

The individual with autism may be practiced in the laboratory as a geographic entity. Hanging prominently on the bulletin board inside the main office of the genetics laboratory is a collection of three world maps: the Hereford Mappa Mundi, the Mercator, and Wegener's Theory of Pangaea. Below each of these world maps is a map of the human body: the chromosomal/ karyotype map, sequencing map, and CNV map. I learned that it was the

director of the laboratory who combined these maps on this sheet of paper, a creative signpost to the work being done within the laboratory: something akin to cartography. Just as each of the world maps portrays a particular kind of world, so too is the human body practiced slightly differently through the various maps constructed in the laboratory.

Figure 7.1: Image of Maps Pinned onto Laboratory X Bulletin Board

Figure 7.1



Through several of the technologies in the laboratory the individual with autism is practiced as a kind of geographical entity, composed of genetic building blocks of various sizes and resolutions. Microarray and sequencing technologies in the laboratory reduce the individual with autism such that a string of nucleotide bases is made to stand in for the individual. At a slightly larger scale, in cytogenetics, the individual is practiced as a set of microscopically visible chromosomes. The particular components that are brought into view

by various technologies reassemble the individual with autism in different ways. Practiced as a geographical entity, there are many different tools in the laboratory that set out to map the individual with autism. Just as a geographer has tools that she uses to map a region of the earth (compass, GPS), so too does the scientist use a large number of tools to map the patient body (e.g., see Appendix B for list of tools needed for various stages of Next Generation Sequencing experiment).

The individual with autism is at times collapsed within a geographical location. For example, a line from the minutes of one of the Monday morning meetings reads,

“ - 16q23.3 deletion who is on the waiting list to have an assessment so not 100% autism at this time”.

The state of a particular location, whether the genetic material is deleted or duplicated or somehow rearranged in this single marked place, becomes the placeholder for the individual person. Practiced in this synecdochal way the individual is 16q23.3, the twenty third band on the short arm of the sixteenth chromosome. The part stands for the whole. In other instances, the body is practiced as a series of locations, each location with a particular address. The Next Generation Sequencing lab manager stated:

So at the end the instrument will look at all these pictures and try to assemble the correlation. There's actually a physical address. So the instrument knows 'I have a bead here and that bead is on the same place in all those pictures (Interview with NGS manager).

In the geographic body, the distance between locations is also important.

There might be other types of regulation that go on. In some cases it might be the actual physical distance between two genes that is important. So imagine, I don't know this is just a hypothetical situation, imagine something has to bind somewhere to have an effect. If the effect is distance dependent and you delete

something in between then the distance will be wrong. So the regulation might not work (Post-Doc in Laboratory X).

The practice of the body as a geographical entity also transforms the scientist into a kind of geographer of the body. In constructing the individual with autism as a geographic entity the scientist is also co-constructed. The body becomes a road of sequence and the scientist is transformed into someone who must map this road. One scientist explained:

So say you have this, you line it up and it's 3.1 billion bases long. You have this road of sequence in front of you.

In mapping the geographic body, the scientist must become oriented to the different landscapes constructed through different technologies. For example, when looking at a Genome Browser together, a scientist explained what we were seeing on the screen in the following way:

So when we say upstream and downstream, we mean relative to a gene. So, a gene is always transcribed or translated, that is, made into a protein in one direction. So the arrow on the figure will let you know which direction that is. So it's made this way. So this is the first exon, second exon, third exon, fourth exon. So the PatchD1 actually just has two exons. And upstream of the gene, or sorry, downstream. So when we say, upstream is before the start. So in the case of the PatchD1 the gene was this way. (Ankit)

The scientist-geographer is re-oriented in relation to a mapped patient body. The scientist is at once working above the genome map and also *in* the genome map.

Say you want to amplify a specific region of the genome, you would design what is called a primer, which would specify whereabouts in the genome you are. And then you can use the reaction to amplify that region from the primer. (Heather, interview 2)

The individual with autism when practiced geographically is an unknown territory, comprised of distinct landscapes depending on the technologies being used in its exploration. The scientist practiced as a geographer or cartographer approaches the patient landscape as something that can be mapped out in comparison to a kind of master map, the human genome. Prior to the mapping of the Human Genome, the human body contained huge tracts of territory that were uncharted. With the master-map of the Human Genome, however, any little region can be located.

So after the whole genome sequence was known, if you have a sequence of DNA, like you isolated a particular sequence of DNA, you can kind of map it to that genome sequence and see which chromosome it lies on and which gene it might effect. So it sort of gives you a whole new context of location in terms of on a genomic scale. (Ankit interview)

Practiced geographically, certain regions of the patient body are more or less elusive to the scientist-geographer. Certain areas refuse to be captured, ordered, and mapped out with the current technologies:

But the issue there is GC rich exomes, they don't sequence well. In certain places, if you have more than 80% GC, chances are you are not going to get coverage there, even if you keep sequencing.

There are a multitude of examples that I have collected from the laboratory observations and interviews in which the individual with autism is constructed as a geographical space to which the scientist must orient herself with the aid of various technologies. In the laboratory, the mapped body is a socio-technical assemblage. It is materially heterogeneous; at times composed of cells and nuclei, at other times made up of chunks of nucleotide base pairs, and still at other times the body is practiced as a series of single nucleotide bases. The various

technologies construct the body as having different resolutions and orient scientists to the body landscape in different ways.

ii) Textual Practices of the Individual with Autism

In other instances in the laboratory, the individual with autism was also practiced as a textual entity. During an interview with a project coordinator in the laboratory, the textual practices of individuals were stated in this way:

Project coordinator: [Describing a CNV] It's a chunk, that's exactly what it is; it's a whole stretch of nucleotides that are either missing or duplicated. And the easiest analogy that I could say is if you summed up the genome as a book, a really large book with a bunch of sequence, these smaller nucleotide changes which we typically call a single nucleotide polymorphism or variant is just like a typo in the book. OK, and these can mean nothing, they can be a severe mutation; they can be anything. A copy number variation is like where you would have a piece, a page either missing or duplicated and so it's a whole bunch of nucleotides involved. And some of these are just normal variation and everybody has them and they could be acting on something. And then in other cases we find these variations in genes that we think are involved in autism.

This analogy between the human genome and a book has been dominant in this discourse for some time (Kay, 2000). It seems to be particularly prevalent when scientists explain genomic work to a lay audience. Certainly, the members of the laboratory did not talk to each other in this way. The excerpt above, for example, was taken from my first interview in the laboratory, when it was clear to the project coordinator that I was unfamiliar with the work and materials of the laboratory. It is a well-crafted analogy set aside to be pulled out and used when explaining laboratory work to non-scientists.

The ordering or assembling of the individual with autism as a text, however, is not only practiced when talking to outsiders. When I open up Nvivo and read through my interview transcripts and observation notes, the practicing of the individual with autism as a text is present in almost every document. In particular, the technologies used in sequencing (in which the body is explored at the highest resolution) involve materials and procedures that when practiced together assemble the individual with autism as a text to be read. I became familiar with Next Generation Sequencing through interviews with two of the post docs running the NGS machines and analyzing NGS data, the manager of the NGS facility, and a bioinformatics specialist. I also observed various steps in the NGS experiments and read the protocol developed by the company that manufactures the technologies and materials required in these experiments. As I observed, listened and read about NGS, I became familiar with the textual practice of the human body. Obviously, in sequencing, the nucleotide bases are labelled A, C, T, G and as such the body is practiced as a string of letters to be read. One of the steps at the beginning of sequencing experiments is called “library prep”. Scientists create a specific library out of the individual patient’s sample. A participant from the NGS lab explained:

So the library preparation is the step where we have to process the sample...And so for Next Generation Sequencing, you get the DNA, for the exome, what you need to do is you have to select all the exomes of that genomic library. So when you are sequencing what you need to do is to deep sequence all those regions.
(NGS lab manager)

This participant went on to explain:

So when you are doing the library preparation you start with a lot of DNA and then you lose DNA as you go. So at the end, the reason you have to start with a lot of DNA is that you’re expecting that you’re going to be losing DNA

randomly. So you expect that in the final library you will have all of the DNA fragments that you need. (NGS lab manager)

The individual with autism is practiced as a kind of textual entity through the activity of library preparation. Another way in which the individual with autism is practiced as a textual entity is in the concept of “read depth”. One of the common concerns raised in the weekly sequencing lab meeting was the issue of “read depth”. Read depth pertains to how many times a particular nucleotide base is captured in an experiment. A deeper read depth allows for more confidence when a particular nucleotide at a particular location is different than expected, different from the reference genome.

So one of the reasons we need to have a lot of reads mapped to a particular region on the genome is because the error rates for some of those machines are higher than they are for Sanger sequencing. So usually we are expecting to see at least twenty reads mapping to a particular position. So when you are looking at something and you see a mutation for example and you say, ok, there are lots for reads here and I know, you can for sure say, this is really a mutation. But let’s say you only have five reads, and let’s say two of them actually point to a mutation and the other three are exactly the same as the reference then you have to make a judgment call there. Is this real? (NGS Lab Manager)

Some technologies allow the patient body to be read more deeply than others. A biostatistician was looking forward to receiving the first data set collected from a newly upgraded sequencing machine and stated, “The SOLID 5 is supposed to give us way more read depth. So a lot more reads are supposed to be sequenced”. This idea of read depth was further explained to me in an interview by the NGS manager:

So basically what you are doing is, since you have millions and millions of fragments, let’s say, if you’re thinking about one exome. You maybe have one

fragment that will cover the whole exome, another that will cover just parts of it. So basically when you start aligning you have all these different fragments spread all over the exome. So when they are talking about read depth what they mean is on a particular position, how many reads are actually covering that position. (NGS manager)

In the laboratory, the individual with autism is often practiced as a textual object. Depending on which aisle you find yourself standing in and depending on the technology being used the body is practiced as analogous to either the individual letters, words, or pages in a book. The body is quite literally read and scientists may be likened to copy editors, honing in on any typos that appear in the body as text.

Sometimes the body is practiced in different ways (as a geographical entity and as a text) in the same instance. These practices are made to cohere. Consider the following statement.

I just pulled out how the intensity chart looks like. This is a good graphical view. So it's P1428 [patient number]. So you can see the different chromosomes.

In this single statement, the individual with autism is being practiced in several ways: as an intensity chart, a graph, a de-identified research subject, and a set of chromosomal building blocks. The various translations of the patient body constructed through various technologies are pulled together.

In other instances various technologies practice the individual in ways that do not necessarily cohere. During my fieldwork, I found that many of the different technologies were practiced separately. For the most part, researchers were either involved in microarray experiments or in sequencing experiments. Researchers would be aware of research going on through other technologies but an individual researcher tended to concentrate their research

in either sequencing or microarrays or cytogenetics. As a single sample traversed the laboratory, it was passed amongst different hands which were trained to practice a sample in ways quite different from one another. The human body as constructed through one technology did not always cohere with the body constructed through another technology. For example, I interviewed a post-doctoral fellow whose main interest was comparing microarray data and NGS data for a single patient. (Conversely, most of her colleagues in the laboratory were concerned with populations.) She found that there was not always a straight-forward relationship between the microarray and NGS data.

The sequencing data is really new. So we've only reported out one family so far that had a single nucleotide variant which resulted in a stop-codon in an important gene. They had microarray data but the microarray data didn't come up with any of the sort of normal suspects, the common things like the NRXNS or Neurolygens or SHANKs. They had other copy number variants but of unknown clinical significance. So it wasn't until they did the sequencing that they could figure out, 'ok, there's actually something going on here' it's just at a different level of resolution.

At one level of resolution, the CNV, a particular mapping of this individual did not distinguish between patient and non-patient, case vs control. Practiced in the laboratory through the microarray technology, this body is not constructed as diseased, pathogenic. When the body is constructed in another resolution, the NGS, the body is pathologized. Thus, the same individual body is constructed differently, in ways that do not overlap, by different technologies within the laboratory.

7.2c The Individual with Autism Practiced at Home

At home, individuals with autism are practiced through familial relationships - a son or daughter, a sister or brother – or in relation to particular roles they play or abilities they

might have – student, athlete, musician, scholar. The individual with autism constructed in the home is, again, entirely different from either the constructions of the laboratory or the clinic. In the laboratory the individual with autism is practiced as a geographical or textual entity and in the clinic the individual with autism is practiced as a cognitive or social entity. While the laboratory and clinical constructions of the individual are sometimes practiced in the home, there are many other ways in which the individual with autism is practiced here as well.

There were a few instances in which the individual with autism was practiced as a patient in the home. For example, the individual is constructed as a patient when parents described their child in relation to a previously imagined non-patient child. One parent stated:

I honestly think it's an issue with coping. The one thing for me, I had difficulty coping and then it got to a point, I actually had a parent say to me, 'you know, it's OK to be angry. Just be angry'. I think you get to a point where you realize, you don't have the kids you thought you were going to have. You have to grieve that and then in doing that you're able to accept the one you've got.

This mother described going through a period of mourning when their child received a diagnosis of autism; at this point she realized she did not have the child she thought she was going to have. Through a diagnosis of autism a child is transformed into a patient. In this way, the individual with autism is constructed in an emotional process of coming to terms with the non-patient child that parents originally anticipated. Ironically, while the mother mourned for the child she thought she was going to have, she also simultaneously had to fight for her child to be recognized as a patient outside of the home. The mother who made the statement above recognized that something was medically wrong with her child and in this way constructed him as a patient in the home. She said:

I really had to kick down our family doctor's door to get a paediatrician involved. So we went to the paediatrician sometime between two and three, closer to three. And I had done my own research and I went in there and said I think he has autism. And the paediatrician gets out a list and he goes through and he checks them off and he goes, 'well the problem is he only has fifteen out of sixteen characteristics'. And I looked at him and said 'are you kidding me?' And I asked what one is he missing and he said, 'well according to your statements he seems to sleep through the night'. And I said 'he screams for eighteen hours a day, of course he's going to sleep'!

Thus, this participant described a situation in which her son was first constructed as a patient at home and only later, after much effort on her part, was he recognized and practiced as a patient in the clinic and laboratory.

While the laboratory and clinical constructions of the individual with autism are sometimes practiced in the home, there are many other ways in which the family member with autism is practiced in the home as well. In the home, the family member with autism is also practiced as a *biographical* entity, with a past, present and future beyond that of a genetic map. This biographical nature of the patient is practiced in the clinic to some extent; through assessments such as the ADI-R the patient is constructed in relation to past events, language and motor milestones for example. Armstrong (1998) has described how medical records reconfigured the clinical patient as a biographical entity. Through medical records, such as the patient chart, "clinical problems were not simply located in a specific and immediate lesion but in a biography in which the past informed and pervaded the present" (D. Armstrong et al., 1998). In the feedback session, the individual with autism is also practiced in relation to the future; in particular, the individual is practiced as a possible future parent whose offspring may inherit genetic variants. In the home, however, the individual with autism is practiced biographically within a temporal trajectory that is deeply entangled

in the biographies of families and friends. The milestones that are captured in the clinic as aspects of an individual biography (captured in a single patient chart) are enmeshed in the life course of family members in the home. Parents quit jobs, change careers in order to accommodate the special needs of their child. The individual with autism at home is practiced through an entangled relational biography. This deep entanglement of the individual biography is not captured in the practices of the patient in the clinic.

7.2d Strategies of Coordinating the Multiply Practiced Individual

i) Feedback Session

During the feedback sessions which I observed, the genetic counsellor first began by describing how the individual with autism is constructed in the laboratory. She enacted the individual as a geographical entity by describing recent technologies which look for subtle changes, missing or extra pieces at particular places on the genome. She showed parents black and white photographs of chromosomes. She used map analogies to help families understand how new technologies allow scientists to zoom in on particular locations on the genome, like an inset on a map. She told them that they have a deletion or duplication at a particular location and gave them details about the size of the deletion or duplication. She drew two vertical lines with the number 16 underneath and marked an “X” on one of the lines. She was orienting the family to the physical address, the place within the individual’s body where the deletion had been mapped.

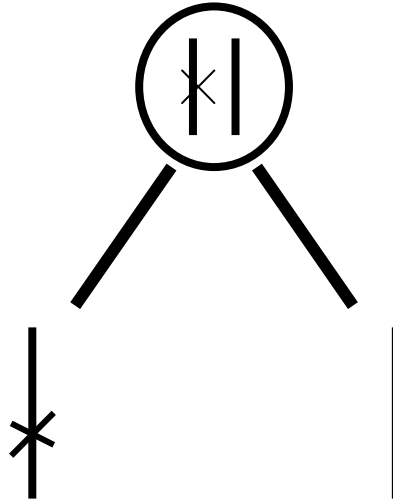


She then described how there have been different sizes of this deletion found in various individuals diagnosed with autism. She draws two more vertical lines on the paper to indicate the size of the missing chunk of DNA.



Here she switched to clinical constructions of the individual with autism. The individual was constructed as a social being and a thinker/knower/puzzle solver as she described that those with the smaller deletion have been reported in the literature as having behavioural difficulties or learning difficulties. Finally, the genetic counsellor asked the family to help her construct a family pedigree, gathering information about extended relatives and any developmental or psychiatric problems they might have experienced. During the making of the family pedigree, I observed that families often began talking about the individual with autism as practiced in the home, in relation to school, friends, specific family gatherings or events, traits or idiosyncrasies that revealed themselves throughout the

practices of daily living. They were practiced as deeply entangled relational biographies.



ii) Patient Identification Number

There are other strategies for coordinating the different practices of the individual with autism found within the laboratory, clinic and home. For example, the patient ID number labelling the tube of extracted DNA ensures that the geographical practices of the laboratory are kept in association with the clinical practices of the patient. This ID number is placed on the top of the research report and is carried into publications as well. All of the information contained within a single patient chart carries the same ID number. In this way, all of the various ways of practicing the individual with autism in the different spaces of the hospital are made to coordinate with one another, to relate to one another.

iii) Cases vs. Controls

The individual with autism was also practiced in the laboratory as a “case”, which was always practiced in relation to “controls”. Cases are samples that have a clinical diagnosis of ASD. The clinical practices of diagnosing individuals with autism were found within the laboratory practice of the individual as a case. In the practicing of the individual as a case vs. control the clinical constructions of the patient are made to relate to laboratory

constructions. They are coordinated. Controls are samples that do not have a clinical diagnosis. Practiced in this case-control relationship, patients are performed as a statistical entity in relation to a control population. The database of genomic variance, for example, is a technology which practices patients statistically, in comparison to a control population.

So what we do, when we find something like this we interpret this variant in the context of the DGV. So this is from thousands and thousands of individuals in the general population and after looking at all those thousands and thousands people have reported only these many CNVs and there's nothing similar to what you see in the two patients.

