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The Nuanced Negative: Meanings of a Negative Diagnostic Result in Clinical Exome Sequencing

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Abstract

Genomic sequencing technology is moving rapidly from the research setting into clinical medicine but significant technological and interpretive challenges remain. Whole exome sequencing (WES) in its recent clinical application provides a genetic diagnosis in about 25% of cases (Berg 2014). While this diagnostic yield is substantial, it also indicates that in a majority of cases, patients are receiving negative results (i.e., no explanatory genetic variant found) from this technology. There are a number of uncertainties regarding the meaning of a negative result in the current context of WES. A negative result may be due to current technological limitations that hinder detection of disease-causing variants or to gaps in the knowledge base that prohibit accurate interpretation of their pathogenicity; or it may indicate that there is not a genetic etiology for the disorder. In this paper we examine the uncertainties and nuances of the negative result from genome sequencing and how both clinicians and patients make meaning of it as revealed in ethnographic observations of the clinic session where results are returned, and in interviews with patients. We find that clinicians and patients construct the meaning of a negative result in ways that are uncertain, contingent, and multivalent; but invested with optimism, promise, and potentiality.

Keywords

genome sequencing; diagnostic results; clinical practice; uncertainty; return of results; meaning making

Introduction

Massive parallel sequencing (MPS) technologies, such as exome sequencing (ES) and whole genome sequencing (WGS), have entered clinical practice for diagnostic purposes (Biesecker and Green 2014). Because of cost and effectiveness, ES is currently more widely used than WGS. This technology sequences the exons—the protein coding regions that constitute only one percent of the human genome, but harbor the deleterious variants that cause the vast majority of Mendelian diseases. In this stage of early clinical application, ES has produced positive results, a genetic diagnosis, for about 25% of patients with a suspected genetic disease (Berg 2014, Lee *et al.* 2014, Yang *et al.* 2014), the rate varying with the type

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of disorder. This diagnostic yield is considered successful for the patient population referred for ES: those who have typically had other forms of genetic and non-genetic testing in their search for the cause of their condition. At the same time, it means that the majority of patients receive a negative diagnostic result, indicating that ES did not detect a genetic variant known or suspected to be associated with the disease for which the patient was referred.

While ES may be viewed as ruling out far more potential diagnoses than a single gene test, thus perhaps giving more weight to a negative result, there are uncertainties about a negative result in the context of ES that are important for clinicians to convey and patients to consider. A negative result could mean that the condition is not genetic in origin (i.e., a "true negative" result), though there is no definitive proof for this possibility. It could also be a false negative in that the genetic cause is lurking in parts of the genome not currently well detected due to limitations in current MPS technologies. Also incomplete databases of variants and evidence for their pathogenicity impede interpretation of what counts as a clinically significant finding (Schrijver *et al.* 2012). A negative result from ES also contains a temporal uncertainty in that re-analyses of the same sequence data or re-sequencing and interpretation done in the future, once technological limitations are overcome and new knowledge accumulates, could reveal the disease-causing variant and thus produce a positive result and a definitive genetic diagnosis. While any medical test result, genetic or otherwise, holds some uncertainty, in ES a negative result can be the outcome of multiple uncertainties. Its meaning remains indefinite, nuanced, and potentially not even negative. Given this, clinicians must interpret the complexities of what a negative ES result means, taking into account their patients' medical and family histories, and communicate this in ways their patients can understand. Patients in turn are engaged in making sense of this result in light of clinicians' explanations and their own beliefs and experiences.