In another interview, the case-control relationship was explained further:

Now I told you that everyone has CNVs like even normal healthy people. But the difference is, what they kept finding is that patients with psychiatric disorders they tended to have these rare deletions or duplications which are not generally found in the normal population. Or even if it is found it's really, really rare. So it would be less than 1 in 10 thousand people or one in twenty thousand. Whereas in cases, so they are rare in cases as well and they might be one in a hundred as opposed to one in twenty thousand in controls. So these rare deletions kept cropping up and perhaps most interestingly these rare deletions seem to affect genes in known brain function more often than not. So using this you sort of get an idea of which genes are being deleted. And this still only explains a very small percentage of cases. So if you took a hundred psychiatric cases and put them on arrays you'd probably get something of relevance 15 to 20 percent of the time.

Through the Database of Genomic Variants, scientists can examine a single region of the genome and the program will tell them how often a variant at that location is found in controls and if a variant has been found in other cases. In this way, the individual body is practiced as part of a population. A PhD student in the lab explained,

These studies usually get a tonne of cases and they also get controls from the general population. So ideally when you say controls you want them to not have whatever disorder you're studying. But that's a little difficult to do in practice for something like autism or ADHD because a) it's relatively common in the general population and b) it's hard to find funding to actually phenotype controls. Because physicians are hard-pressed for time and there's not enough money to line up a hundred people on the street and try to see if they have ADHD or Autism. So what people generally do is take a huge number of controls, like let's say in the thousands, put them on arrays, but not phenotype them too well. Then take cases, these are phenotyped pretty well because they actually come to the hospital or their paediatricians. So they actually have problems and they come to the hospital so they are pretty well phenotyped. So they put them on microarrays or sequencing or whatever and then you see particular regions of the genome which have either point mutations which you can detect from sequencing or they have CNVs, like deletions or duplications and see, exactly like you said before, look at genes in which two or more people who are unrelated or two or more people with the same disorder who are unrelated genetically, they have mutations in those genes. Whereas in the controls you have either none or extremely few. So these might still be rare in the cases. Like out of a hundred only two might have them.

In the above quote, several practices are juxtaposed in relation to one another. The individual with autism is a geographical entity with different genetic regions that can be mapped in different resolutions (point mutations or duplications/deletions). The individual with autism as a thinker/knower/ puzzle solver and as a social entity is held within the practice of clinical diagnosis, which turns the patient into a case. This individual is also a statistical entity and practiced in relation to populations. In the practicing of the individual with autism as a case vs a control, different constructions of the individual are coordinated and come together.

7.3 Autism(s) in Practice(s)

In the previous section, I focused on the individual with autism as a site in which to explore multiplicity. The ways that the individual is practiced in the clinic and in the laboratory may or may not cohere. I now turn to another example in order to explore this idea of multiplicity: autism as an entity in itself. In the context of the clinic, autism is invoked

through psychological tests (ADOS, ADI-R, intelligence tests) and through taking a “history” through discussions with parents and teachers. In the context of the laboratory, autism is invoked through alleles, the human genome, microarrays, PCR, and “next generation sequencing”. Each of these contexts has disciplined ways of focusing, centering on specific features, so that autism is either arrived at or ruled out. In the clinic, various tests are scored. In the laboratory, a risk classification from one to four is given. These scores and classifications that are produced in the clinic and laboratory result from vary different practices in either context. In each of the settings, autism is *done* in different ways. When the scores in the clinic correspond to the risk classification given in the laboratory, the different autisms practiced in each setting are made to cohere. In the following section I will describe how autism is practiced in the laboratory and the clinic. I will then provide examples of how these different enactments of autism are sometimes coordinated as well as instances in which the practices do not cohere, at least, not yet.

7.3a Practicing Autism in the Clinic

“Nothing can replace clinical judgement. It all comes down to clinical judgment.” (Interview with psychology student at an autism clinic)

In the clinic, autism is practiced as a nuanced and diverse phenotype. In the clinic, autism has a complex social, behavioural, linguistic nature. Autism is practiced through direct interaction between people. It is also practiced as something that unfolds over time. One of the assessment tools that are involved in the clinical practice of autism is the ADI-R. Through the ADI-R, autism is practiced as having a temporally unfolding ontology. One participant explained the ADI-R in this way:

I start off by asking what were some of the first things that alerted them that there might not be something quite right with their development. How old were they at

that point. When did they start toileting, bowel, we ask about specifics around imagination, about types of play they engaged in. The ADI, it all depends on the age of the child. So let's say the child is above age five, you ask about current functioning but you also ask about what it was like between four and five. If the child is younger than that then it's around current functioning. You ask about language development, first words, first phrases, you ask about gesture use, how many gestures, you ask about facial expressions, anything that's under communication. Then you ask them about friendships, interest in other children, things like that. Then there are questions around behaviors, repetitive behaviours. So specific interests, unusual interests, how do they deal with changes in routine. (Mary – psychology PhD Student)

Thus, different situations, events, important milestones in one's life become implicated in the clinical practice of autism. Toilet training, friendships, first words – all of these enter into the network of autism as it is practiced in the clinic. There are various assessments which are used to capture autism in the clinic. As such, autism in the clinic is practiced as a particular score arrived at by a diagnostic algorithm. One participant explained the scoring in this way:

There's a scoring system and you have to be trained and get reliability on that. And the scores go from 0 where there's nothing that indicates autism or any kind of developmental issue, to a score of one or two. Two or three are usually the highest you can get. So the diagnostic algorithm only uses scores of 0, one and two. So a three turns into a two. There are other, in certain questions, in language or motor movement where if a kid has a severe physical disability or has a stutter or something like that then you would put a different type of score. So each question indicates which number you should be putting in. (Mary – psychology PhD student)

Scores from these various assessments are looked at together to form a large picture of whether or not an individual has autism. The various clinicians who conducted the assessments come together to do a “formulation”, discussing strengths and weakness of the

child. These formulation sessions last about two hours. They take into consideration several rating scales and standardized assessments as well as informal information gathered by chatting with parents and interacting with the child. Based on all of this the clinicians make a decision about whether the individual has autism or not. The clinicians compare what they observed and heard in their meetings with the individual's family with the criteria of autism that is listed in the DSM. One participant stated:

So impairment of social interaction, impaired communication and stereotyped behaviors and things like that. And then a lot of it just seeing whether the information we gathered matches those things. (Clinical Psychologist)

At times, an individual receives scores on the various assessments that are considered "borderline". In these cases, clinical judgment is particularly important in the practicing of autism. Some assessment tools practice autism in a particular way that may not capture various nuances within the autism spectrum. For example, through the ADOS autism is practiced as a lack of verbal communication.

A lot of times, especially for the higher functioning kids, and especially girls, like girls with Aspergers, the ADOS does not capture autism very well. So most of the time they will actually come out "not autistic". So they won't meet the criteria. But that doesn't mean they don't have autism. So we have to figure out ways to support our decision in giving them a diagnosis... On the ADOS you score for things like if they don't talk a lot, but they're very chatty. They're actually very chatty but then it comes to a point where it's like a fine line between do they understand are they being too chatty, like someone may not want to listen to them anymore. But those things aren't what you score on the ADOS. They don't score for that but that is social impairment. So the ADOS itself doesn't capture those individuals very well. So they will actually score . . . their scores are under basically on the ADOS. (Janine – psychology PhD Student)

In clinical practice, ASD is a complex set of behaviours that are teased out through various assessments and interactions with patients. Scores from these assessments are assembled together to construct a nuanced understanding of ASD. While individuals are either given or not given a diagnosis of ASD, within that diagnosis there is much variation in the way that autism can be practiced.

7.3b Practicing Autism in the Laboratory

To describe the practice of autism in the laboratory is complicated, largely because autism is a clinical diagnosis. A lack of laboratory findings does not preclude a clinical diagnosis of autism. Indeed, there is no need for a genetic component for a clinical diagnosis of autism. In the laboratory, however, phenotypic information is required to interpret the genotype information produced. It is only after the genotype information has been coupled with an autism phenotype that the genotype comes to be recognized as causing or contributing to autism. The genotype can never stand alone as meaning autism. There could be individuals who have a genetic variation consistent with autism that do not display the phenotypic characteristics of autism, and are therefore not diagnosed with autism. However, certain mutations are becoming closer to standing in for a diagnosis at the clinical level. Certain mutations are repeatedly found to have an autistic phenotype. Certain CNVs or SNPs are becoming recognized in the laboratory, according to one post-doctoral fellow, as “the usual suspects”: the NRXNs, the SHANKs, the Neurolygens.

Autism is ontologically fuzzy and ambiguous as it is probed in the laboratory. Its genetic ontology, the genetic nature of its existence is only achieved after its clinical ontology has been established. There is a complicated reversal that occurs in which autism is first clinically identified through the tests and examinations carried out in the clinic.

Following this, a whole bunch of work is done in the laboratory which sometimes results in genetic findings being reported. If the genetic findings segregate with the clinical findings across the family pedigree, then the genetic ontology is recognized. In these cases, autism becomes genetic in nature. The genetic ontology is used to explain the underlying cause of the clinical nature of autism. Here, autism multiplies; it has both a clinical nature and a genetic nature. However, if genetic findings do not segregate with the phenotypic findings of a family pedigree then a genetic ontology for autism is thwarted and the clinical nature of autism stands alone.

In practice, most of the variants found in the laboratory are classified as having “unknown clinical significance”. Usually, this occurs when variants are found in genes for which function is not yet known. The genes may or may not be impacting the brain in a way that contributes to an autistic phenotype. These genetic variants may or may not relate to autism as it is done in the clinic. Thus, most of the time in the laboratory, autism is still in the process of *becoming* genetic. It is assumed that advances in technology will eventually lead to a concrete and defined genetic nature of autism in all cases. But for now, the ontological boundaries of autism as it is constructed through genetics are still being negotiated. Therefore, when I describe how autism is practiced genetically, in the laboratory, it is to be understood as a fuzzy autism. It will only become solid once it has been mapped onto the clinical enactment of autism. Once that happens, only then do we look back on the genetics being done in the laboratory and recognize the outputs as being autism. Autism is given a genetic ontological status retrospectively. At this point the reversal occurs and it is assumed that it was the genetics that was there all the time, lying behind the clinic ontology of autism.

A pervasive concern that hangs around all of the work in the laboratory is whether or not findings are “real” or just “error”. Regardless of the technology being used, microarray or

sequencing, error is a fundamental problem. Scientists in the laboratory want to be confident about the existence of the CNVs or SNPs which they report out of the laboratory back into the clinic. In order to gain confidence in the variants that are eventually reported, there are many places along the experimental trajectory in which a different technology, a different way of looking, seeing, measuring, is used for validation. Just as the individual with autism is practiced in different ways within the clinic, through ADOS or Intelligence tests, so too is autism *done* differently by the various technologies used in different spaces within the laboratory. Previously I described how the laboratory is not actually a single, unified place but rather a set of related spaces in which different technologies and tools are used to probe the world in various ways. When walking from one place in the laboratory to another, from one aisle to another, the object that is made to come into view changes. In the previous chapter, I described the journey of DNA, in order to convey all of the changes, the translations, that occur as DNA is probed by different technologies.

All of these various experiments are finally translated into the report. The words on this report summarize the months of work that has been done and the results that were arrived at. The report classifies genetic variants into four categories or classes. A class four indicates that a variant is commonly found in controls. A class three is given to variants that are not found in controls but which do not overlap with any genes. They are intronic rather than exonic. A class two denotes variants that are not in controls and they do overlap genes; however it is not known whether they are significant. Class one is reserved for a known pathogenic locus. Something interesting happened here, when the scientist was explaining these classifications to me. For classes four to two, he described the class in relation to a variant. Specifically, he said: “*class four is CNVs that are in controls as well, Class three is CNVs that are not in controls but don’t overlap any genes, Class 2 are not in controls and*

they overlap some genes but we're not sure what they mean. Like, they could be significant or they might not be." (Ankit)

When he described class one, however, he said *"And class 1 is it's a known syndrome"*.

What is a known syndrome? The variant is a known syndrome. The variant at a particular genomic location is the syndrome. Its ontological status is solidified. Class one variants are allowed to stand in for the syndrome. When a class one variant is called and reported, autism is done genetically. Autism acquires an ontological status. In that instance, autism is practiced as a genetic variant at a particular locus on the human genome. Autism is practiced as a genotype.

The practice of autism as a genotype is very precarious as associations between genotype and phenotype are not always straight forward. When scientists are engaged in the work they are doing with their hands, when I pay attention to the work of the technologies in the laboratory, autism is being practiced as a genotype. However, when scientists in the laboratory are asked to stop and think about it the tenuous nature of the relationship between genotype and phenotype is brought to awareness. For example, in a Monday morning meeting that I observed early on in my data collection the director of the laboratory explained how someone at a conference had asked him to explain the difference between a mutation and a single nucleotide variation. The people sitting around me laughed uncomfortably and many of those in the room said there is not a difference. One scientist asked the laboratory director how he had responded to this question. The director responded, "a mutation is expressed phenotypically, while an SNV refers to the genotype". Here, he makes clear a distinction between genotype and phenotype. At times, however, genotype and phenotype are becoming blurred in reports of class 1 variants; in some cases, the genotype is beginning to stand in for a syndrome.

7.3c Autism in the Family Home

How is autism done in the home? How is it practiced? All of the participants I interviewed had previously been engaged in genetic feedback, meaning that a clinically significant genetic result had been mapped to the clinical findings. For these families autism had already been practiced both clinically and genetically. It already had two natures. It was practiced as scores on clinical tests, such as the ADOS, and ADI-R and it was practiced as a genetic variant. Autism was a genotype and a phenotype. Given the limitations of data collection in the home, the lack of participant observation in this context, my understanding of the practices of autism in the home are very limited. Through interviews, however, I have come to learn that in the context of the home, the practice of autism proliferates. Autism is *done* in a variety of ways. Moreover, it is difficult to separate the practice of autism from the practice of the individual with autism. It becomes a part of so many different activities during the day and night. I could say that autism is practiced through the lived experience of the body. For example, participants described autism as a way of living temporally and spatially. Routines are established and adhered to.

We're very routine. We get up at the same time, we have breakfast, we do everything in order in regards to getting to school.

Autism is also practiced retrospectively, as parents look back and remember specific, memorable habits or abilities that set the child apart from other children. For example, one mother said:

You see he was very eccentric since he was little and he was brilliant, absolutely brilliant. At two and a half he could recite *The Night Before Christmas*. And he would tell me when to turn the page and it was word for

word. So we knew. And he always had difficulty socially and sensory and then in grade four he got identified gifted LD.

Autism is practiced in relation to certain material objects:

We really started to see the stickiness, like he couldn't handle, change the colour of his socks and he'd freak out. He had this hat he had to wear. A hundred degrees and he still had to wear a wool hat.

Autism is practiced in the roles that family members take on:

I'm an advocate for them. I've met advocates. They've trained me. I've had all my training at [an autism centre]. I became an autism intervener for them, not for anyone else. So they let me know what courses there are and I've taken them all. So I think I know what I'm doing with them. I'm like their extra teacher.

Autism is practiced in special foods that are prepared and eaten:

I give them power smoothies. I'm trying to enhance their brains. I spend a huge amount of money on berries. So every day they have a 12 oz smoothy and that motivates [my son].

A description of the enactments of autism in the home is particularly difficult for me to capture. My difficulty in writing about autism practiced in the home is perhaps data in itself. I think the difficulty is because, unlike the laboratory or the clinic, in the home autism is not easily reduced; it can not be boiled down to scores on an assessment or a classification of genetic variants. When I read over the interview transcripts with parents, I find it difficult to discern where autism is *not* being practiced. Autism is part of the life of the family; it is enacted through disparate situations, people, objects, settings, times, places. Moreover, each home is different. While clinic and laboratory practices are very similar, or even standardized

in some cases, from one lab to another or one clinic to another, homes are not. The interviews I conducted only scratch the surface of autism as it is practiced in the home.

7.3d Non-Coherence in the Practices of Autism

i) Genetic Variant with no Clinical Diagnosis

At times the clinical and laboratory practices of autism did not cohere. One woman I interviewed described the difficulty she was having in understanding the relationship between the genetic and clinical constructions of autism. This woman had a son who was diagnosed with autism and who had a Class 1 genetic variant, the NRXN3. The mother had also given blood and been genetically tested. She too had been identified as having the genetic variant but had never been given a diagnosis of autism. She had a genotype associated with autism in the laboratory but she did not have the phenotype associated with autism in the clinic. She described her uncertainty about the ambiguous relationship between clinical and genetic practices of autism. For example, she stated:

Not to say that I have Asperger's and I've never been diagnosed with ADHD but it does help in understanding my tiny idiosyncrasies ... it does explain some of the things.

In respect to this woman's son, autism had a clear clinical and genetic ontology. The two practices of autism cohered. For her son, the gene is retrospectively recognized as the cause of the clinical nature of autism. For this woman, however, the genetic practice of autism did not cohere to the clinical practice of autism. This raised important questions for the mother:

I often wonder does that gene impact on, my question, I have a number of questions. So what it does is it brings forth more questions about myself. So because I have the gene I am the carrier or do I have autism on a lower part of the spectrum? What does it exactly mean is my question?

At home, participants traverse a number of different practices of autism, translating in and out of genetic and clinical constructions. For this woman, for whom the genetic and clinical practices of autism did not cohere, being in the genetic research was like being on a tightrope.

To have been a part of this research team is like being on a tight rope. You're on the edge and you don't know anything more. So sometimes you feel like you're left hanging. OK I do have this gene but what does that mean? ... Am I a carrier or do I have it [autism]? So it does bring up a lot of questions and it would be nice to have some follow up with the family so that you can ask these questions. But you are like on a tightrope, like you're wondering, okay, now what does this mean? Where do I go from here?

For this woman, genetic and clinical practices of autism do not cohere. She does not have a clinical diagnosis of autism. She does have a variant, NRXN3, which for her son did cohere with a clinical practice of autism. For her son, the two practices, laboratory and clinic, pointed in the same direction. One came to be understood within and explained by the other. Conversely, the lack of coherence between laboratory and clinical practices as they pertain to this woman has left her feeling stranded, confused, uncertain about whether or not she has autism.

ii) Feedback Session

The feedback session can be particularly difficult because here clinical geneticists and genetic counsellors have to navigate between different practices of autism. It is in the feedback session that attempts are made to try to make the different practices of the clinic, lab, and home cohere and connect meaningfully. The feedback sessions that the genetic

counsellors reported to be the most difficult were the ones in which the different practices of autism did not cohere. For example, when researchers in the laboratory sometimes prematurely wrote a research report before the genetic results were classified as clinically significant, feedback still had to be given to an individual. The findings of the laboratory did not, in these cases, relate to the findings of the clinic. The laboratory report did not indicate Class 1 variants but the clinical assessments did produce scores indicating autism. In this situation, autism was practiced phenotypically but not genotypically. The genetic tests capable of being carried out in Laboratory X were so new, and very few samples have been deemed clinically significant thus far. During the time of my field work, the scientists and clinicians were still figuring out when and under what circumstances a research report should be written. Over the course of a few meetings, it was decided that research reports should only be written when findings were clinically significant. In other words, when the various practices of autism in the laboratory could be made to relate to the various practices of autism in the clinic. When the different practices and enactments of autism did not cohere, the report was not supposed to be written and feedback was not supposed to be given to the patient family.