Understanding how both clinicians and patients interpret results from ES/WGS is a topic that has generated intense interest as MPS technologies are rapidly being adopted by clinical medicine before all of the scientific, interpretive, and ethical issues of their use have been fully addressed (McEwen *et al.* 2013, Ormond and Cho 2014). In the U.S., the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) has funded collaborative translational research, such as the Clinical Sequencing Exploratory Research (CSER) projects, to identify and address these challenges. Examinations by the social scientists, legal scholars, and bioethicists who are a part of these and other projects have centered on the issues raised by the incidental or secondary findings produced by genome sequencing (which can also be diagnostic, but are unexpected and additional to the result related to the referral condition), and the need for informed consent and patient choice related to such findings (Burke *et al.* 2013, Clarke 2014, Wolf *et al.* 2013). The focus on ES/WGS as a diagnostic tool has tended to be the purview of molecular laboratorians, bioinformaticians, and medical geneticists who are working to improve sequencing technology and build databases that compile evidence for the (non)pathogenicity of genetic variants (MacArthur *et al.* 2014, Ramos *et al.* 2014, Rehm *et al.* 2013). The sociological dimensions of ES/WGS, such as its impact on patients and clinical practice, the emergence of new diagnostic categories and biocollectives, and the production of standards and

evidence for interpreting variants as disease-causing have received little attention from social scientists and bioethicists to date (but see Nelson *et al.* 2013, and Timmermans 2015).

Here we examine the clinical application of genome sequencing with a more sociological eye. Our focus is primarily on the ways in which researcher-clinicians and participant-patients make meaning of a negative ES result, especially around its potentiality, but we extend our inquiry to consider how the expansion of genomic medicine and molecular diagnosis may affect clinical practice and the emergence of global diagnostic biocollectives. Similar to Rabeharisoa and Bourret's (2009) multi-sited ethnographic work on molecular diagnostics in oncology, current use of ES for diagnosing suspected Mendelian diseases brings together molecular laboratorians and analysts, bioinformaticians, clinical geneticists, and other medical specialists in a "bioclinical collective". Clinical judgment becomes distributed among members of this collective as they perform the technical and interpretive labor of detecting disease-causing variants and determining "the fit" of these variants to the phenotype presented by the patient in question (see also Moorthie *et al.* 2013, Timmermans 2015). To make this clinical judgment requires amassing and weighing diverse bodies of knowledge distributed in multiple (and as yet incomplete and sometimes inaccurate) datasets and in the genetic expertise and clinical experience of the team (see also Armstrong & Eborall, 2012). Through this process, thousands of variants are filtered out and discarded while one may emerge that meets the collective bar for its clinical significance—hence a positive genetic diagnosis of the particular patient's disorder.

Receiving a positive genetic result terminates the diagnostic quest, but for patients who receive uncertain or negative results, the search may not end. Recent theoretical work on notions of "potentiality" as related to genomics (Taussig *et al.* 2013, Timmermans and Buchbinder 2013) suggest that while a negative or uncertain ES result may be inherently ambiguous, it is also imbued with the potentiality to transmute into a result with clinical significance in the future. The promise is that as genomic knowledge and technologies advance, far more will be known about which variants are deleterious and associated with specific disease phenotypes, and more treatment options will be developed. This potential for the ES negative result to become "not negative" in the future bestows it with multiple meanings, some perhaps undefined and ambiguous, some possible but not yet present. As such the negative result becomes a referent not only for uncertainty but also for the potential of future definitive outcomes.

How patients conceive and act on this uncertainty or potentiality is a primary concern for clinicians, social scientists, and bioethicists who fear that patients could interpret ambiguous or negative results in a way that could cause harm (e.g., undertaking unnecessary interventions or deciding standard screenings are not necessary). Studies of how patients incorporate clinical genomic results into their understandings and health behaviors have just begun, but the extensive literature on how people make sense of biomedical discourses of genetics and risk indicate that they will likely draw on a variety of sources of information and beliefs to inform evaluations of what their genomic results mean for their health and propensity for disease (Hallowell 1999, Hallowell *et al.* 2004, Lock 2005, Mozersky 2012, Rapp 2000, Raspberry and Skinner, 2011); and as Atkinson and colleagues (2013) concluded from a meta-analysis, they will make sense of genetic knowledge within a nexus

of family history, relationships, and experiences of everyday life (see also Featherstone *et al.* 2006, Geelen *et al.* 2011).