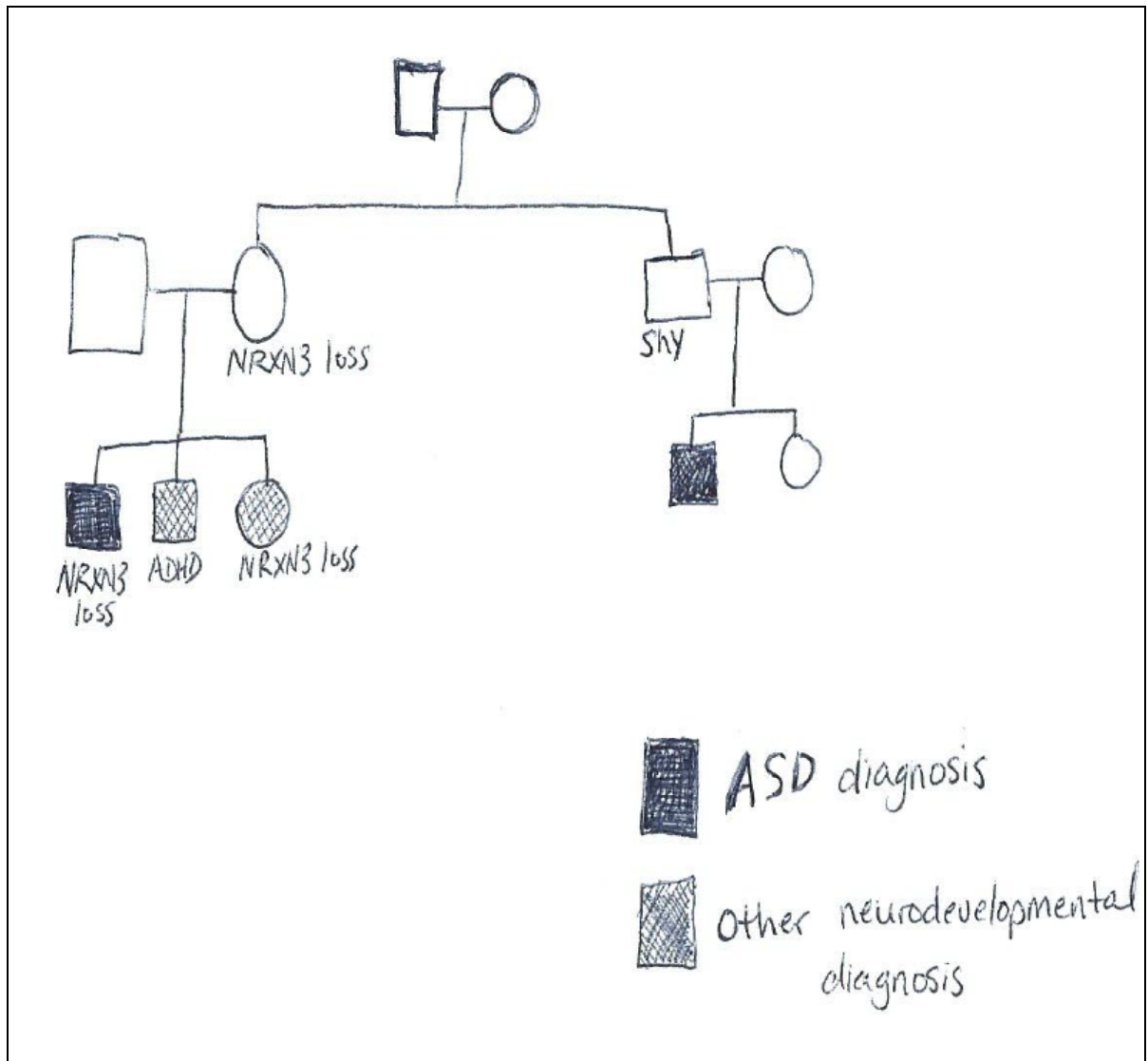
It was assumed that the lack of coherence between the laboratory and clinical enactments of autism were consequences of the limitations in the technology. Patient samples were kept in storage, immortalized cell lines established, so that as technology progressed connections would eventually be made between the various practices of autism. Indeed, there were several examples that I observed in which samples that had been collected a decade earlier were re-run on current technologies and the laboratory work was able to be connected to the work performed in the clinic.

7.3e Strategies of Coordination

i) The Pedigree

The “pedigree” is a ubiquitous site in which different practices of autism are coordinated. Through the pedigree autism is practiced as a genotype and as a phenotype. It is practiced as a geographic location and a clinical diagnosis. The construction of the pedigree involves families, clinicians and scientists. Below is part of an extended pedigree copied in my notes from a Monday morning meeting.

Figure 7.2: A Pedigree



Through the pedigree, different practices of autism are brought together and made to cohere. This coordination comes at a cost. Much of the detail, the nuances of practicing autism in the clinic and laboratory and home are removed, bracketed off from the pedigree. For example, in the pedigree clinical practices of autism are reduced to a basic binary opposition. One is either on or off the spectrum, a circle or square on a pedigree is either coloured in black or left white. The nuances and specific circumstances around which an autism diagnosis is made are not part of the autism that is practiced through the pedigree. All of the clinical judgment and interpretation of social, cognitive, language information gathered through clinical tests is eclipsed from the pedigree.

Similarly, all of the actors, activities, translations that form the practices of autism in the laboratory are not captured in the pedigree. A gene, perhaps SHANK or NRXN stands in for all the other work, all the other actors in the laboratory. The microarray, primers, PCR, chromosomes, buffers, robots, sequencers – all of these have been black boxed within a few letters printed underneath the circle or square.

Likewise, the many of the practices of autism in the home are not found in the pedigree. Indeed, the rich, complex daily minutia of getting the right socks on or adhering to routines, through which autism is practiced in the home, are absent in the pedigree. Parents, however, are not only involved in reporting the pedigree but are likewise re-made by the pedigree. Through the process of making a pedigree, parents who just found out they passed down a genetic marker for autism to their child began to reassemble themselves and their connection with extended family members around genetics. A new type of kinship is constructed and enacted through the pedigree. One of the mothers described in an interview her complete shock in learning that her son had inherited a CNV from her. As the genetic

counselor delivered the preamble about not having to share any of this new information with anyone and how it was her own personal and private information, the woman thought to herself, “Why is she telling me all this? This is strange.” She had anticipated that the genetic variant would have been inherited through her husband. She said:

So I was quite surprised and shocked because I thought it was my husband. But then when you look back it sort of made sense in some respects because my mother. So I said to [the genetic counselor], well you know, my mother’s side, my mother’s sister has three children and the oldest boy was very, very eccentric...And then my mother’s first cousin has a grandson with autism. So it just sort of made sense.

As the counselor began writing out the connections in the form of a pedigree, collecting information on traits and neuropsychiatric diagnoses of extended family members, this woman’s kinship ties were reassembled according to another layer of connection. Extended family members who were once imagined as quite distant are suddenly transformed as new lines of connection tracing phenotypic similarities are re-imagined with the possibility of genetic similarity. Rabinow’s (1992) concept of biosociality is a particularly fertile concept through which to explore how we will increasingly come to understand ourselves in terms of genetics. Silverman (2004; 2008a; 2008b) described this process of biosociality among individuals with autism and their family members. In particular, she describes how new individual and collective identities formed around genetics were leveraged by a parent advocacy group, Cure Autism Now (CAN), in order to change that way in which genomic research was being practiced. Frustrated by competitive, rival scientists who would not collaborate and share DNA samples, the parents who started CAN used their own new genetic identities as parents of children with autism to access and recruit other parents in order to create their own gene repository.

Parent knowledge of the quirky traits of extended family members is increasingly important and essential in the construction of the pedigree in a condition (ASD) with a broad and variable phenotype. As the blurry boundaries of ASD are extending further and further, with terms such as the broader autism phenotype (BAP), individuals who do not strictly meet the criteria for diagnosis are included in the pedigree. While these types of pedigrees may not show up in peer-reviewed publications, this anecdotal information gathered from parents about extended family members was frequently included in the pedigrees exchanged at Monday morning meetings. Descriptive traits and anecdotal information are increasingly included in pedigrees for ASD, making parents a vital actor in the construction of the pedigree. A new liminal type of *potential* patienthood is being practiced through the making of the pedigree – one in which extended family members who do not have a clinical diagnosis are reconstructed as interesting cases for the laboratory to explore. The changing nature of the patient through genetic testing has been explored further by Kessler (1993). Kessler explored how the category of “patient” has been reconfigured through DNA testing from something that described an individual to a term applied to the entire family. Abby Lippman (1998) coined the term “geneticization”, to indicate a process in which differences between individuals are reduced to genetic explanations. Gibbon (2002) has specifically explored family trees through the concept of geneticization. According to Novas and Rose (2000), advances in science, including genetics, are constructing a new figure of an individual “genetically at risk” (2000, p.486).

The pedigree has been the discussion of many science studies papers (Armstrong, Michie, & Marteau, 1998; Atkinson, Parsons, & Featherstone, 2001; Nukaga & Cambrosio, 1997; Silverman, 2008). Pedigrees are extremely portable, produced with a pen, paper and ruler. It is simple to produce and easily moved from one place to another. Fujimura (1996)

has commented that the portability of a tool increases its likelihood of being reproduced in other situations. I frequently observed pedigrees being constructed on the back side of journal articles or loose paper available in genetic counseling situations. Claudia would often have scribbled pedigrees along with her in the files she brought to Monday morning meetings at Laboratory X; the pedigrees would be reproduced in PowerPoint presentations in later Monday morning meetings and finally would be published in journal articles. Through the pedigree the practices of the laboratory, clinic, and home intersect; the practice of autism as a genotype is coordinated with the practice of autism as a phenotype. Nukaga (2002), for example, adopted a historical approach in exploring the intersection of laboratory genetics and clinical medicine through the pedigree in the specific case of Huntington's disease. As such, the pedigree can be thought of as a coordinating strategy that brings the fluid practices of autism into coherence.

ii) The Published Manuscript

One of the primary goals of both the laboratory and the clinic is to publish findings in peer-reviewed journals. These publications incorporate many different constructions of autism. In the published manuscript connections are drawn between different constructions of autism. Columns in tables, for example, lay down genotype and phenotype constructions of autism, as well as bringing in new networks that construct autism in terms of brain function. Consider a recent article (Berkel et al, 2010) published in *Nature Genetics* which describes the SHANK2 mutation. In this article ASD is described as a “clinically distinct neurodevelopmental disorder”; it is also described as having a “complex genetic aetiology”. The article describes SHANK2 as a candidate susceptibility gene. This gene is involved in the production of proteins that “localize to postsynaptic sites of excitatory synapses in the

brain”. The article describes the phenotypic testing using ADOS and ADI assessments, as well as the details of the microarray and sequencing performed on cases and controls.

A table in this article has eight columns, labelled: Nucleotide Change/ CNV, Amino Acid Change, ASD, MR, controls, name, sex of proband, and transmission source. Under the third column, ASD, there is either a 0 or a 1 for each of the cases. It is practiced as a binary phenomenon, on or off the spectrum.

Over lunch one day, I was talking with Ankit about publications. I told him that in my discipline, it is really great to publish a paper as a single author, to demonstrate that you can work independently. He said that would never happen in science, that it would be rare to see a paper with fewer than ten authors in human genetics. This is because so many different groups, laboratories, experiments and technologies have to come together in order to produce a paper. I probed more about how a paper is produced. He gave me the example a recent paper produced in Laboratory X. One of the post docs had presented a poster at a conference describing the deletions in SHANK3 that she had found in two ASD cases. While at the conference, a few other people approached the post doc and told her that they too had SHANK3 deletions in their samples. So they collaborated and brought their four cases together to make a stronger argument for the significance of a SHANK3 deletion in autism. There might also be experimental labs involved in the publication. These laboratories might do work on understanding, for example, the function of SHANK3, elucidating what it does in the brain. They might be working with mouse embryos to identify how a gene is expressed. There might also be human cell lines showing where the gene is expressed in human body tissue. There are also computational labs involved. These are the people who develop all the algorithms used for analyzing data outputs, determining if variants are real or not. Such labs

do not have any biological data of their own but instead constantly collaborate with other labs. Finally, there are clinicians who provide the phenotypic information used in interpreting the molecular biology results. Ankit said,

This is all done by different people. So the functional work was done by a functional lab, and the pedigrees were done by the clinical, like the Autism Clinic, and this figure was done in an array facility, the CNV analysis. So we put the whole thing together, write a discussion and then get the editors and reviewers to buy it. That's the tricky part.

Author lists are so long in the area of human genetics because a variety of different people, working in very different actor-networks, have to come together in order for the manuscript to be produced. The manuscript is a coordinating strategy amongst the various ways of constructing autism.

iii) Hybrid spaces as sites of coordination

Hybrid spaces bring together various combinations of clinical, home, and laboratory practices. In these hybrid spaces, details, nuances, ambiguity are left aside. One hybrid space, for example, was a monthly meeting between laboratory and clinical employees. It was primarily a meeting to discuss and prioritize feedback sessions. At one meeting I observed, the clinic research coordinator mentioned that the phenotype measure for a particular genetics study had been a year in planning and they were still not sure about the exact measurements they wanted to include. The laboratory coordinator responded bluntly: "All of it is irrelevant to me." In the laboratory, the details of the clinical practice of autism are not important. All the laboratory needs to know is whether or not an individual is on or off the spectrum. In hybrid spaces, the nuances of autism are truncated. Here, phenotypic and genotypic constructions of autism are brought together; however, in an effort to discuss as

many patients as possible in the meeting, the practices of the laboratory and clinic were expected to be reduced, black-boxed within this hybrid space.

Conclusion

In this chapter I have tried to describe the various ways in which the patient body and autism are practiced. Through the different practices of the clinic, laboratory and the home, the individual with autism multiplies, and so too does autism. I have described instances in which the practices have been brought together through strategies of coordination. In these instances some of the practices cohere; they are made to relate to one another. I have also described situations in which the various practices of the home, clinic, and laboratory do not cohere. In these situations, practices point in different directions, exclude one another. The individual with autism multiplies. Autism multiplies.

Thus far, I have not explicitly explored how these ideas of multiplicity and difference relate to knowledge translation. The reader might be asking herself, ‘but how does a discussion of the multiply practiced individual with autism relate to knowledge translation’? Perhaps the reader is wondering why I have not focused on “knowledge” as it is practiced in these various spaces. As such, questions pertaining to the validity of my interpretation may be raised at this point. Have I really been describing knowledge? In the following chapter, my goal is to convince the reader that I have, in fact, been describing knowledge all along. Following actor-network theory, however, knowledge has been de-centred. It has been treated as a materially heterogeneous practice. Knowledge is *done*, with the body; it is *practiced* through patients, assessment tools, pedigrees, classifications, reports, meetings, diagnoses, bedtime routines. Following practice theory, embedded within constructionism, the “knowledge” that I have been describing does not only inhabit the mind of the subject but is also incorporated in material heterogeneous practices. I aim to de-center an overly

cognitive construction of knowledge by rejoining knowledge and practice. As Mol has suggested, we can spread the activity of knowing more widely; “Instead of talking about subjects *knowing* objects we may then, as a next step, come to talk about *enacting* reality in practice” (2002, p.50).

In the particular case of autism genomics, knowledge translation involves understanding how the various practices of the laboratory, clinic and home, which may enact different realities, are made to relate to one another. Thus, in describing how the individual is practiced or how autism is practiced in the laboratory, clinic, and home I am at the same time describing a process of knowledge translation. Here, knowledge translation might be better understood as an on-going process of *ontological translations*. It is this particular conceptualization of knowledge translation, which is grounded in constructionist theories of practice and heavily influenced by actor-network theory that I will explore more fully in Chapter 8.

Chapter 8: Reassembling Knowledge Translation

The thesis under consideration is that the products of science are contextually specific constructions which bear the mark of the situational contingency and interest structure of the process by which they are generated, and which cannot be adequately understood without an analysis of their construction. This means that what happens in the process of construction is *not* irrelevant to the products we obtain.
(Knorr-Cetina 1981, pp.5)

8.1 Reassembling Knowledge Translation

a) Conceptualizing KT – What is being translated?

8.2 KT according to the CIHR

a) Discussion of the KTA cycle

8.3 Time for a new Conceptualization of KT?

a) On the nature of knowledge: constructing reality through knowledge practices

b) Local Translations of Knowledge in Practice (LTKP) Framework

c) The LTKP Model

8.4 Comparing the KTA and LTKP frameworks

a) Implications

8.5 Conclusion

Throughout this dissertation I have described how knowledge translation can be reconceptualized through examples from a particular case study of autism genomics. I explored the changes and transformations that occur through the process of translation in Chapter 4, as I followed some of the important actors involved in autism genetic testing amongst the clinic, laboratory, and family home. In chapter 5, I then unpacked the political dimension of the translation process through a framework developed by Callon (1986). Chapter 6 highlighted the ontological implications of knowledge translation, illustrating that

it is not only knowledge that is being translated but also constructions of reality. In this chapter, I take these insights laid out in previous chapters and apply them to a more general discussion of knowledge translation.

8.1. Reassembling Knowledge Translation

The KT literature addresses the “research to practice” gap, with the goal of “moving evidence into practice” (Lang, Wyer, & Hanes, 2007). A burgeoning literature has developed to explore the process (D. Davis et al., 2003b; Davison, 2009) and evaluate the outcomes of KT initiatives (Danseco et al., 2009; Bhattacharyya & Zwarenstein, 2009). Knowledge translation (KT) has become an important concept in the Canadian health research environment (Straus, Tetroe, & Graham, 2009). In this chapter, I will outline how knowledge translation is typically described in the Canadian health sciences literature. After this general discussion of KT, I then focus on knowledge translation as it is described by the Canadian Institutes of Health Research (CIHR) through the Knowledge to Action (KTA) model (I. Graham et al., 2006). I then juxtapose this CIHR understanding of KT with a description of knowledge translation that emerges from my interpretation of the work going on in the autism genetics study. I introduce an alternative description and framework for KT that is based on a constructionist, post-humanist epistemology and strongly influenced by actor-network theory. Finally, I compare the CIHR model with the framework I have developed and explore ways in which they might complement each other as well as the places where they disrupt and conflict with each other.

8.1a Conceptualizing Knowledge Translation – What is being translated?