Despite the multiple factors that influence how individuals understand health and risk information, clinicians are the primary conveyors and interpreters of the meaning of a diagnostic result, especially an uncertain one, in their direct encounter with patients. For example, Latimer's (2007, 2013) detailed ethnographic study of a dysmorphology clinic illustrates that while parental participation was a necessary part of the production of a particular result, clinical expertise was still privileged. In this clinic, as in many genetic encounters, patients and parents of patients were engaged in the work of producing an expert judgment in relation to test results, as well as how to interpret and act on genetic risk information (Latimer *et al.* 2006). The lack of a definitive diagnosis did not end the authority of the clinic or this joint work, but rather continued parents' need for further genetic studies and clinicians' expert judgment.

This production of meaning on the part of both clinicians and patients in the context of ES is the central focus of our paper. Our analysis is based on ethnographic observations of the clinical encounter that took place during a sequencing research project where negative ES results were communicated and on interviews with research participants/patients who received these results. We find that the dynamics and communications in the clinic turned a negative result into the 'nuanced negative'--a result that becomes uncertain and contingent, but invested with optimism and promise in ways that continued to engage patients with the clinic and extended the diagnostic biocollective beyond the lab and clinic to these patients and their families.

The Study: Methods and Analysis

NCGENES (North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing) is one of nine CSER research projects currently funded by NIH/NHGRI to identify and address the scientific, clinical, and ethical challenges of using sequencing technology in clinical medicine. Clinicians associated with the University of North Carolina Hospitals refer adult and pediatric patients to NCGENES. Patient groups include adults with cancer, adults and children with cardiogenetic disorders, children with intellectual disability and/or congenital malformations, adults with neuromuscular or neurodegenerative conditions, and adults and children with ophthalmological disorders. Referred patients may have previously undergone testing that did not reveal a genetic cause, but because aspects of their personal and/or family medical history strongly suggested a genetic etiology, they became "the sequence-worthy"—good candidates for measuring the diagnostic potential of ES. Major aims of NCGENES are to evaluate how well ES performs for clinical diagnostic use and to assess participants' understandings of and responses to ES.

It is important to note that NCGENES and other CSER projects may be viewed as a hybrid of clinical care and human subjects research. Though first and fully a research project that implements all federal and institutional procedures for the protection of human subjects, NCGENES enrolls and meets with patients in a clinic setting, and returns individual diagnostic results, some of which may affect patients' medical care. Confirmed positive

results are placed in the medical record with the patient's signed consent. De-identified genetic data become part of the local and global research enterprise to improve multiple, shared databases used to evaluate the (non)pathogenicity of variants.

As part of the research team responsible for assessing participants' responses to genetic information, we conducted an ethnographic study, observing clinical encounters where NCGENES clinician-researchers returned ES results, and interviewing the adult patients and parents of child patients who participated in these sessions. We contacted a subgroup of participants, representative of the larger sample by disease condition, age, and type of diagnostic result, for their willingness to participate in the clinic observation and a follow-up interview. This study is based on the 30 participants selected for this subgroup who received negative results: 20 adult patients and 10 parents of pediatric patients. The 20 adult patients ranged in age from 18–66 years with an average age of 47 years, were predominantly non-Hispanic white (85%), and women (75%). They were referred to the study for cancer (45%), cardiogenetics (10%), neuromuscular problems (25%) and other conditions (20%), including ophthalmology and mitochondrial. Parents were predominantly mothers (80%) and non-Hispanic white (90%). Child patients ranged in age from 1–9 years with an average age of 3 years, and were referred to the study for congenital malformations and/or intellectual disability.