There are several frameworks or theories in the KT literature that unpack the idea of knowledge translation in slightly different ways. For example, the diffusion of innovations

theory (Rogers, 1962) highlights the spread of ideas and innovations and how the uptake or use of knowledge differs depending on the user's needs. Elsewhere, the push-pull framework (Curry, 2000; Landry, Lamari, & Amara, 2007) proposes that knowledge is translated according to push factors on the supply side by knowledge producers as well as pull factors on the demand side by knowledge users. Lavis et al's (Lavis et al., 2003) five-point framework for KT highlights: the message, the target audience, the messenger, the knowledge translation process and support and evaluation. Tugwell et al (Tugwell, Robinson, Grimshaw, & Santesso, 2006) have put forward a framework that explicitly forefronts health equity, with an emphasis on identifying barriers and facilitators to KT, choosing interventions to address the barriers, evaluation, and facilitating knowledge sharing. Meanwhile, the CIHR framework for knowledge translation highlights an iterative cycle between knowledge producers and users (Canadian Institutes of Health Research, 2004). Finally, the two-communities theory (Bowen, Martens, & Need to Know Team, 2005; Canadian Institutes of Health Research, 2004; Caplan, 1979) emphasizes cultural differences between researchers and decision makers. This idea is described in the CIHR Knowledge Translation Strategy 2004-2009 (2004, p.4) suggesting that the difficulty in moving research into practice could be due to the "two-communities" problem, in which "researchers and policy makers inhabit different worlds with different language and culture".

Within the KT literature, some writers have made the distinction between tacit and explicit knowledge (Kothari, Bickford, Edwards, Dobbins, & Meyer, 2011; McWilliams, 2007; Nonaka & Noboru, 1998; Straus et al., 2009). McWilliams (2007), captured the complexities involved in integrating new knowledge into tacitly-held understandings and beliefs, emphasizing the role of transformative learning and reflective practice in addressing the social and cultural dimensions of KT. Greenhaalgh and Russel (T. Greenhalgh & Russell,

2006) conceptualized knowledge in KT as being socially shared and tacit. Tacit knowledge is “non-verbalized, intuitive, and unarticulated” (T. Greenhalgh & Russell, 2006; Polanyi, 1966). Explicit knowledge can be articulated in formal language, codified, and is more easily transmitted amongst people (Collins, 2010). Nonaka and Noboru (Nonaka & Noboru, 1998) likened the idea of tacit knowledge to the Japanese concept of *ba*. *Ba*, can be thought of as “a shared space for emerging relationships...a context which harbors meaning” (1998, p.40). According to Nonaka and Noboru, knowledge resides in *ba*; however, when separated from *ba* knowledge turns into information. Elsewhere, in the context of knowledge management, Alavi and Leidner (2001) have compared knowledge as a state of mind, an object, a process, a condition of having access to information, and a capability. Each way of conceptualizing knowledge has implications for how translation is imagined.

While KT research tends to focus on research knowledge (Collins, 2010; D. Davis et al., 2003a; Grimshaw, Santesso, Cumpston, Mayhew, & McGowan, 2006; Lavis et al., 2003; Lavis, 2006), the question of what constitutes knowledge and evidence is beginning to be explored (Estabrooks, 1999) leading to calls for more theory-driven approaches to KT (R. Greenhalgh et al., 2004; McWilliams, 2007). For example, Estabrooks (1999) problematized the emphasis on research knowledge as evidence in KT, drawing attention to the many types and sources of knowledge that are used in nursing practice. Weiss (1979) critically addressed the various uses of research (problem solving, tactical, political, etc), indicating that the practice-based goals or intended outcomes for knowledge use might be other than those anticipated by researchers. Greenhalgh et al (2004, p.615-616) have called for a much broader conceptualization of KT, arguing that it should be "theory-driven, process rather than ‘package’ oriented, ecological, address common definitions, measures, and tools, be collaborative and coordinated, multidisciplinary and multi method, meticulously detailed,

and participatory.” Drawing on concepts in continuing education, McWilliams (2007) has also called for more theory-based strategies in KT.

One of the central concerns that has been repeatedly pointed out in various KT publications is the issue of context (Jacobson, Butterill, & Goering, 2003; Reimer Kirkham, Baumbusch, Schultz, & Anderson, 2007). Recent models of KT have explicitly considered local contextual factors that can impede the objectives of knowledge uptake (Kitson, Harvey, & McCormack, 1998; Logan & Graham, 1998; McCormack et al., 2002; Rycroft-Malone et al., 2004). For example Dobrow et al (2006) questioned whether the same evidence should lead to the same decisions in different contexts. Using a multiple case study design within a policy-making context, they found that resource constraints, political interests, and varying skills and abilities to use decision-support tools were some of the factors leading to different interpretations and utilization of available evidence. The authors pointed out that while hierarchies of evidence are useful tools when interpreting the quality of effectiveness for interventions, as we shift toward an examination of appropriateness of interventions these same hierarchies might not be as useful. The authors proposed a model that acknowledge three different objectives for using evidence (effectiveness, appropriateness, and implementation issues) alongside three stages of evidence utilization (identification, interpretation, and application).

Kothari and Armstrong (2011) recently emphasized the need for local information with contextual relevance in community-based knowledge translation. These authors acknowledge that local information is often criticized for not being related to the broader literature or mapping well onto “evidence hierarchies”. However, they suggest, a preference for local information may be based on epistemological differences. These authors call for a

broader conceptualization of evidence and state that “there are health service delivery systems for which traditional ways of approaching KT are insufficient” (2011, p.e5).

Thus, a more complex conceptualization of the process of KT is starting to be captured in this body of literature. Fox's description of practice-based evidence, "re-privileges the role of the practitioner in generating useful knowledge" (Fox, 2003, p.82). Fox explored the role of criteria such as internal and external validity in producing exclusionary definitions of evidence and consequently setting up a binary dualism, constructing "practice as an irrational *other*" to research. Within a post-structuralist and action-research-oriented approach, Fox challenged this research-practice opposition by positioning research within practice, adopting a perspective that knowledge is local and contingent. Thus, for Fox (2003), research and evidence should be both produced and used within practice.

8.2. Knowledge Translation According to the CIHR

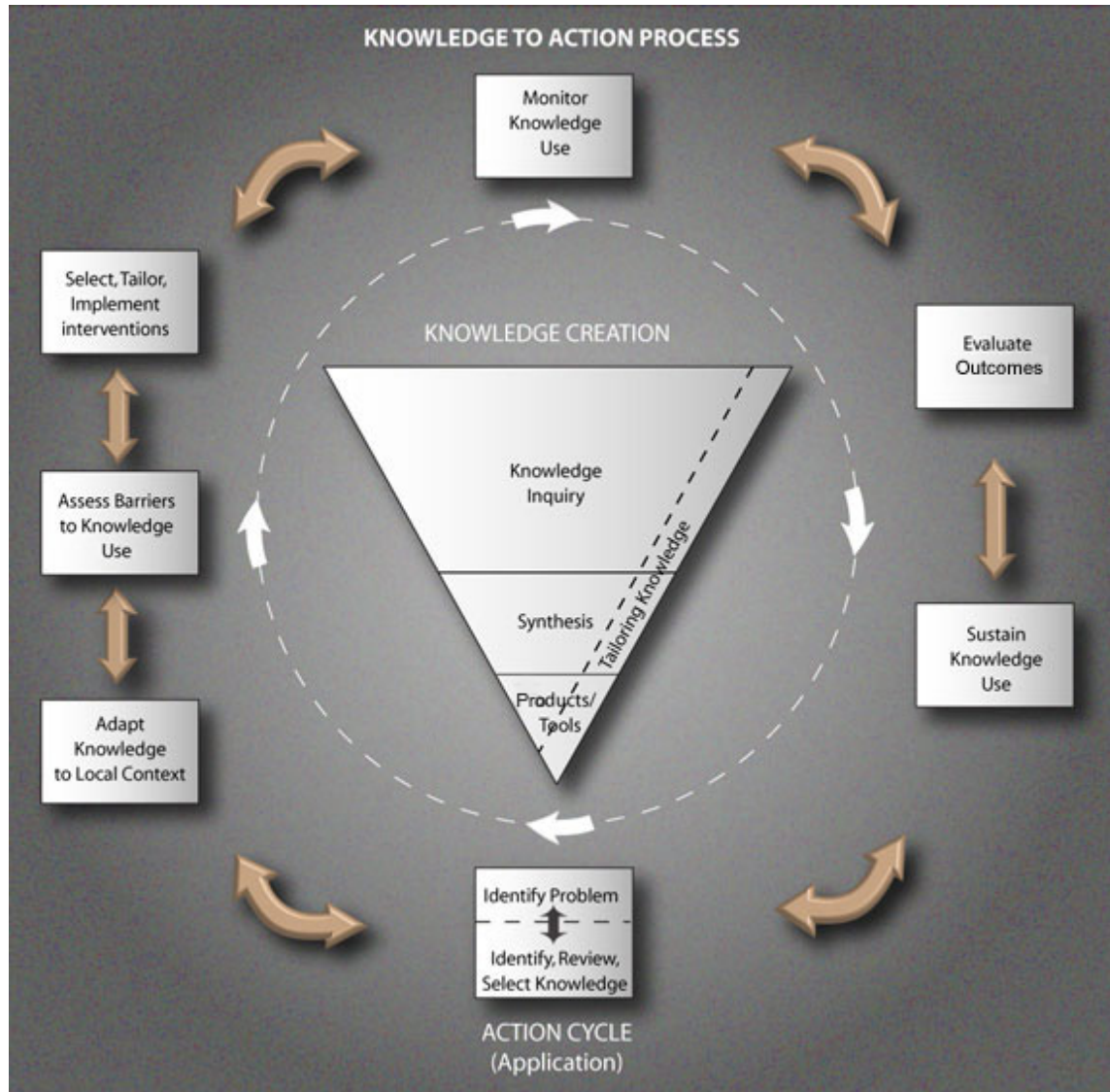
The Canadian Institutes of Health Research (CIHR) is the major funding agency in Canada for health-related research. It was created in 2001 under an Act of Parliament (<http://laws-lois.justice.gc.ca/eng/acts/c-18.1/index.html>). The CIHR consists of 13 institutes which together shape Canada's health research agenda. The CIHR funds four types of research or “pillars” as they are called by the CIHR: clinical; biomedical; health systems and services; and population and public health. Recent changes to the mandate of another tri-council agency, the Social Sciences and Humanities Research Council (SSHRC), have streamlined funding opportunities, forcing all social science and humanities research that is related to health to be funded by the CIHR (J. Graham et al., February 7, 2011). The CIHR, by mandating a knowledge translation component in each of its funded projects, has popularized a particular conceptualization of KT for Canadian health researchers. The

rationale for this keen interest in knowledge translation is given by CIHR as two fold: first, the creation of new knowledge does not automatically lead to widespread adoption or health impact, and second, the CIHR cites that it needs to be accountable for the tax dollars invested in health research and wants to increase the benefits of this investment by moving research into practice (www.cihr-irsc.gc.ca/e/33747.html). According to the CIHR, knowledge translation is defined as:

...a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system (Straus et al., 2009).

According to Tetroe (2007, p.2) knowledge translation is a broad concept that “encompasses all steps between the creation of new knowledge and its application to yield beneficial outcomes for society”. Reading through the CIHR documents and publications, it is quickly clear that the word knowledge has a very specific meaning and is confined to a particular type of knowledge, namely knowledge acquired through *research*. Graham et al (2006) described the confusion and inconsistency in terms related to the concept of knowledge translation used in health research and health services. The authors then put forward the idea of the knowledge to action (KTA) process, which they identify as having 2 components: knowledge creation and action. Their KTA model involves two sets of individuals: knowledge producers-researchers and knowledge implementers-users.

Figure 8.1: The CIHR's KTA Process



As stated above, the KTA process consists of a knowledge creation component as well as an action component. According to Graham and co-authors (2006, p.18), the knowledge creation component is best illustrated by a funnel, which the authors describe as follows:

As knowledge moves through the funnel, it becomes more distilled and refined and presumably more useful to stakeholders. Another analogy would be to think of the research being sifted through filters at each phase so that, in the end, only the most valid and useful knowledge is left (Graham et al, 2006, p.18).

The funnel begins with knowledge inquiry. This knowledge is described by the authors as

comprised of the “unmanageable multitude of primary studies or information of variable quality that is out there”. The authors describe this as “first-generation knowledge that is in its natural state and largely unrefined, like diamonds in the rough” (Graham et al 2006, p.18). In order to make sense of all of this “first generation” knowledge, the second stage, knowledge synthesis involves systematic reviews to appraise all the knowledge out there. Finally, the most refined section of the funnel consists of knowledge tools or products, such as practice guidelines, decision aides, and care pathways. These tools are intended to present knowledge in clear concise and user-friendly formats “thereby facilitating the uptake and application of knowledge” (2006, p.19). This then, the tools, are the end result of the knowledge creation process. According to the KTA model it is practice guidelines, decision aides and care pathways that are the objects of translation. These tools are what count as knowledge and what ought to be applied in the second part of the KTA process, the Action Cycle.

The second component of the KTA process is what Graham and co-authors call the Action Cycle, which “represents the activities that may be needed for knowledge application” (Graham et al, 2006, p.20). This action phase is modeled after planned-action theories which deliberately engineer change in groups. Lomas (Lomas, Sisk, & Stocking, 1993) for example, is often cited for his differentiation between dissemination (tailoring a message for a particular audience), diffusion (a more passive process such as a journal publication), and implementation (planned efforts to encourage adoption). Graham et al (2006) suggest the following as being integral to a planned action approach:

Identify a problem that needs addressing; identify, review, and select the knowledge or research relevant to the problem (e.g., practice guidelines or research findings); adapt the identified knowledge or research to the local context; assess barriers to using the knowledge; select, tailor, and implement interventions to promote the use

of knowledge (i.e., implement the change); monitor knowledge use; evaluate the outcomes of using the knowledge; sustain ongoing knowledge use” (Graham et al, 2006, p.20).

The authors are clear that “generic knowledge is seldom taken directly off the shelf and applied without some sort of vetting or tailoring to the local context”. Graham et al (2006) also describe various types of knowledge use. Conceptual use describes changes in understanding or attitudes. Instrumental use describes changes in behaviour or practice. Finally, strategic use is described by the authors as the manipulation of knowledge “to attain specific power or profit goals”

8.2a Discussion of the KTA cycle as proposed by the CIHR

The KTA cycle developed by Graham et al (2006), widely promoted by the CIHR, is a model of knowledge translation that is exclusively focused on *widespread adoption* of research knowledge. It describes a large-scale, deliberate and planned attempt to move research knowledge into practice. Furthermore, this model describes a process in which the objects of translation are the distilled tools that culminate at the end of a research funnel. The KTA model of translation put forward by the CIHR, however, excludes certain types of research translation. For example, Graham et al 2006 stated:

Translational research (the transfer of basic science discoveries into clinical applications) does not fall under our conceptualization of KTA because translational research falls short of widespread adoption (Graham et al 2006, p.18).

In a related article, Tetroe further explained:

Translational research is about finding solutions to clinical problems. Ideally it involves two-way interactions between basic/fundamental scientists and clinicians and requires moving between scientific discoveries and clinical applications. Translational research stops short of widespread dissemination of the clinical application once it has been proved beneficial by clinical research (2007, p.2).

The KTA model, then, describes a process that is removed from the local practices and

places in which knowledge is actually produced. There are many types of interactions and activities that are not captured in the KTA model of knowledge translation. For example, the on-going, day-to-day local interactions and meetings in which research is discussed between different groups of scientists, clinicians, and families are not captured in this model.

Embedded within the “knowledge creation funnel” are some of the assumptions on which the KTA model rests, assumptions about what constitutes knowledge, how this knowledge is created and by whom. For example, in the KTA model the knowledge that is created at the end of the funnel are tools and products. One of the limitations of the KTA model which explores only distilled tools that have been tailored through the knowledge creation funnel is that we lose appreciation for the underlying contexts in which research knowledge is first produced. When we zoom in and examine the local conditions of knowledge production, we are better able to pay attention to the assumptions, values, and cultures of the groups of people who produce knowledge. These assumptions, values and cultures are not necessarily lost when knowledge is distilled down to tools. They are, perhaps, embedded within the tools.

However, the KTA model does not capture this context of knowledge production. The KTA model considers the cultural and contextual factors that might impede widespread adoption of knowledge by *users* but it is limited to exploring the culture and context of knowledge users themselves, not the culture and context of knowledge production. Since this model only begins after the research has already been published, how could it be otherwise? By the time tools and products are tailored it would be very difficult to trace them back and uncover the original contexts and cultures in which the research was conducted upon which the tools are based.

The KTA model brackets off the work that occurs during the production of knowledge

prior to publication from a discussion of knowledge translation. The conditions of knowledge production are exempt from scrutiny and examination in the KTA model. In a positivist epistemology, scientific knowledge mirrors nature or reality. Positivist science is not supposed to have values or assumption, biases or culture. From a positivist perspective, the conditions of knowledge production are irrelevant when considering cultural barriers to knowledge adoption because the knowledge itself is assumed to be culture-free.

There is a second, related, concern that I have about the KTA model and the notion of KT that is promoted by the CIHR. In the KTA model, knowledge is assumed to be something that is separate from the contexts in which it was produced. It can be severed off from the laboratories and clinics, captured in a journal article, distilled, funneled and tailored into tools and products, all the while never losing its shape, its essence, its relation to nature. From an actor-network theory perspective, however, knowledge cannot be extricated from the network of humans and non-humans that constructed it, at least not without changing. To be fair, an iterative and on-going quality to knowledge translation is captured in the KTA model. The arrows move around in a circle, the cycle is repeated indefinitely. What is lost, however, is an understanding of how the knowledge has changed as it has moved out of the contexts of production and down through the Knowledge Creation Funnel. How is knowledge synthesized and tailored? According to what values and assumptions? What new networks of human and non-human actors does the knowledge become a part?

8.3. Time for a New Conceptualization of KT?

While the KTA cycle might accurately describe some of the activities that took place in the settings in which I conducted my research, much more is going on that is not being captured in this KTA model. All models have limitations and no single model could possibly

hope to describe all contexts and situations in which one might consider KT. Limitations are inevitable and this is not a criticism of the KTA model or of the CIHR definition of KT.

Unlike the KTA model, I propose that the local conditions in which knowledge is created are important to the discussion of KT. In the KTA model the “doing” of science in the first place is left untouched, unexamined. The KTA model starts with an “unmanageable multitude” of peer-reviewed journal articles. All of the work and collaborations that lie behind these primary studies is precluded from this model of KT. In other words, *the KTA model begins where my research ends*. According to the KTA model, translation happens *after* knowledge has been created. While my research suggests that knowledge translation is occurring long before research results are reported in journals.

The recent calls for theory-driven conceptualizations of knowledge translation and the fervent attention being paid to the concept of “context” are an entryway for a constructionist, post-humanist description and framework of KT that I will put forward in this chapter, based on my research in autism genomics and influenced by actor-network theory and theories of practice. Knowledge translation is enacted very differently when approached through a language of difference, multiplicity, non-coherence and partial connections. Approaching the notion of knowledge translation through actor-network theory (ANT) raises questions about some of the assumptions typically made in the KT literature. Specifically, ANT affords the opportunity to forefront a different set of actors, events, and practices than those that are typically acknowledged and explored in KT. Through ANT and constructionism, I aim to explore the softer underbelly of KT, in which knowledge is not confined to the cold, hard facts residing at the top of evidence hierarchies. Instead knowledge is viewed as transforming and changing through the process of translation.