We obtained written consent from adult and parent participants and the NCGENES clinicians (medical geneticists and genetic counselors) before observing and audio recording the clinic session. Four weeks after the clinic observation, we conducted a semi-structured telephone interview with each participant. Interview questions were designed to elicit accounts of their experiences in the NCGENES study, including understandings of what was communicated in the return of results clinic session, and how they came to make sense of and value the negative result. Clinic observations and interviews lasted about one hour each, were audio recorded, and transcribed verbatim. The university IRB approved all procedures and protocols.

We followed techniques for abductive analysis (Tavory and Timmermans 2014) and grounded theoretical analysis (Charmaz 2006), and employed data display matrices to summarize and systematically compare findings (Miles *et al.* 2013). We closely read clinic transcripts and collated all data for each participant related to how the negative result was conveyed and how its meaning was constructed in the moment of the clinic encounter. We compared these communications across each clinic observation for commonalities and variations. We then linked interpretations made in the clinic to participants' understandings as recounted in follow-up interviews. We made special note of whether their interpretations were congruent with the clinicians, especially in relation to whether they considered their condition to have a genetic etiology despite receiving a negative result.

Findings

Our analysis focused on the interpretation and significance of a negative ES result from both clinician and participant perspectives. Throughout the clinic session, the medical geneticist, genetic counselor, adult or parent participant, and sometimes accompanying family members

discussed the meaning of the ES negative result. By the end of these exchanges, the negative result had been interpreted either as a genetic explanation being unlikely, or still very likely but not yet revealed. As we describe below, in about 75 percent of the cases, clinicians presented the negative result as provisional, with an emphasis on a genetic explanation not (yet) identified. For the others, they presented the negative result as supporting the likelihood that the condition was not genetic in origin. Interviews indicated that participants four weeks later had overwhelmingly incorporated the interpretation produced in the session into their understanding of the result and their condition. In our presentation of the ways in which this agreed-upon interpretation unfolded, we highlight how any perceived uncertainty or provisional nature of a negative result was tempered by reassurances of the quality and scope of ES and imbued with significance by promises of its potential to produce a genetic diagnosis in the future.

Meaning making in the clinical moment

Clinic sessions where negative ES results were communicated often began with the clinician's immediate declaration that "no genetic explanation was found" or "we did not find a reason for your condition," quickly qualified by "yet." For example, one clinician told a woman who suffered various neurological problems: "Let me cut to the chase with the results first. We did not find a reason for your condition. And I will add to that, we did not *yet* find a reason for your condition. So let me now backtrack and fill in the details." Clinicians then moved to explanations of the two main reasons why a result could be negative: the cause of the condition is not genetic, or a genetic cause for the condition is highly likely, but given the nascent state of ES, the deleterious variant was not detected. As clinicians reviewed the participant's research results report, they described these possibilities in more detail, as for example, in this clinician's communication with a father of a young boy with multiple congenital malformations:

> So this section really goes through in detail some of the caveats or limitations to the analysis that we've done and why the absence of a definitive disease-causing variant does not exclude the possibility of a genetic basis. And in many people we suspect that despite these negative results that there is something genetic, and we just haven't found it yet. There are other people in the study where we don't find anything, and we conclude that that might actually mean that their condition is non-genetic.

In contrast to a positive result that identifies the disease-causing variant, a negative result is not so much negative as "not positive", and as such carries inherent ambiguity. Clinicians devoted about a quarter of the session delineating and explaining current technological and knowledge limitations of ES. These limitations, included on the research report, state that it is possible that the disease-causing mutation(s) exists in a region of the genome that is not captured by exome analysis; or the deleterious mutation exists but was not detected due to technical sequencing platform limitations (e.g., low coverage or base quality in the assay performed); or it exists in a gene not closely scrutinized because of no known association with the patient's disease or symptoms; or genetic variations that were found are not (yet) recognized as deleterious due to incomplete scientific knowledge about the causation of human diseases.