ANT brings attention to the non-human actors (the material world) as central to a discussion of translation. It also includes and focuses squarely on the networks of knowledge production as integral to (and not separate from) the process of knowledge translation. As Armstrong et al (R. Armstrong, Waters, Roberts, Oliver, & Popay, 2006) have commented, most models of knowledge translation “have generally been used to explore links between researchers and end-users rather than those involved in the generation of knowledge” (2006, pp 384). Conversely, my research has attempted to explore the local contexts of knowledge production and the day-to-day translations amongst laboratories, clinics, and families of individuals with autism.

8.3a On the Nature of Knowledge: Constructing Reality through Knowledge Practices

In this thesis, I have tried to illustrate how knowledge might be conceptualized as much broader and more diffuse than it is typically represented in the scientific literature. In particular, knowledge is not detached or separate from the actors bound together in the networks that create knowledge. Knowledge is not something that lives in the mind, apart from the physical world. Instead, I adopt a philosophical position in which knowledge is practiced in the material world. The Cartesian split between mind and body is side-stepped by focusing on how knowledge is continuously constructed, through interacting hands, tools, bodies, machines. From this position, knowledge is not exclusively relegated to the mind; it is performed and enacted through the body and through heterogeneous material objects in the physical world. Following this, I propose that the science of knowledge translation should consider the broader ontological implications of the KT endeavour.

Constructionism assumes that knowledge is not a perfect mirror of nature. From this standpoint, the scientists in the laboratories and clinician-scientists in the clinics are not merely

discovering nature, already there. They are actively participating in constructing and shaping nature, and in turn being constructed by it. Latour views constructivism as the only way to bypass the dichotomy between an unconstructed world that is "already there" and a world made purely of subjective value claims (Latour, 2005). Starting from a constructionist position, then, considering the conditions of knowledge production is very important in a discussion of knowledge translation. When considering obstacles to widespread adoption, a constructionist model might scrutinize not only the cultures of "so-called" potential knowledge *users* but also the cultural contexts of knowledge *producers*. A constructionist model might be better able to understand the conflicts and places of non-coherence that might arise between the practices of knowledge production upon which tools and products are derived and the practices of knowledge users.

Following from a notion of knowledge that is practiced in the material world, translation could be conceptualized as a process of ontological politics (Mol, 2003), as actors (e.g., researcher, stakeholders) vie to become obligatory passage points, constructing through practice what counts as *real*. This conceptualization of KT is informed by Callon's (1986) framework which considered four moments of translation: problematization, interessement, enrolment, and mobilization. Another way of approaching translation, however, is to follow the work of Mol (2003) and Law (2000; 2012). These authors emphasize multiplicity and coordination. From this perspective knowledge translation may be conceptualized as finding windows of partial connection among networks of knowledge practices interacting with one another. Translation might only require that connections are made between networks, that actors might be simultaneously enrolled in several networks at once. Each of these conceptualizations of the translation process allows us to redirect our focus, de-centering the object of translation, and attend to the complex connections and associations through which

the reality of an object is constructed and reconstructed.

8.3b Local Translations of Knowledge in Practice (LTKP) Framework

Drawing on theories of practice, a methodology of actor-network theory and based in a constructionist epistemological position, I propose a new framework for exploring knowledge translation. This framework is called the Local Translations of Knowledge in Practice (LTKP). Underpinning this new framework for KT are five key ideas. First, *knowledge* is intricately tied to the networks of human and non-human actors within which knowledge is constructed. Knowledge is considered an on-going activity, a process, which is constantly enacted or practiced. Perhaps it would be more useful to think of knowledge not as a noun (a thing) but rather to think about *knowing*, a verb (an action). As this conceptualization of knowledge relates to KT, it would probably be more accurate to describe this as “knowing translation” rather than knowledge translation. From an ANT perspective, understanding the process of knowledge translation depends on one’s ability to unpack and “de-centre” knowledge. In many ways the framework I am putting forward considers knowledge in the opposite way as the KTA model. Where the KTA model seeks to distil and refine knowledge into a tangible applied tool or product, the LTKP framework seeks to trace the expansive, heterogeneous practices which together shape a particular way of knowing. Knowledge, here, is a much more diffuse concept and not as easily bounded as the distilled tools and products described in the KTA model. In the KTA model, knowledge is objectified; through the distillation of the knowledge funnel it becomes reified in an object (e.g., a practice guideline or care pathway), separated from the practices in which it was constructed. In my constructionist description of KT, knowledge is not understood as an ontologically stable object but rather as a materially-heterogeneous practice.

Secondly, in the LTKP framework, *translation* is conceptualized as the fluid

movement and associations of human and non-human actors between and amongst networks. It is an on-going affair and is never completed. Translation implies change and transformation. Stability is not an inevitable quality of that which is being translated. For example, in Neylands (2006) work on a university strategy for managing information, the movement of information is conceptualized as “a series of sociotechnical connections, each connection forming an opportunity to confirm the continuity of information usage or to reconstruct the usage and, thereby, the information itself” (2006, p.35). Any addition or subtraction of an actor (human or nonhuman) in a network changes the network and all the actors involved. Actors exist in practice as they relate to one another. As new humans and non-humans enter or leave a network the relationships between the remaining actors change.

Thirdly, in the LTKP framework, both human and non-human actors are integral to the enactment of KT. In any effort to describe and examine the KT process, one must consider a wide range of *heterogeneous materials involved*. In the ANT literature this is often referred to as agnosticism – remaining open to whom or what is doing the acting (Callon 1986). We can not assume that non-humans are passive in the KT process. Instead, non-human actors are acknowledged to play an active role in shaping how knowledge is constructed and in how knowledge changes as it moves amongst various networks.

Fourthly, in the LTKP framework the knowledge translation process can be approached as an inherently *political process*. Translation involves a process of problematization and enrolment of actors, with certain actors vying to be the spokesperson, attempting to mobilize a host of silent actors behind them. The stability of a network, however, is always in question. A network can always fail. Over time, some networks manage to maintain stability better than others.

Fifthly, actors may belong to more than one network and as such they may be

practiced in relation to different sets of actors. An example from my research would be an individual diagnosed with autism. Such an individual exists in a clinical network, a laboratory network and a home network (as well as others). In each of these networks, “the individual with autism” is enacted or practiced in relation to a different set of actors. As such, the individual with autism changes as he/she moves amongst networks. Thus, any actor (in this example an individual with autism) cannot be assumed to be a single unified phenomenon. Indeed, the very process of translation (moving between networks) often results in multiplicity. This is not an opening into a fragmented and incommensurable post-modern world. Instead, translation is the key to maintaining connections, points of coherence amongst multiple ways of enacting the world.

Multiplicity, here, might be related to the literature on boundary objects (Star & Griesemer, 1989), in which a single object is recognized by two different groups but retains an idiosyncratic meaning within either group. Polzer & Robertson (2010) for example, have explored the genetic pedigree as a boundary object between clinic and patient family. The loosely recognized object enables and facilitates a point of connection and a conduit through which members of different groups might interact.

With each of these ideas in mind, I have constructed a framework to illustrate how KT might be considered from a constructionist, actor-network theory perspective. To be sure, there are many different ways one could imagine the KT process and this framework is in no way meant to replace or supplant any other KT model in the literature. One of the main reasons for constructing this framework is to demonstrate that the epistemological assumptions one holds deeply influence a discussion of knowledge translation. So far, in the field of health research in Canada, this discussion has been overwhelmingly situated within positivism. Thus, I have attempted to examine knowledge translation from another

philosophical standpoint and in so doing I hope to open up new possibilities for understanding the KT process.

This framework highlights five key components of a constructionist, ANT-informed understanding of knowledge translation: (i) networks; (ii) human actors; (iii) non-human actors; (iv) multiplicity, and (v) strategies of coordination. These five components are also embedded within a political process of translation involving problematization, interestment, enrolment, and mobilization. Below, I will consider each of these components in turn. Appendix B illustrates how this framework might be modeled in the case of autism genomics and Appendix C illustrates a more generalized model of the LTKP framework.

(i) Networks

In Appendix C, there happens to be three networks being examined as they relate to autism genomics: the laboratory, the clinic, and the family. These networks are each depicted by a circle circumscribed by a dashed line. The dashed line indicates the permeability of the network, as human and non-human actors enter and leave a network over time. The boundaries of a network can always change. The notion of the network is central to the LTKP framework for understanding KT, as knowledge is not viewed as a black-boxed object but rather as a complex practice that exists in the associations between and among actors within a network. Each network, with its distinct constellation of actors, practices knowledge in a particular way. A focus on the networks of associations amongst actors involved in knowledge translation helps to ensure that knowledge is not reified as a single, stable object. While I have considered three networks in this research, there are, of course, a multitude of other networks that could be considered (e.g., a child's school network, an autism support group network, etc.). One of the effects of conceptualizing KT through an ANT approach is that one becomes aware of the limitations of one's understanding. One could not presume to

have explored all the networks that affect a particular local context of KT. This model cannot determine how or where a researcher ought to “cut the networks”. The inclusion or exclusion of various networks would presumably be informed by the specific, local, context in which KT is being explored. There are also pragmatic and logistical considerations to be taken into account (e.g., funding, time, the jurisdiction of ethics review boards, etc.) when deciding how extended one’s exploration will be.

(ii) Human Actors

An important component of this framework of KT is to include all of the relevant human actors within the networks. It is important not to assume too quickly who is and who is not involved in the KT process. For example, when I first began my fieldwork a young post-doctoral fellow approached me and stated that she would be happy to participate in my study but that she felt her work would probably seem really boring and all she did was fiddle about in the lab. She wasn’t sure if or how her role would be relevant but she was willing to let me observe and talk with her. A project manager who happened to be listening to my interaction with the post-doc stated, after the post-doc had left the room, “You won’t want to talk with her for your study. She doesn’t talk to anyone. She wouldn’t be relevant to knowledge translation”. In the end, I found this post-doc was actually an extremely important actor in the KT process. She was intimately involved in the production of genetic information and in tweaking the quality control processes which helped to filter out the real and true variants from experimental artifacts. The project manager was correct that this post-doc was not involved in directly translating genetic knowledge with clinicians through meetings or research reports. She was however, deeply important to the production of the knowledge that was later translated with clinicians and patient families. From a constructionist perspective of KT, this post-doc was an important actor because the contexts and practices of knowledge

production are part of a constructionist description of knowledge translation. The knowledge itself cannot be considered in isolation from the human actors, such as this post-doc, who shape the knowledge into being.

(iii) Non-Human Actors

While human actors are considered in the KTA model (although, not the humans who produce knowledge before it is funneled down), non-human actors are perhaps less explicitly acknowledged. In my model, along with humans, non-human actors are recognized as important throughout knowledge production and translation. Knowledge is practiced in relationship with a variety of non-human actors within any network. If you take away the non-human actors, the knowledge could not be the same. For example, if there were no microarray chips, no pipettes, no PCR, no tubes, no research reports, no ovens or centrifuges – if any of these non-human actors were to be excluded in the network of the laboratory – the genetic knowledge being translated amongst the laboratory, clinic and homes would not be the same. Likewise, if you took away the ADOS, ADI-R, intelligence testing scores, patient file or consent forms – if any of these non-human actors were to be removed from the clinic network – the genetic knowledge translated amongst laboratory, clinic, and home would not be the same. In a constructionist, ANT-informed understanding of knowledge translation, non-human actors must be described.

(iv) Multiplicity

Multiplicity is another idea important to my constructionist understanding of KT. By exploring multiplicity, one is able to understand how an object that is typically considered to be a unified, taken-for-granted phenomenon is practiced or enacted differently in different networks. Paying attention to multiplicity forefronts the ways in which a phenomenon might

be practiced in different ways and thus attempts to prevent any single definition or practice of a phenomenon from obfuscating other ways of practicing or defining that phenomenon. In Appendix C, I have used the individual diagnosed with autism to illustrate this notion of multiplicity. The individual with autism is an integral actor in each of the three networks but the ways in which the individual with autism is constructed in relation to the human and non-human actors in each network is profoundly different. From a constructionist perspective, this recognition of multiplicity allows one to explore the different, sometimes conflicting, practices amongst (and even within) networks. Multiplicity allows us to understand how an actor is practiced within local contexts, and how an actor changes as it is practiced in relation to different sets of actors in different networks.

(v) Strategies of Coordination

If multiplicity illustrates how an object can be enacted differently in different networks, then strategies of coordination describe the spaces in which differences are made to cohere and to relate to one another (Law, 2000). In addition to describing the differences and non-coherence amongst various networks, this model also explores the sites at which practices are temporarily coordinated. These strategies of coordination are integral to the knowledge translation process, linking the practices of one network with the practices of another network. Opportunities which bring actors from various networks together might be called hybrid spaces. For example, in my fieldwork the regular Monday morning meetings brought laboratory and clinical actors together. Meanwhile the feedback session brought clinical and family home actors together. Strategies of coordination often emerge out of these hybrid spaces. For example, the pedigree is constructed in the feedback session and reconstructed through Monday morning meetings. Related to hybrid spaces and strategies of coordination is the notion of the boundary object. Boundary objects may be a key idea for

coordination, as highly idiosyncratic practices in local contexts might only need to be loosely or partially enacted in hybrid spaces or sites of coordination, such as the pedigree. Boundary objects enable partial translations of multiply practiced phenomena. Through strategies of coordination that often emerge through hybrid spaces, a phenomenon is practiced as “more than one but less than many” (Mol, 2002).

Each of these five components of the LTKP framework can be viewed as embedded within a political process of translation (Callon 1986). The networks described are involved in an ongoing negotiation of problematization, interessement, enrolment, and mobilization (as described in Chapter 5). Callon’s (1986) framework allows us to connect the local, day-to-day micro dynamics of translation amongst a few networks to a range of expanding networks. For example, in the case of autism genomics, problematization of autism as something that needed to be “cured” was contested by some participants in the clinical network. These participants were also active in other networks, such as those associated with disability rights. Thus, these participants worried about their ongoing enrolment as actors in the laboratory network. This example of contested problematization illustrates that actors are multiply positioned in other networks and as such there is a fluidity and instability to the translation process. Thus, Callon’s framework highlights an element of uncertainty and ongoing flux in the associations of actors.

8.3b The LTKP Model

In Appendix D the Local Translations of Knowledge in Practice framework is illustrated in a general model. Each of the five components within the LTKP framework is highlighted in the model. Networks are depicted as circles circumscribed by dashed lines; human actors are illustrated with a face symbol; non-human actors are represented with yellow triangles. Meanwhile, I have tried to demonstrate the concept of multiplicity with a

star shape. As the star moves amongst the networks the colour changes. With this changing of colours I am illustrating how we cannot assume that an actor remains the same as it traverses various networks and is practiced in relation to different human and non-human actors. Finally, the explosion symbol represents strategies of coordination which indicate sites in which actors and practices from various networks are combined. For example, the pedigree combines practices derived from the family, the clinic, and the laboratory. Hybrid spaces, such as Monday morning meetings and feedback sessions are integral spaces that bring actors together so that strategies of coordination can occur.

8.4. Comparing the KTA and LTKP Frameworks

There are several differences in the CIHR's KTA model and the framework and model I have proposed. Table 1, compares these models in respect to their conceptualization of knowledge, conceptualization of translation, intended purpose, methodological underpinnings, and epistemological and theoretical underpinnings.

Table 8.1: Comparison of the KTA model and LTKP framework

	Knowledge-to-Action (KTA)	Local Translations of Knowledge in Practice (LTKP)
Conceptualization of Knowledge - What is translated?	Distilled and tailored products and tools; reified objects	Less tangible, materially heterogeneous practices; ontologically fluid
Conceptualization of Translation Process	Occurs after knowledge has been distilled; iterative cycle between producers and users of knowledge	Process in which associations among human and non-human actors are reassembled in a new network; implies change
Intended Purpose	Prescriptive; directive; widespread adoption of knowledge	Descriptive exploration of local translations in everyday practice
Methodological Underpinnings	Quasi-experimental research; survey research	Actor-Network Theory; Ethnography
Theoretical and Epistemological Underpinnings	Planned Action Theories; Cognitive Psychology Theories of Change;	Practice Theory; Constructionism/ Interpretivism

	Objectivism/ Positivism	
--	-------------------------	--

Conceptualization of Knowledge

First, the KTA model and LTKP framework differ in what they considered to be the object of translation, particularly in how *knowledge* is conceptualized. In the KTA model knowledge is distilled and tailored into products and tools through a funnel. The knowledge that is translated consists of these tools and products. In the KTA model knowledge is bound within an object, a best practice guideline for example. In my framework, knowledge is diffuse and less tangible. Knowledge is a practice. Again, it would be more useful to think of the verb knowing (an action that is engaged in) rather than the noun knowledge (a thing that one can possess). The LTKP model attempts to describe the processes of translation between different ways of *knowing in practice*. The KTA model explores how a reified piece of knowledge, a tool or product, is translated. The object of translation in each of these models is derived from very different epistemological starting points. While the KTA model might be best described as being situated within an epistemology of possession, my model can be described as positioned within an epistemology of practice (Brown & Cook, 1999). From an Actor-Network Theory perspective, the KTA model treats knowledge as if it were a black box, a single actor. The LTKP model, however, seeks to peer inside the box and uncover the vast networks of associations amongst a multitude of human and non-human actors; here, knowledge is a permeable, changing network-in-practice rather than a tailored, filtered actor being tossed about amongst producers and users. Central to my framework for KT is an appreciation for the ontological fluidity of that which is translated.

Conceptualization of Translation

A second difference between the two models is in how *translation* is conceptualized.

In particular, these models have very different starting points. In the KTA model, the very raw materials that enter the knowledge funnel are the journal articles derived from primary studies. It is assumed that the knowledge producers are not the same as the knowledge users. In my model, the translation of knowledge occurs far before journal articles are produced and it is assumed that knowledge producers are also knowledge users and vice versa. Every network both produces and uses knowledge. The distinction between knowledge producers and users becomes moot when one considers knowledge from a constructionist epistemology. Instead, it might be more helpful to acknowledge that all networks *practice* or *enact* knowledge. It is knowledge practices that are translated, rather than a reified hunk of knowledge. This translation occurs long before a tool or product is distilled. From a constructionist, ANT perspective, when a best practice guideline or care pathway is translated, it does not exist in isolation. It carries with it its association with a host of hidden actors, both human and non-human with which it was constructed through practice. Translation is the process in which associations between actors are re-assembled and practiced in relation to other networks of actors.

Intended Purpose

A third difference is in the purpose of the models and how they might be used. The KTA model is directive; it aims to prescribe a step-by-step template of how translation should happen and what factors should be considered for successful translation to occur. The KTA model, as proposed by the CIHR, limits its application to the widespread adoption of knowledge. The KTA model might best be used when attempting to implement a particular tool across a widespread group of users. Conversely, the LTKP framework that I propose is descriptive. It explores the undirected, sometimes haphazard, local dynamics of translation that unfold in everyday practice. It is not a “how-to” guide or template for moving a piece of

evidence into practice. The LTKP framework might be considered when trying to understand who and what is involved in knowledge translation. The LTKP emphasis on knowledge as a materially heterogeneous practice affords a more symmetrical, multi-directional understanding of the KT process. The emphasis on multiplicity, difference and coordination could contribute, for example, to an exploration of why a tool is not being used in a particular situation.

8.4a Implications

When I think back to my fieldwork experiences, the focus of the interactions between the laboratory, clinic, and families was not just the translation of genetic results or any reified, tangible piece of information. To be sure, the construction and communication of genetic results were important. However, much more than that was going on. The translation process that I observed was not only about genetic results, but about coordinating different ways of practicing autism. As I explored in my research, the nature of autism multiplied as it was practiced through different sets of human and non-human actors. In the context of knowledge translation, I think when we focus on a particular object (a best practice guideline or tool) to be translated we miss the boat; we fail to appreciate that what is being translated are different ways of practicing the world. Instead of paying such fervent attention to an object of translation (distilled guideline or care pathway), I wonder if the KT process might be better understood if we de-centre the object and approach the object as a mere vehicle through which we might understand difference, multiplicity and non-coherence as well as the places where practices overlap and come together amongst various networks of actors.

In the quickly changing, cutting-edge world of genomics where new technologies rapidly reconfigure the way the body is practiced, it is assumed that results are contingent and could change in the future. It is not only a result that is being translated in a feedback

session, but a way of practicing autism, such that autism is *becoming* genomic. By de-centering the object of translation, we are able to step back and explore what practices and ways of knowing and *doing* the world are implicit in that object. How might these implicit practices, which carry epistemological and ontological assumptions, rub up against another way of knowing and doing the world? Are there places where partial connections and coherence can be found or might a particular object with its implicit epistemological and ontological assumptions be incommensurable with another context?

8.5 Conclusion

My research has explored the process of knowledge translation from a constructionist epistemology and an Actor-Network Theory methodology with an emphasis on theories of practice. This approach has informed my interpretation of knowledge translation within the context of autism genomics. Insights emerged from my case study of autism genomics that might be applied to a more general discussion of knowledge translation. In particular, the idea that translation involves transformation and change was demonstrated as I followed human and nonhuman actors amongst the clinic, laboratory, and family home. I also raise the idea that knowledge translation is an inherently political process and explore Callon's (1986) framework for unpacking the political dynamics involved in translation. Finally, when knowledge is conceptualized as being practiced in the material world, knowledge translation becomes reassembled as ontological translation; the KT endeavour becomes one of translating between different ways of practicing reality. With each of these insights in mind, I have constructed the Local Translations of Knowledge in Practice framework and model of knowledge translation which highlights networks of human and non-human actors, multiplicity, and strategies of coordination.

My aim in doing this research is to contribute to the current Canadian

discussion on the science of knowledge translation by exploring KT from a philosophical and theoretical position that is novel to the prevailing positivist discourse championed by the CIHR. I have tried to demonstrate how a constructionist, actor-network theory- inspired conceptualization of knowledge translation might offer new insights into the on-going, local micro-dynamics of knowledge translation. My aim is to demonstrate how the methodological and theoretical starting point of any KT research profoundly shapes what is examined and what is left untouched and unexplored. Methodological pluralism is needed in order to explore knowledge translation in new ways. Expanding the range of philosophical positions attended to in KT research will contribute to a richer understanding of the KT process.

References

- Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: On the threshold of a new neurobiology (vol 9, pg 341, 2008). *Nature Reviews Genetics*, 9(6), 341-355.
- Akrich, M. (1992). The de-scription of technical objects. In W. Bijker, & J. Law (Eds.), *Shaping technology/ building society: Studies in sociotechnical change* (pp. 205-224). Cambridge, MA: The MIT Press.
- Akrich, M., & Latour, B. (1992). A summary of a convenient vocabulary for the semiotics of human and nonhuman assemblies. In W. Bijker, & J. Law (Eds.), *Shaping technology/ building society: Studies in sociotechnical change* (pp. 259-264). Cambridge, MA: The MIT Press.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders - TR* (4th ed.). Washington, D.C.: American Psychiatric Association.
- Armstrong, D., Michie, S., & Marteau, T. (1998).
Revised identity: A study of the process of genetic counselling. *Social Science & Medicine*, 47, 1653-8.
- Armstrong, R., Waters, E., Roberts, H., Oliver, S., & Popay, J. (2006). The role and theoretical evolution of knowledge translation and exchange in public health. *Public Health*, 28(4), 384-389.
- Asch, A. (1999). Prenatal diagnosis and selective abortion: A challenge to practice and policy. *American Journal of Public Health*, 89(11), 1649-1657.
- Asch, A. (2000). In Parens E., Asch A. (Eds.), *Prenatal testing and disability rights*. Washington, DC: Georgetown University Press.

- Asch, A. (2005). Big tent bioethics: Toward an inclusive and reasonable bioethics. *The Hastings Centre Report*, 35(6), 11-13.
- Atkinson, P., Coffey, A., Delamont, S., Lofland, J., & Lofland, L. (Eds.). (2001). *Handbook of ethnography*. Thousand Oaks, California: Sage Publications, Inc.
- Atkinson, P., Parsons, E., & Featherstone, K. (2001). Professional constructions of family and kinship in medical genetics. *New Genetics and Society*, 20, 5-24.
- Atkinson, P. (2001). Ethnography and the representation of reality. In R. Emerson (Ed.), *Contemporary field research: Perspectives and formulations* (2nd ed., pp. 89-101). Prospect Heights, Illinois: Waveland Press, Inc.
- Barge-Schaapveld, D., Maas, S., Polstra, A., Knegt, L., & Hennekam, R. (2011). The atypical 16p11.2 deletion: A not so atypical microdeletion syndrome? *American Journal of Medical Genetics Part A*, 9999, 1-7.
- Barnes, B. (2001). Practice as collective action. In T. Schatzki, K. Knorr-Cetina & E. von Savigny (Eds.), *The practice turn in contemporary theory* (pp. 17). London: Routledge.
- Bartlett, C. W., Gharani, N., Millonig, J. H., & Brzustowicz, L. M. (2005). Three autism candidate genes: A synthesis of human genetic analysis with other disciplines. *International Journal of Developmental Neuroscience*, 23(2-3), 221-234.
- Berg, M., & Mol, A. (Eds.). (1998). *Differences in medicine: Unraveling practices, techniques, and bodies*. Durham: Duke University Press.
- Berkel, S., Marshall, C. R., Weiss, B., Howe, J., Roeth, R., Moog, U., . . . Rappold, G. A. (2010). Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. *Nature Genetics*, 42(6), 489-91.

- Bettelheim, B. (1955). *Truants from life: The rehabilitation of emotionally disturbed children*. New York: The Free Press.
- Bettelheim, B. (1967). *The empty fortress: Infantile autism and the birth of the self*. New York: The Free Press.
- Bhattacharyya, O., & Zwarenstein, M. (2009). Methodologies to evaluate effectiveness of knowledge translation interventions. In S. Straus, J. Tetroe & I. Graham (Eds.), *Knowledge translation in health care: Moving from evidence to practice* (Oxford ed., pp. 249-260) Blackwell Publishing.
- Bloor, D. (1999). Anti-latour. *Studies in History and Philosophy of Science*, 30(1), 81-112.
- Bonora, E., Lamb, J., Barnby, G., Bailey, A., & Monaco, A. (2006). Genetic basis of autism. In S. O. Moldin, & J. L. R. Rubenstein (Eds.), *Understanding autism: From basic neuroscience to treatment* (pp. 25-48). London: Taylor & Francis.
- Bowen, S., Martens, P., & Need to Know Team. (2005). Demystifying knowledge translation: Learning from the community. *Journal of Health Services Research & Policy*, 10(4), 203-11.
- Brown, J. S., & Cook, S. D. (1999). Bridging epistemologies: The generative dance between organizational knowledge and organizational knowing. *Organization Science*, 10(4), 381-400.
- Brown, N., Rappert, B., & Wester, A. (2000). *Contested futures: A sociology of prospective techno-science*. Aldershot, U.K.: Ashgate.
- Bruni, A. (2005). Shadowing software and clinical records: On the ethnography of non-humans and heterogeneous contexts. *Organization*, 12(3), 357-378.

- Buchanan, J., & Scherer, S. (2008). Contemplating effects of genomic structural variation. *Genetics in Medicine, 10*(9), 639-647.
- Callon, M. (1991). Techno-economic networks and irreversibility. In J. Law (Ed.), *A sociology of monsters: Essays on power, technology and domination* (pp. 132-164). London: Routledge.
- Callon, M. (1987). Some elements of a sociology of translation: Domestication of the scallops and the fishermen at st. brieuc bay. In J. Law (Ed.), *Power, action and belief: A new sociology of knowledge* (). London: Routledge and Kegan Paul.
- Canadian Institutes of Health Research. (2004). *The CIHR knowledge translation strategy 2004-2009: Innovation in action*. (). Ottawa, ON: Canadian Institutes of Health Research.
- Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada. (2010). *Tri-council policy statement: Ethical conduct for research involving humans*. Retrieved
- Caplan, N. (1979). The tow-communities theory and knowledge utilization. *American Behavioral Scientist, 22*(3), 459-70.
- Casper, M. (1998). Working on and around human fetuses: The contested domain of fetal surgery. In M. Berg, & A. Mol (Eds.), *Differences in medicine: Unravelling practices, techniques and bodies* (pp. 28-52). Durham: Duke University Press.
- iuladait , Z., & et al. (2011). Mental retardation and autism associated with 16p11.2 microdeletion: Incomplete penetrance and variable expressivity *Journal of Applied Genetics, 52*, 443-449.

- Clifford, J. (1997). *Routes: Travel and translation in the late twentieth century*. Cambridge, MA: Harvard University Press.
- Collins, H. M. (2010). *Tacit and explicit knowledge*. Chicago: The University of Chicago Press.
- Collins, H., & Yearley, S. (1992). Epistemological chicken. In A. Pickering (Ed.), *Science as practice and culture* (pp. 301-326). Chicago: University of Chicago Press.
- Cook, E. H., & Scherer, S. (2008). Copy-number variations associated with neuropsychiatric conditions. *Nature*, *455*, 919-923.
- Crotty, M. (1998). *The foundations of social research: Meaning and perspective in the research process*. London: Sage Publications.
- Curry, S. J. (2000). Organizational interventions to encourage guideline implementation. *Chest*, *118*(2), S40-S46.
- Cussins, C. (1996). Ontological choreography: Agency through objectification in infertility clinics. *Social Studies of Science*, *26*, 575-610.
- Cussins, C. (1998). Ontological choreography: Agency for women patients in an infertility clinic. In M. Berg, & A. Mol (Eds.), *Differences in medicine: Unravelling practices, techniques and bodies* (pp. 166-201). Durham: Duke University Press.
- Dansecu, E., Sundar, P., Kasprzak, S., Witteveen, T., Woltman, H., & Manion, I. (2009). Are we there yet? evaluation and the knowledge translation journey. *J can Acad Child Adolesc Psychiatry*, *18*(1), 7-15.
- Davis, D., Evans, M., Jadad, a., Perrier, L., Rath, D., & Ryan, D. (2003a). The case for knowledge translation: Shortening the journey from evidence to effect. *British Medical Journal*, *327*, 33-5.

- Davis, D., Evans, M., Jadad, A., Perrier, L., Rath, D., Ryan, D., . . . Zwarenstein, M. (2003b). The case for knowledge translation: Shortening the journey from evidence to effect *British Medical Journal*, 327(5), 33.
- Davison, C. (2009). Knowledge translation: Implications for evaluation. In J. M. Ottoson, & P. Hawe (Eds.), *Knowledge utilization, diffusion, implementation, transfer, and translation: Implications for evaluation. new directions for evaluation* (pp. 75-87)
- Denzin, N. K. (2004). The art and politics of interpretation. In S. Nagy Hesse-Biber, & P. Leavy (Eds.), *Approaches to qualitative research: A reader on theory and practice* (pp. 447-472). Oxford: Oxford University Press.
- Devlin, B., & Scherer, S. (2012). Genetic architecture in autism spectrum disorder. *Current Opinion in Genetics and Development*, 22, 1-9.
- Dobrow, M. J., Goel, V., Lemieux-Charles, L., Black, N. A. (2006) The impact of context on evidence utilization: a framework for expert groups developing health policy recommendations. *Social Science & Medicine*, 63(7), 1811-1824.
- Eakin, J., & Mykhalovskiy, E. (2003). Reframing the evaluation of qualitative health research: Reflections on a review of appraisal guidelines in the health sciences. *Journal of Evaluation in Clinical Practice*, 9(2), 187-194.
- Edwards, E. (2007). An ethics for working up? japanese corporate scandals and rethinking lessons about fieldwork. *Critical Asian Studies*, 39(4), 561-582.
- Estabrooks, C. (1999). The conceptual structure of research utilization. *Research in Nursing Health*, 22, 203-16.
- Evans-Pritchard, E. (1937). *Witchcraft, oracles and magic among the azande*. Oxford: Oxford University Press.

- Fombonne, E. (2005). The changing epidemiology of autism. *Journal of Applied Research in Intellectual Disabilities, 18*, 281-294.
- Fombonne, E. (2006). Past and future perspectives on autism epidemiology. In S. O. Moldin, & J. L. R. Rubenstein (Eds.), *Understanding autism: From basic neuroscience to treatment* (pp. 25-48). London: Taylor & Francis.
- Fox, N. J. (2003) Practice-based evidence: towards collaborative and transgressive research. *Sociology, 37*(1), 81-102.
- Freitag, C. M. (2007). The genetics of autistic disorders and its clinical relevance: A review of the literature. *Molecular Psychiatry, 12*(1), 2-22.
- Fujimura, J. (1996). *Crafting science: A socio-history of the quest for the genetics of cancer*. Cambridge: Harvard University Press.
- Geertz, C. (1973). *The interpretation of cultures: Selected essays*. New York: Basic Books.
- Geertz, C. (1988). *Works and lives: The anthropologist as author*. Stanford, California: Stanford University Press.
- Geertz, C. (2001). Thick description: Toward an interpretive theory of culture. In R. Emerson (Ed.), *Contemporary field research: Perspectives and formulations* (2nd ed., pp. 55-75). Prospect Heights, Illinois: Waveland Press, Inc.
- George, A., Marquis-Nicholson, R., Zhang, L. T., Love, J. M., Ashton, F., Aftimos, S., . . . Williams, L. C. (2011). Chromosome microarray analysis in a clinical environment: New perspective and new challenge. *British Journal of Biomedical Science, 68*(2), 100-108.

- Gibbon, S. (2002). Family trees in clinical cancer genetics: Re-examining geneticization. *Science as Culture*, 11(4), 429-57.
- Gillberg, C., & Coleman, M. (2000). *The biology of the autistic syndromes*. Cambridge: Cambridge University Press.
- Giordano, J., O'Reilly, M., Taylor, H., & Dogra, N. (2007). Confidentiality and anonymity: The challenge(s) of offering research participants a choice of disclosing their identity. *Qualitative Health Research*, 17(2), 264-275.
- Goffman, E. (1959). *The presentation of self in everyday life*. New York: Anchor.
- Graham, I., Logan, J., Harrison, M., Straus, S., Tetroe, J., Caswell, W., & Robinson, N. (2006). Lost in translation: Time for a map? *Journal of Continuing Education in the Health Professions*, 26(1), 13-24.
- Graham, J., Adelson, N., Fortin, S., Bibeau, G., Lock, M., Hyde, S., . . . Waldram, J. (February 7, 2011, The end of medical anthropology in canada? A manifesto *University Affairs*,
- Greenhalgh, R., Macfarlane, F., Bate, P., & Kyriakidou, O. (2004). Diffusion of innovations in service organizations: Systematic review and recommendations. *Milbank Quarterly*, 82, 581-629.
- Greenhalgh, T., & Russell, J. (2006). Promoting the skills of knowledge translation in an online master of science course in primary health care. *The Journal of Continuing Education in the Health Professions*, 26(2), 100-108.
- Grimshaw, J. M., Santesso, N., Cumpston, M., Mayhew, A., & McGowan, J. (2006). Knowledge for knowledge translation: the role of the Cochrane Collaboration. *The Journal of Continuing Education in the Health Professions*, 26, 55-62.

- Grinker, R. R. (2007). *Unstrange minds: Remapping the world of autism*. New York: Basic Books.
- Gropman, A., & Batshaw, M. Epigenetics, copy number variation, and other molecular mechanisms underlying neurodevelopmental disabilities: New insights and diagnostic approaches. *Journal of Developmental and Behavioural Pediatrics*, *32*(7), 582-591.
- Guba, E., & Lincoln, Y. (2004). Competing paradigms in qualitative research: Theories and issues. In S. Nagy Hesse-Biber, & P. Leavy (Eds.), *Approaches to qualitative research: A reader on theory and practice* (pp. 1-17). New York: Oxford University Press.
- Gusella, J., Wexler, N., Conneally, M., Naylor, S., Anderson, M. A., Tanzi, R., . . . Martin, J. A polymorphic DNA marker genetically linked to huntington's disease. *Nature*, *306*, 234-238.
- Gusterson, H. (1997). Studying up revisited. *PoLAR: Political and Legal Anthropology Review*, *20*(1), 114-119.
- Hacking, I. (1999). *The social construction of what?*. Cambridge, MA: Harvard University Press.
- Happé, F., & Ronald, A. (2008). The 'fractionable autism triad': A review of evidence from behavioral, genetic, cognitive and neural research. *Neuropsychological Review*, *18*, 287-304.
- Heath, D. (1998). Locating genetic knowledge: Picturing marfan syndrome and its travelling constituencies. *Science, Technology & Human Values*, *23*(1), 71-97.
- Hertz-Picciotto, I., Croen, L. A., Hansen, R., Jones, C. R., van de Water, J., & Pessah, I. N. (2006). The CHARGE study: An epidemiologic investigation of genetic and

- environmental factors contributing to autism. *Environmental Health Perspectives*, *114*(7), 1119-1125.
- Hine, C. (2007). Multi-sited ethnography as a middle-range methodology for contemporary STS. *Science, Technology & Human Values*, *32*(6), 652-671.
- Jacobson, N., Butterill, D., Goering, P. (2003) Developing a framework for knowledge translation: understanding user context. *Journal of Health Services Research & Policy*, *8*(2), 94-99.
- Jensen, C. B. (2004). A nonhumanist disposition: On performativity, practical ontology, and intervention. *Configurations*, *12*, 229-261.
- Jensen, C. B., & Rodje, K. (Eds.). (2010). *Deleuzian intersections: Science, technology, anthropology*. New York: Berghahn Books.
- Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*, 217-250.
- Kanner, L., & Eisener, L. (1956). Early infantile autism 1943-1955. *American Journal of Orthopsychiatry*, *25*, 55-65.
- Kaiser, K. (2009). Protecting respondent confidentiality in qualitative research. *Qualitative Health Research*, *19*(11), 1632-1641.
- Kay, L. (2000). *Who wrote the book of life: A history of the genetic code*. Stanford, CA: Stanford University Press.
- Kelly, A. (2009). In defence of anonymity: Rejoining the criticism. *British Educational Research Journal*, *35*(3), 431-445.
- Kerem, B., Rommens, J., Buchanan, J., Markiewicz, D., Cox, T., & Chakravarti, A. (1989). Identification of the cystic fibrosis gene: Genetic analysis. *Science*, *245*, 1073-80.