After these explanations, which were consistent across clinicians, the remainder of the session focused on what a negative result meant for the specific patient and his/her family. This more interactive discussion was framed within a clinical judgment that considered the patient's phenotype and medical and family history. Up to this point the interpretation of ES results had been generated by the clinical geneticists and molecular analysts in the molecular sign-out committee, which met weekly to review and adjudicate results. These interpretations, sometimes made with only limited information about the patient, were now re-formed by the clinicians in the presence of the actual patient. During this phase, clinicians actively encouraged questions and information offered by participants, as seen in this exchange with a woman referred for ES because of neurodevelopmental problems:

> Adult patient: So this can be a gene y'all know nothing about?
>
> Medical geneticist: That's right. And it probably means – actually the negative result probably means it's not in a gene that we know a lot about. Does that make sense?
>
> Adult patient: And it's probably a rare disease?
>
> Medical geneticist: Yeah. It could be.
>
> Adult patient: That nobody's ever heard of?
>
> Medical geneticist: It could be.
>
> Adult patient: But how can that be?
>
> Genetic counselor: I don't know. Good question.
>
> Patient's husband: It's got to be in her genetics because her grandma had it.
>
> Genetic counselor: That's what we think.
>
> Patient's husband: She's got it.
>
> Medical geneticist: Yeah. It's actually – it's very suspicious.
>
> Genetic counselor: Agree with you.
>
> Patient's husband: And her brothers have symptoms of it.
>
> Medical geneticist: Yeah. That's why we're so confident that we will eventually be able to find the answer. It's just a question of-
>
> Adult patient: When.
>
> Medical geneticist: Of having science catch up to – to you.

In this example, the patient's phenotype and her family history, based on her medical record and updates given during the clinic visit, were key elements in the clinicians' endorsing the possibility of finding a genetic diagnosis in the future despite the negative result in the present. Similarly, in a session with parents of a young girl with congenital malformations, the clinician emphasized that there was most likely a genetic explanation, as yet unknown, that could not be detected for a variety of reasons:

> The results show here that we didn't find a reason, a genetic reason. There are a number of possibilities for that. One possibility is that it's not genetic. If it isn't genetic, then we could look at the genes forever, and we'd never find a reason, but Dr. [pediatric geneticist] felt that a possibility was quite high that this was genetic, and I would agree, looking through [your daughter's] records, that genetics may play an important role in this. So other explanations for why we didn't find an answer would be that perhaps this technique that we're using which looks at all of the genes, that even that exhaustive of a look doesn't include the part of somebody's DNA that might cause it. For example there are genes, but there are areas in between genes that we don't really understand. So we don't even really look at those because we wouldn't know what to make of them in the first place, but here's another possibility, and I think this is the most likely possibility. That this may well be genetic, meaning the results that explain [your daughter's] problems may be sitting in our results, but that we aren't smart enough yet to figure out how to pull that out and find it.

Later in the visit the mother updated the clinician on her daughter's recent symptoms, adding information that she thought could be relevant for re-analysis:

> Mother: If she's been diagnosed with something since [the ES analysis], would you go back?
>
> Clinician: And that's interesting. So the cardiac issue?
>
> Mother: No. No, now she's been diagnosed with a stomach emptying delay. So like since that's happened in the past couple of months.
>
> Clinician: That is really important to know. Because that will help us, and we will put that in the record so that when we re-analyze for results we'd have the most up-to-date information. So the gastric emptying delay isn't – there are certain things where it'd be like "Oh, gosh. That really helps us narrow it down." Gastric emptying doesn't as much […] But still knowing those things is important because it might be that that could be tied in. We find a variant when we re-analyze things in six months, and that variant has been associated with gastric emptying, and that'd be important […]. So we will make a note of that in her record so that when we re-analyze we can take that into account.

As these examples highlight, clinicians drew on symptoms and family history that arose during the visit to offer participants a contextualized interpretation that rendered the meaning of the negative result less certain and imbued with the possibility that a genetic explanation would one day be found.