- Kielinen, M., Linna, S., & Moilanen, I. (2000). Autism in northern Finland. *European Child and Adolescent Psychiatry, 9*, 162-167.
- Kinsella, A., & Whiteford, G. (2008) Knowledge generation and utilization in occupational therapy: Toward epistemic reflexivity. *Australian Occupational Therapy Journal*,
- Kitson, A., Harvey, G., & McCormack, B. (1998). Enabling the implementation of evidence-based practice: A conceptual framework. *Quality in Health Care, 7*, 149-158.
- Knorr-Cetina, K. (2001). Objectual practice. In T. Schatzki, K. Knorr-Cetina & E. von Savigny (Eds.), *The practice turn in contemporary theory* (pp. 175-188). London: Routledge.
- Kothari, A., & Armstrong, R. (2011). Community-based knowledge translation: Unexplored opportunities. *Implementation Science, 6*, 59.
- Kothari, A., Bickford, J., Edwards, N., Dobbins, M., & Meyer, M. (2011). Uncovering tacit knowledge: A pilot study to broaden the concept of knowledge in knowledge translation. *BMC Health Services Research, 11*, 198.
- Kumar, R., S, K., Sudi, J., Conrad, D., Brune, C., Badner, J., . . . Cook, E. (2008). Recurrent 16p11.2 microdeletions in autism. *Human Molecular Genetics, 17*, 628-638.
- Lander, E. (1996). The new genomics: Global views of biology. *Science, 274*, 536-539.
- Lather, P. (1993). Fertile obsession: Validity after poststructuralism. *The Sociological Quarterly, 34*(4), 673-694.
- Landry, R., Lamari, M., & Amara, N. (2007). Extent and determinants of utilization of university research in government agencies. *Public Administration Review, 63*, 193-206.
- Lang, E., Wyer, P., & Hanes, B. (2007). Knowledge translation: Closing the evidence to practice gap. *Annals of Emergency Medicine, 49*, 355-363.

- Lather, P. (1993). Fertile obsession: Validity after poststructuralism. *The Sociological Quarterly*, 34(4), 673-694.
- Latour, B. (1988). The politics of explanation: An alternative. In S. Woolgar (Ed.), *Knowledge and reflexivity: New frontiers in the sociology of knowledge* (). London: Sage Publications.
- Latour, B. (1992). Where are the missing masses? the sociology of a few mundane artifacts. In W. Bijker, & J. Law (Eds.), *Shaping technology/ building society: Studies in sociotechnical change* (pp. 225-258). Cambridge, MA: MIT Press.
- Latour, B. (1999). *Pandora's hope: Essays on the reality of science studies*. Cambridge, MA: Harvard University Press.
- Latour, B. (2005). *Reassembling the social: An introduction to actor-network theory*. Oxford: Oxford University Press.
- Latour, B. (2008). A textbook case revisited: Knowledge as a mode of existence. In E. J. Hackett, O. Amsterdamska, M. Lynch & J. Wajcman (Eds.), *The handbook of science and technology studies* (pp. 83-112). Cambridge, MA: MIT Press.
- Latour, B. (2012). "What's the story?": Organizing as a mode of existence. In J. Passoth, B. Peuker & M. Schillmeier (Eds.), *Agency without actors* (pp. 163-177). London: Routledge.
- Latour, B. (1986). The powers of association. In J. Law (Ed.), *Power, action and belief: The new sociology of knowledge?*(pp. 264-280). London: Routledge & Kegan Paul.
- Latour, B. (1987). *Science in action: How to follow scientists and engineers through society*. Milton Keynes: Open University Press.

- Latour, B. (1993a). Pasteur on lactic acid yeast: A partial semiotic analysis. *Configurations*, *1*(1), 129-146.
- Latour, B. (1993b). *We have never been modern*. Cambridge, MA: Harvard University Press.
- Latour, B. (1999a). For david bloor... and beyond: A reply to david bloor's 'anti-latour'. *Studies in History and Philosophy of Science*, *30*(1), 113-129.
- Latour, B. (1999b). On recalling ANT. In J. L. a. J. Hassard (Ed.), *Actor-network theory and after* (pp. 15-25). Malden, MA: Blackwell Publishers.
- Latour, B. (1999c). *Pandora's hope: Essays on the reality of science studies*. Cambridge, MA: Harvard University Press.
- Latour, B. (2003). The promises of constructivism. In D. Ihde, & E. Selinger (Eds.), *Chasing technoscience: Matrix for materiality* (pp. 27-46). Indianapolis: Indiana University Press.
- Latour, B. (2004). *Politics of nature: How to bring the sciences into democracy*. Cambridge, MA: Harvard University Press.
- Latour, B. (2005). *Reassembling the social: An introduction to actor-network theory*. Oxford: Oxford University Press.
- Latour, B. (2008). A textbook case revisited: Knowledge as a mode of existence. In E. J. Hackett, O. Amsterdamska, M. Lynch & J. Wajcman (Eds.), *The handbook of science and technology studies* (pp. 83-112). Cambridge, MA: MIT Press.

- Latour, B., & Callon, M. (1992). Don't throw the baby out with the bath school!: A reply to collins and yearley. In A. Pickering (Ed.), *Science as practice and culture* (pp. 343-368). Chicago: University of Chicago Press.
- Latour, B., & Woolgar, S. (1986). *Laboratory life: The construction of scientific facts*. Princeton, NJ: Princeton University Press.
- Lavis, J. (2006). Research, public policymaking, and knowledge translation processes: Canadian efforts to build bridges. *The Journal of Continuing Education in the Health Professions*, 26, 37-45.
- Lavis, J., Roberston, D., Woodside, J., McLeod, C., Abelson, J., & Knowledge Transfer Study Group. (2003). How can research organizations more effectively transfer research knowledge to decision makers? *Milbank Quarterly*, 81, 221-248.
- Law, J. (2000). On the subject of the object: Narrative, technology, and interpellation. *Configurations*, 8, 1-29.
- Law, J. (2012). Reality failures. In J. Passoth, B. Peuker & M. Schillmeier (Eds.), *Agency without actors* (pp. 146-160). London: Routledge.
- Law, J. (1999). After ANT: Complexity, naming, and topology. In J. L. a. J. Hassard (Ed.), *Actor-network theory and after* (pp. 1-14). Malden, MA: Blackwell Publishers.
- Law, J., & Callon, M. (1992). The life and death of an aircraft: A network analysis of technical change. In W. Bijker, & J. Law (Eds.), *Shaping technology/ building society* (pp. 21-52). Cambridge, MA: The MIT Press.
- Law, J., & Callon, M. (1997). After the individual in society: Lessons on collectivity from science, technology and society. *Canadian Journal of Sociology*, 22(2), 165.

- Law, J., & Singleton, V. (2000). Performing technology's stories: On social constructivism, performance, and performativity. *Technology and Culture, 41*, 765-776.
- Law, J. (2002). *Aircraft stories: Decentering the object in technoscience*. Durham: Duke University Press.
- Law, J. (2003). *Transduction/Trahison: Notes on ANT*. (). Lancaster University: The Center
- Law, J., & Mol, A. (Eds.). (2002). *Complexities: Social studies of knowledge practices*. Durham, NC: Duke University Press.
- Law, J., & Mol, A. (2008). The actor-enacted: Cumbrian sheep in 2001. In C. Knappett, & L. Malafouris (Eds.), *Material agency: Toward a non-anthropocentric approach* (pp. 57-77). New York: Springer.
- Law, J. (2007). *Actor network theory and material semiotics*. Retrieved
- Lawler, C. P., Croen, L. A., Grether, J. K., & Van de Water, J. (2004). Identifying environmental contributions to autism: Provocative clues and false leads. *Mental Retardation and Developmental Disabilities Research Reviews, 10*(4), 292-302.
- Lawless, E. (1992). 'I was afraid someone like you...an outsider... would misunderstand': Negotiating interpretive differences between ethnographers and subjects. *Journal of American Folklore, 105*, 302-314.
- Leblond, C., Heinrich, J., Delorme, R., Proepper, C., Betancur, C., Huguet, G., Melke, J. (2012). Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders. *PLoS Genetics, 8*(2), e1002521.
- Lee, N., & Brown, S. (1994). Otherness and the actor network: The undiscovered continent. *American Behavioral Scientist, 37*(6), 772-790.

- Levy, D., & et al. (2011). Rare de novo and transmitted copy-number variation in autistic spectrum disorders. *Neuron*, *70*, 886-897.
- Lionel, A., Crosbie, J., Barbosa, N., Goodale, T., Thiruvahindrapuram, B., Rickaby, J., . . . Scherer, S. W. (2011). Rare copy number variation discovery and cross-disorder comparison identify risk genes for ADHD. *Science Translational Medicine*, *3*(95ra75), July 19, 2012.
- Lippman, A. (1992). Led (astray) by genetic maps. *Social Science & Medicine*, *35*(12), 1470.
- Lippman, A. (1994). The genetic construction fo prenatal testing. In K. H. Rothenberg, & E. J. Thomson (Eds.), *Women and prenatal testing* (pp. 13-14). Columbus: Ohio State University.
- Lippman, A. (1998). The politics of health: Geneticization versus health promotion. In S. Sherwin (Ed.), *The politics of Women's health: Exploring agency and autonomy* (pp. 64-82). Philadelphia: Temple University Press.
- Lock, M., & Gordon, D. (Eds.). (1988). *Biomedicine examined*. Dordrecht, The Netherlands: Kluwer Academic Publishers.
- Lock, M., & Nguyen, V. (2010). *An anthropology of biomedicine* Wiley-Blackwell.
- Lomas, J., Sisk, J., & Stocking, B. (1993). From evidence to practice in the united states, the united kingdom, and canada. *Milbank Quarterly*, *71*(3), 405-10.
- Lord, C. (1989). Autism diagnostic observation schedule: A standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, *19*, 185-212.

- Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview - revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*, 659-685.
- Lord, C., & Spence, S. (2006). Autism spectrum disorders: Phenotype and diagnosis. In S. O. Moldin, & J. L. R. Rubenstein (Eds.), *Understanding autism: From basic neuroscience to treatment* (pp. 1-24). London: Taylor & Francis.
- Lynch, M. (2000). Against reflexivity as an academic virtue and source of privileged knowledge. *Theory, Culture & Society, 17*(3), 26-54.
- Malinowski, B. (1922). *Argonauts of the western pacific*. London: Routledge.
- Marshall, C. R., & Scherer, S. W. (2012). Detection and characterization of copy number variation in autism spectrum disorder. In L. Feuk (Ed.), *Genomic structural variants: Methods and protocols* ()
- Marshall, C., Noor, A., Vincent, J., Lionel, A., Feuk, L., Skaug, J., . . . Scherer, S. (2008). Structural variation of chromosomes in autism spectrum disorder. *The American Journal of Human Genetics, 82*, 1-12.
- Martin, E. (1987). *The woman in the body: A cultural analysis of reproduction*. Boston: Beacon.
- McWilliams, C. (2007). Continuing education at the cutting edge: Promoting transformative knowledge translation. *Journal of Continuing Education in the Health Professions, 27*(2), 72-9.

- Mead, M. (1928). *Coming of age in samoa: A psychological study of primitive youth for western civilization*. New York: Harper Collins.
- Mol, A. (1999). Ontological politics: A word and some questions. In J. L. a. J. Hassard (Ed.), *Actor-network theory and after* (pp. 74-89). Malden, MA: Blackwell Publishers.
- Mol, A. (2002). *The body multiple: Ontology in medical practice*. Durham, NC: Duke University Press.
- Mol, A., & Berg, M. (1994). Principles and practices of medicine: The co-existence of various anemias. *Culture, Medicine, and Psychiatry*, 18, 247-265.
- Mol, A., & Law, J. (1994). Regions, networks, and fluids: Anaemia and social topology. *Social Studies of Science*, 24, 641-671.
- Mol, A., & Law, J. (2003). *Emobdied action, enacted bodies: The example of hypoclycaemia*. (). Lancaster University: The Centre for Science Studies.
- Mol, A., & Mesman, J. (1996). Neonatal food and the politics of theory: Some questions of method. *Social Studies of Science*, 26, 419-444.
- Nadesan, M. (2005). *Constructing autism: Unravelling the 'truth' and understanding the social*. London: Routledge.
- Nader, L. (1969). Up the anthropologist: Perspectives gained from "studying up". In D. Hymes (Ed.), *Reinventig anthropology* (pp. 284-311). New York: Pantheon Books.
- Nelkin, D., & Lindee, M. S. (1995). *The DNA mystique: The gene as cultural icon*. New York: Freeman.
- Nespor, J. (2000). Anonymity and place in qualitative research. *Qualitative Inquiry*, 6(4), 546-569.

- Neyland, D. (2006). Dismissed content and discontent: An analysis of the strategic aspects of actor-network theory. *Science, Technology & Human Values*, 31(1), 29-51.
- Nisker, J., & Daar, A. (2006). Moral presentation of genetics-based narratives for public understanding of genetic science and its implications. *Public Understanding of Science*, 15(1), 113-123.
- Nonaka, I., & Noboru, K. (1998). The concept of *ba*: Building a foundation for knowledge creation. *California Management Review*, 40(3), 40-54.
- Novas, C., & Rose, N. (2000). Genetic risk and the birth of the somatic individual. *Economy and Society*, 29(4), 485-513.
- Nukaga, Y. (2002). Between tradition and innovation in new genetics: The continuity of medical pedigrees and the development of combination work in the case of huntington's disease. *New Genetics and Society*, 21(1), 39-64.
- Nukaga, Y., & Cambrosio, A. (1997). Medical pedigrees and the visual production of family disease in canadian and japanese genetic counselling practice. In M. A. Elston (Ed.), *The sociology of medical science and technology* (pp. 29-55). Oxford: Blackwell.
- Ortner, S. (1996). *Making gender: The politics and erotics of culture*. Boston: Beacon Press.
- Ortner, S. (1999). Introduction. In S. Ortner (Ed.), *The fate of culture: Geertz and beyond* (pp. 1-13). Berkeley: University of California Press.
- Ortner, S. (2006). *Anthropology and social theory: Culture, power, and the acting subject*. Durham: Duke University Press.

- Ottenberg, S. (1990). Thrity years of fieldnotes: Changing relationships to the text. In R. Sanjek (Ed.), *Fieldnotes: The makings of anthropology* (pp. 139-160). Ithaca, NY: Cornell University Press.
- PGCC Committee. (2009). Genomewide association studies: History, rationale, and prospects for psychiatric disorders. *The American Journal of Psychiatry*, *166*(5), 540-556.
- Pickering, A. (2001). Practice and posthumanism: Social theory and a history of agency. *The practice turn in contemporary theory* (pp. 163). London: Routledge.
- Pickering, A. (1995). *The mangle of practice: Time, agency, and science*. Chicago: University of Chicago Press.
- Pickler, L., & Elias, E. (2009). Genetic evaluation of the child with an autism spectrum disorder. *Pediatric Annals*, *38*(1), 26-29.
- Pinto, D., Pagnamenta, A., Klei, L., Anney, R., Merico, D., Regan, R., & Conroy, J. (2010). Functional impact of global rare copy number variation in autism spectrum disorder. *Nature*, *466*(7304), 368-372.
- Polanyi, M. (1966). *The tacit dimension*. Garden City, New York: Doubleday & Company.
- Polzer, J., & Robertson, A. (2010). Seeing and knowing in twenty-first century genetic medicine: The clinical pedigree as epistemological tool and hybrid risk technique. *New Genetics and Society*, *29*(2), 133-47.
- Pritchard, J. (2001). Are rare variants responsible for susceptibility to complex diseases? *American Journal of Human Genetics*, *69*(1), 124-137.

- Priyadharshini, E. (2003). Coming unstuck: Thinking otherwise about "studying up".
Anthropology & Education Quarterly, 34(4), 420-437.
- Rabinow, P. (1996). *Making PCR: A story of biotechnology*. Chicago: The University of Chicago Press.
- Rabinow, P. (1992). Artificiality and enlightenment: From sociobiology to biosociality. In J. Crary, & S. Kwinter (Eds.), *Zone 6: Incorporations* (). New York: Zone.
- Rapp, R. (1988). Chromosomes and communication: The discourse of genetic counselling.
Medical Anthropology Quarterly, (2), 143-57.
- Reimer Kirkham, S., Baumbusch, J., Schultz, A., & Anderson, J. (2007). Knowledge development and evidence-based practice: Insights and opportunities from a postcolonial feminist perspective for transformative nursing practice. *Advances in Nursing Science*, 30(1), 26-40.
- Richardson, L. (2004). Writing: A method of inquiry. In S. Nagy Hesse-Biber, & P. Leavy (Eds.), *Approaches to qualitative research: A reader on theory and practice* (pp. 473-495). Oxford: Oxford University Press.
- Riggs, E., Church, D., Hanson, K., Horner, V., Kaminsky, E., Kuhn, R., . . . Martin, C. (2012). Towards an evidence-based process for the clinical interpretation of copy number variation. *Clinical Genetics*, 81, 403-412.
- Riordan, J., Rommens, J., Kerem, B., Alon, N., Rozmahel, R., Grzelczak, Z., . . . Chou, J. (1989). Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. *Science*, 245, 1437.

- Risch, N., Spiker, D., Lotspeich, L., Nouri, N., Hinds, D., Hallmayer, J., . . . Dimiceli, S. (1999). A genomic screen of autism: Evidence for a multilocus etiology. *American Journal of Human Genetics*, *65*, 493-507.
- Ronald, A., Happe, F., Bolton, P., Butcher, L. M., Price, T. S., Wheelwright, S., . . . Plomin, R. (2006). Genetic heterogeneity between the three components of the autism spectrum: A twin study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*(6), 691-699.
- Rogers, E. M. (1962). *Diffusion of innovations*. New York: The Free Press.
- Rose, M. (2012,). DNA unlocks iceman's secrets. *The London Free Press*, pp. 1.
- Rutter, M. (2000). Genetic studies of autism: From the 1970s into the millennium. *Journal of Abnormal Child Psychology*, *28*(1), 3-14.
- Salyakina, D., Cukier, H., Lee, J., Sacharow, S., Nations, L., & et al. (2011). Copy number variants in extended autism spectrum disorder families reveal candidates potentially involved in autism risk. *PLoS ONE*, *6*(10), July 18, 2012-e26049.
- Sanjeck, R. (Ed.). (1990). *Fieldnotes: The makings of anthropology*. Ithaca, NY: Cornell University Press.
- Schaaf, C., & Zoghbi, H. (2011). Solving the autism puzzle a few pieces at a time. *Neuron*, *70*, 806-808.
- Schatzki, T. (2001). Introduction: Practice theory. In T. Schatzki, K. Knorr-Cetina & E. von Savigny (Eds.), *The practice turn in contemporary theory* (pp. 1-15). London: Routledge.