The interpretation of the negative result as multivalent and context-dependent also originates from ES's ability to exclude genes or genetic variants known to be associated with the disease in question. In other words, while ES does not rule out a genetic cause, it can provide evidence that known deleterious variants are not present in an implicated gene and therefore not causative of the condition. The following exchange among clinicians and a mother of a young boy with undiagnosed neurodevelopmental issues provides an example:

> Medical geneticist: So this section [of the report] kind of goes over the reasons why we might have gotten a negative result. And it's important to know that absence of a definitive disease-causing variant does not exclude the possibility [that it is genetic]…
>
> Mother: Doesn't mean anything. Yeah.
>
> Genetic counselor: It means a little bit, but it doesn't mean-
>
> Medical geneticist: It means something. And in fact what it actually means is that we have excluded a lot of things.

The research results report reviewed with every participant provided a list of the specific genes that were analyzed. Although all genes were sequenced, only those known to be associated with a patient's phenotype were closely scrutinized for disease-causing variants both bioinformatically and by the molecular sign-out committee (see Timmermans 2015, and van Zelst-Stams *et al.* 2014 for a description of similar processes in comparable contexts). In NCGENES, 31 distinct diagnostic lists have been developed for the conditions under study (e.g., cancer, cardiomyopathy, neuropathy, seizures, developmental delay). Each list can include hundreds of genes known to be implicated in certain diseases. A negative result indicates that no known or likely pathogenic or variants were found in any of these genes, thus ruling out numerous possible diagnoses (provided the sequencing quality was adequate), but leaving open the possibility that as yet unknown deleterious variants could be lurking in these genes, or that other genes not on the lists might in the future become associated with particular diseases.

Although it is possible that being observed may have affected how the eight NCGENES clinicians interacted with patients, we did not observe any sessions where communication was of poor quality or confrontational in any way. There was a great deal of consistency across clinicians in the content and thoroughness of their communications about the negative result, perhaps as a result of team discussions about the important messages to convey and of working from a standardized research report. Any variations were mostly related to the complexity of language and amount of detail. All clinicians had years of experience communicating genetic results to a diverse patient population in clinical settings, and could quickly switch to simpler or more complex explanations in response to perceived signals from the participant.

We did observe, however, that the presence of the physician who referred the patient for NCGENES could influence the interpretation of the negative result. The following exchange ensued when a neurologist attended the clinic session for a patient she had referred, a young boy with dystonia:

> Neurologist: You know just watching him, I think his tone and everything is so normal. I think I would take this, despite this negative result, as a positive thing. […] Without finding anything I think this is a very positive thing, and so very likely this is something that would either resolve on itself or, you know, so for I think for the last half a year it's been going on.
>
> Mother: It's been a year.

Father: Almost a year.

Neurologist: A year, and for this year nothing [the dystonia issues] progressed.

Mother: Right.

Neurologist: And he's doing so well. I would be very, very optimistic you know this is something on the minor side.

Mother: Okay.

Medical geneticist: That's actually a really important point that we do genetic testing when we think there might be a genetic condition, which isn't to say that there is a genetic condition. We just do the testing to see if we can either confirm it or rule it out. It's often very difficult to rule out genetic conditions entirely, but clinically if the clinical suspicion for a genetic form of dystonia is relatively low, and now we've done a test for hundreds of genes that could be involved in those conditions and haven't found anything, that helps us to even further reduce that, you know, that gut feeling that it's genetic.

Neurologist: It's useful information. Yeah.

In this instance, the negative result along with the child's improvement was used as evidence for a prior clinical misdiagnosis. The neurologist's expert assessments of the child in the moment, combined with the negative result and the parents' corroboration that his movement issues had improved over the last 12 months, created a compelling and agreed-upon interpretation that the boy's dystonia did not have a genetic basis, and would continue to improve over time.