- Schellenberg, G., Dawson, G., Sung, Y., Estes, A., Munson, J., Rosenthal, E., . . . Wijsman, E. (2006). Evidence for multiple loci from a genome scan of autism kindred. *Molecular Psychiatry, 11*, 1049-1060.
- Scheper-Hughes, N. (2000). Ire in ireland. *Ethnography, 1*(1), 117-140.
- Schwartz Cowan, R. (1987). The consumption junction: A proposal for research strategies in the sociology of technology. In W. Bijker, T. P. Hughes & T. Pinch (Eds.), *The social construction of technological systems* (pp. 261-280). Cambridge, MA: MIT Press.
- Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., . . . Yoon, S. (2007). Strong association of de novo copy number mutations with autism. *Science, 316*, 445-449.
- Shendure, J., & Hanlee, J. (2008). Next generation DNA sequencing. *Nature Biotechnology, 26*(10), 1135-1145.
- Silverman, C. (2004). *A disorder of affect: Love, tragedy, biomedicine, and citizenship in american autism research, 1943-2003*. University of Pennsylvania Editor). , 599.
- Silverman, C. (2008a). Brains, pedigrees and promises: Lessons from the politics of autism genetics. In S. Gibbon, & C. Novas (Eds.), *Biosocialities, genetics and the social sciences: Making biologies and identities* (pp. 38-55). London: Routledge.
- Silverman, C. (2008b). Fieldwork on another planet: Social science perspectives on the autism spectrum. *BioSocieties, 3*, 325-341.
- Singleton, V., & Michael, M. (1993). Actor-networks and ambivalence: General practitioners in the UK cervical screening programme. *Social Studies of Science, 23*, 227-264.

- Snyder, L. (2002). Confidentiality and anonymity: Promises and practices. In W. van den Hoonard (Ed.), *Walking the tightrope: Ethical issues for qualitative researchers* (pp. 70-78). Toronto: University of Toronto Press.
- Star, S. L. (1999). The ethnography of infrastructure. *American Behavioral Scientist*, 43(3), 377-391.
- Star, S., & Griesemer, R. (1989). Institutional ecology: Translations and boundary objects: Amateurs and professionals in Berkeley's museum of vertebrate zoology. *Social Studies of Science*, 19(3), 387-420.
- Star, S. L. (1991). Power, technology, and the phenomenology of conventions: On being allergic to onions. In J. Law (Ed.), *A sociology of monsters: Essays on power, technology and domination* (pp. 26-56). London: Routledge.
- Stengers, I. (2010). Experimenting with what is philosophy? In C. B. Jensen, & K. Rodje (Eds.), *Deleuzian intersections: Science, technology & anthropology* (pp. 39-56). New York: Berghahn.
- Strathern, M. (1996). Cutting the network. *The Journal of the Royal Anthropological Institute*, 2(3), 517-535.
- Straus, S., Tetroe, J., & Graham, I. (Eds.). (2009). *Knowledge translation in health care: Moving from evidence to practice*. New York: Wiley-Blackwell.
- Tilley, L., & Woodthorpe, K. (2011). Is it the end of anonymity as we know it? A critical examination of the ethical principle of anonymity in the context of 21st century demands on the qualitative researcher. *Qualitative Research*, 11(2), 197-212.
- Timmermans, S., & Berg, M. (2003). *The gold standard: The challenge of evidence-based medicine and standardization in health care*. Philadelphia: Temple University Press.

- Tolich, M. (2004). Internal confidentiality: When confidentiality assurances fail relational informants. *Qualitative Sociology*, 27, 101-6.
- Tugwell, P., Robinson, V., Grimshaw, J., & Santesso, N. (2006). Systematic reviews and knowledge translation. *Bulletin of the World Health Organization*, 84, 643-51.
- Van den Hoonaard, W. (2003). Is anonymity an artifact in ethnographic research? *Journal of Academic Ethics*, 1, 141-151.
- Van Maanen, J. (2004). An end to innocence: The ethnography of ethnography. In S. Nagy Hesse-Biber, & P. Leavy (Eds.), *Approaches to qualitative research: A reader on theory and practice* (pp. 409-426). New York: Oxford University Press.
- VanGuilder, H., Vrana, K., & Freeman, W. (2008). Twenty-five years of quantitative PCR for gene expression analysis. *BioTechniques*, 44, 619-26.
- Viney, W., & King, D. B. (2003). *A history of psychology: Ideas and context*. Boston: Allyn & Bacon.
- Walford, G. (2005). Research ethical guidelines and anonymity. *International Journal of Research & Method in Education*, 28(1), 83-93.
- Weiss, C.H. (1979) The many meanings of research utilization. *Public Administration Review*, 39, 426-431.
- Weiss, L., Shen, Y., Korn, J., Arking, D., Miller, D., Fossdal, R., . . . Stefansson, H. (2008). Association between microdeletion and microduplication at 16p11.2 and autism. *New England Journal of Medicine*, 358, 667-675.
- Weksberg, R., Hughes, S., Moldovan, L., Bassett, A., Chow, E., & Squire, J. (2005). A method for accurate detection of genomic microdeletions using real-time quantitative PCR. *BMC Genomics*, 6, 180.

- Willems, D. (1998). Inhaling drugs and making worlds: The proliferation of lungs and asthmas. In M. Berg, & A. Mol (Eds.), *Differences in medicine: Unravelling practices, techniques, and bodies* (pp. 105-118). Durham: Duke University Press.
- Williams-Jones, B., & Graham, J. E. (2003). Actor-network theory: A tool to support ethical analysis of commercial genetic testing. *New Genetics and Society*, 22(3), 271-296.
- World Health Organization. (2001). *International classification of functioning, disability, and health (ICF)*. Geneva, Switzerland: World Health Organization.
- Xu, B., Roos, J., Dexheimer, P., Boone, B., Plummer, B., Levy, S., . . . Karayiorgou, M. (2012). Exome sequencing supports a de novo mutational paradigm for schizophrenia. *Nature Genetics*, 43(9), 864-8.
- Zwaigenbaum, L., Scherer, S., Szatmari, P., Fombonne, E., Bryson, S., Hyde, K., & et al. (2011). The NeuroDevNet autism spectrum disorders demonstration project. *Seminars in Pediatric Neurology*, 18, 40-48.

Appendices

Appendix A: Key Concepts in Genomics

Allele - A form of a gene. We inherit one allele of a gene from our mother and the other allele from our father. These two alleles can be the same (homozygous) or they can be different (heterozygous).

Phenotype denotes the observable characteristics of an organism. For example, having brown eyes is a phenotypic expression. In the context of this research, rigid and repetitive interests and activities is considered a phenotypic expression of autism.

Genotype – A genotype is an organism's full hereditary information, even if not expressed.

Single nucleotide polymorphism (SNP) - There are four nucleotides (Adanine, Thymine, Cytosine, and Guanine) that make up deoxyribonucleic acid (DNA). Normally, A and T align together and C and G align together; these are called *nucleotide base pairs*. Sometimes, however, DNA is not replicated exactly and a different nucleotide is inserted. If this occurs the DNA sequence has been altered. SNPs can be inherited or spontaneous.

Copy number variation (CNV) – A copy number variation includes either a deletion or duplication of DNA. In a CNV, a chunk of DNA is either deleted or duplicated. All humans have CNVs and most of the time these CNVs have no noticeable effect on the individual's phenotype. When CNVs are located in particular places within the genome, such that they interrupt a gene, CNVs can affect the phenotype. When CNVs occur in regions that are gene-rich they are more likely to be clinically significant than CNVs in regions of the genome that are gene-poor. Generally, deletions tend to be more pathogenic than duplications (Gropman & Batshaw).

Genome – The genome is the entire sequence of DNA for an individual organism. Each individual has a unique genome, with slight variation. In 2001, the Human Genome Project

completed the first mapping of a complete human genome. A **reference genome** is an aggregated genome, in which several human genomes are sequenced and the most frequent nucleotide base in each position is adopted. In the laboratory in which I conducted fieldwork, reference genomes were ubiquitous and invaluable in the process of data interpretation.

Polymerase Chain Reaction (PCR) – PCR allows one to identify precise segments of DNA and to produce millions of copies (called amplification) of that segment of DNA. The invention of PCR completely altered the microbiology laboratory and is described in detail by Rabinow (Rabinow, 1996). This technology is ubiquitous in laboratory experiments I observed.

Microarray – A microarray, or gene chip, contains a collection of various sections of a genome. Each of these sections is called a probe. A single array contains millions of probes at specific locations across the genome. Different arrays are designed to specifically probe particular areas on the genome. When patient DNA is added to the chip, the sections that align to the probes will bind to the probes through hydrogen bonding. A dye is added to the chip so that when scanned in the microarray machine each location will become fluorescent and can be photographed. The strength of a fluorescent signal for any one location is dependent on the amount of patient DNA that binds to a particular probe. The microarray is used to detect copy number variations (CNVs).

Next Generation Sequencing – This technology is used to sequence the order of nucleotide bases (A, C, T, G) in a particular stretch of DNA. This sequencing technology is used to detect single nucleotide polymorphisms (SNPs) but can also detect CNVs.

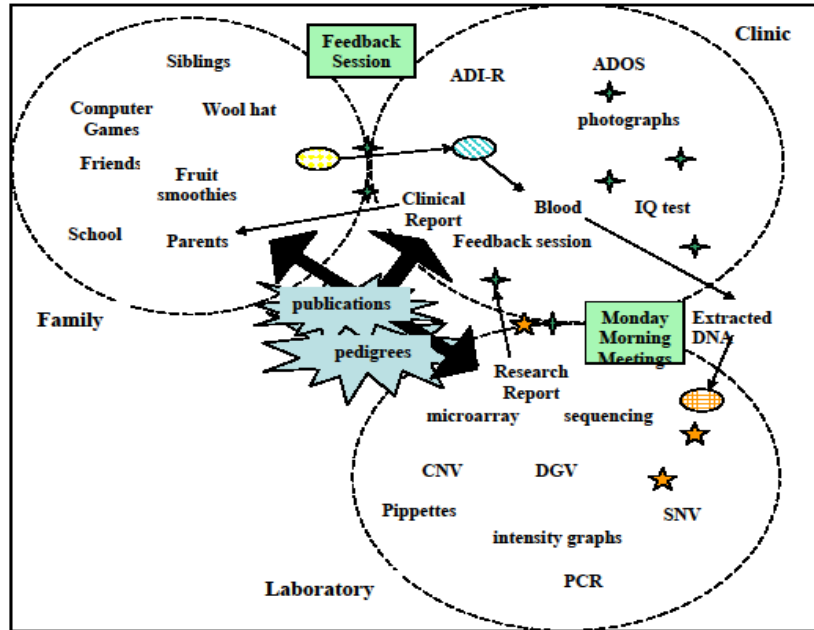
Appendix B: Some of the Equipment Needed for Next Generation Sequencing

Agilent 2100 Bioanalyzer Agilent p/n G2938C Thermal cycler Applied Biosystems Veriti Thermal Cycler, BioRad (MJ Research) DNA Engine PTC 200, or equivalent Covaris S, series Single Tube Sample Preparation System, Model S2 Covaris Covaris microTUBE with AFA fiber and snap cap Covaris p/n 520045 Eppendorf Microcentrifuge Model 5417R Eppendorf p/n 022621807 (120 V/60 Hz), Eppendorf p/n 022621840 (230 V/50 Hz) or equivalent Eppendorf fixed angle rotor with standard lid Eppendorf p/n 022636006 DNA LoBind Tubes, 1.5 mL PCR clean, 250 pieces Eppendorf p/n 022431021 or equivalent E, Gel Safe Imager Combo Kit, 2 magnetic stand, 21D or equivalent P10, P20, P200 and P1000 pipettes Pipetman P10, P20, P200, P1000 or equivalent Vacuum concentrator Savant SpeedVac or equivalent Mx3005P Real Time PCR System Stratagene p/n 401449 or equivalent Ice bucket Powder free gloves Sterile, nuclease, free aerosol barrier pipette tips, Timer, Vortex mixer, Heat block at 37°C







Optional Equipment

Mx3000P/Mx3005P 96-well tube plates Agilent p/n 410088 or equivalent
 Mx3000P/Mx3005P optical strip caps Agilent p/n 401425 or equivalent MicroAmp Clear Adhesive Film Applied Biosystems p/n 4306311 or equivalent BD Clay Adams Nutator Mixer BD Diagnostics p/n 421105 or equivalent Dynal DynaMag-2 magnetic stand Invitrogen p/n 123-21D or equivalent P10, P20, P200 and P1000 pipettes Pipetman P10, P20, P200, P1000 or equivalent Pipet-Light Multichannel Pipette, 12 channels Rainin p/n L12-20 or equivalent Sterile, nuclease-free aerosol barrier pipette tips Thermal cycler Applied Biosystems Veriti Thermal Cycler, BioRad (MJ Research) DNA Engine PTC-200, or equivalent Timer Vortex mixer Water bath or heat block set to 65°C, Tube-strip capping tool Agilent p/n 410099

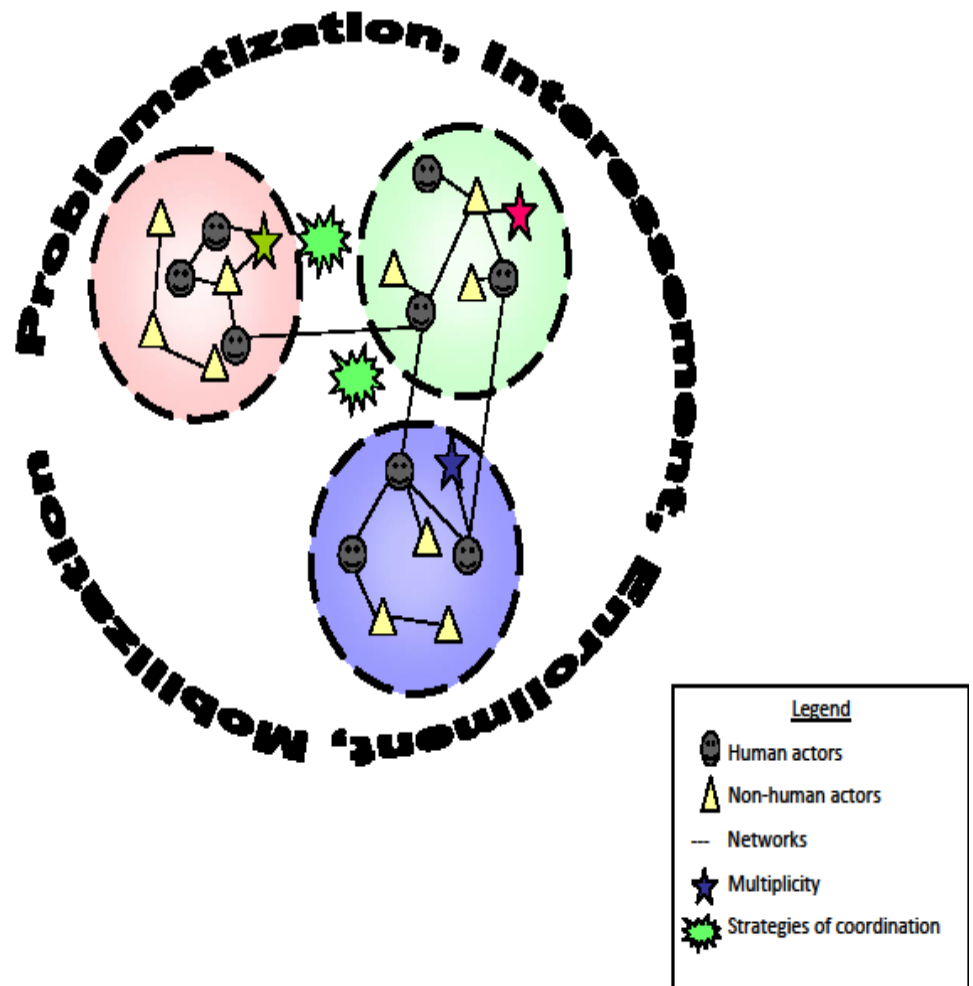
Appendix C: Knowledge Translation in Autism Genomics



Legend

-  Individual Diagnosed with Autism
-  Strategies of Coordination
-  Hybrid Spaces
-  Networks
-  Clinicians
-  Scientists

Appendix D: The Local Translation of Knowledge in Practice (LTKP) Model



Curriculum Vitae

Name: Julia Bickford

Post-secondary Education and Degrees: The University of Western Ontario
London, Ontario, Canada
1997-2001 B.A.

The University of Calgary
Calgary, Alberta, Canada
2002-2004 M.A.

The University of Western Ontario
London, Ontario, Canada
2007- 2012 Ph.D.

Honours and Awards: Social Science and Humanities Research Council (SSHRC)
Master's Scholarship
2003-2004

Social Science and Humanities Research Council (SSHRC)
Doctoral Fellowship
2009-2012

Related Work Experience Research Coordinator
University of Calgary
2004-2005

Research Coordinator
The University of Western Ontario
2005-2008

Publications:

Kothari A, **Bickford J**, Edwards N, Dobbins M, Meyer M. 2009. Uncovering Tacit Knowledge: A Pilot Study to Broaden the Concept of Knowledge in Knowledge Translation. BMC Health Services Research.

Brown JB, Beckhoff C, **Bickford J**, Stewart M, Freeman T, Kasperski J. 2009. Women and their Partners' Perceptions of the Key Roles of the Labour and Delivery Nurse. Clinical Nursing Research 18(4): 323-335.

Bickford J, Kothari A. 2008. Research and Knowledge in Ontario Tobacco Control Networks. *Canadian Journal of Public Health* 99(4):297-300.

Kothari A., Driedger M., **Bickford J.**, Morrison J., Sawada M., Graham I., Crighton E. 2008. Mapping as a knowledge translation tool for Ontario Early Years Centres: views from data analysts and managers. *Implementation Science*, 3:4

Herbert C, Bainbridge L, **Bickford J**, Baptiste S, Brajtman S, Dryden T, Hall P, Risdon C, Solomon P. 2007. Factors that influence engagement in collaborative practice: How eight health professionals became advocates. *Canadian Family Physician* 53:1318-1325.

Crowshoe L, **Bickford J**, Decottines M. May 2005. Interactive drama: teaching Aboriginal health medical education. *Medical Education* 39(5):521.

Bickford JJ, Mather CM, Fleising U. 2005. Time and the structuring of ritual performance in the xenotransplantation debate. *Public Understanding of Science* 14: 235-247.

Mather CM, **Bickford JJ**, and Fleising U. 2004. Unpacking animal metaphors for commercial relationships in the biotechnology industry. *New Genetics and Society* 23(2):187-203.