As these cases illustrate, the significance of the result itself, and by extension ES as a diagnostic tool, depended in part on clinicians' interpretations made in the context of the patient's phenotype and family history. In some circumstances, this information combined to support an interpretation of the negative result as pointing towards a non-genetic cause of the condition, as in the example above. But in the majority of cases, the negative result was interpreted as provisional, not ruling out a genetic cause. This characterization often included a promise of overcoming current shortcomings of ES, and the potential of finding an answer in the future. As we discuss in the next section, the predominant emphasis on "yet" during the clinician's explanation was fundamental to how participants understood the negative result and its significance.

When is a negative not a negative? Optimism, reassurance, promise and potential

The previous section explored the interactive process of making sense of a negative result in the clinical moment as one that either continues to implicate genetics as a likely answer for the given condition, or lessens this possibility. We now examine how the interpretation moved with participants from the clinic into their daily lives and the significance they attached to it. We find that most were in agreement with the interpretation derived in the clinic, and imbued the negative result either with a sense of the promise and potential that future reanalysis could reveal the genetic cause, or with a reassurance that there was none to find.

As noted earlier, we found that for three-fourths of the participants (14 adults and 9 parents), clinicians presented the negative result as provisional, one in which ES analysis (so far) had not identified a suspected genetic explanation. For the rest, they interpreted it as meaning a genetic cause was less likely. Given this, we wanted to explore whether participants adopted the clinician's view, or created a different understanding. An analysis of interviews conducted one month after the clinic visit shows that most participants held the same interpretation as constructed within the clinic session (18/20 adult patients and 10/10 parents of a child patient). We also examined other meanings participants attached to the interpretation. As the examples below demonstrate, whether participants viewed the negative result as provisional or as an indication that a genetic cause was unlikely, they imbued it with hope and reassurance and stopped their active search for a genetic diagnosis. In addition, they conveyed an abundant optimism for future advances in genomic sequencing technology and knowledge.

Participants expressed their belief that the NCGENES clinicians and others on the research team had "done all they could" at the present moment to discover a genetic diagnosis. They understood that ES was the most advanced genetic testing available, as well as a science still in its early stages. For many, ES signified the last stop on a long diagnostic quest. Participants had no plans to pursue more diagnostic testing, assured that the experts had the data they needed to continue to look for an answer on their behalf. Parents in particular interpreted the negative ES result as ending their diagnostic quest; while not providing a definitive answer, it did offer some resolution. They had now "tried everything". Despite not succeeding in finding the cause of the condition, they had done all that was in their power. For example, a mother of a girl with congenital malformations said, "We're just going to have to be at peace that we're not going to have an answer. So for us it was a big deal because it was kind of like the final hurrah. Like no more hospitals, no more testing. This was it for us."

Clinicians' assurance that the latest technology had been employed gave participants permission to leave further testing and analyses to the experts. While clinicians urged participants to inform them of any new information they might find related to genes associated with their condition, at the same time they referred to the continued search for a genetic answer—the future application of emerging technology and research, reanalysis, and reinterpretation —as being largely their responsibility. For example, another mother whose young daughter's congenital malformations remained unexplained by ES felt hopeful and reassured by the medical geneticist's opinion that there was a genetic cause to be found, and his promise that further analysis would be performed:

> For them each person they look at is going to give them more information, but just in genetics in general—this is just a time that they're making advances and discoveries, and you know everyone is sharing all this information. So I think we're happy. We're hopeful that hopefully sooner rather than later somewhere in the world all these genetic doctors … make me feel like they're not going to give up. So hopefully as they learn more and more, they will be able to put the puzzle together.

While this parent expressed her disappointment over ES not (yet) being able to identify a specific genetic cause, she shared with the clinicians the belief that a genetic explanation would at some point be discovered through the ongoing efforts of genomic experts. Similarly, the father of a toddler with undiagnosed multiple congenital malformations explained why he was not going to pursue any further testing: “At this time I think we’re probably content to continue to let the research process play out, and if at some point it’s recommended by [the pediatric geneticist] or someone else that it may make sense to go do some clinical testing, then we’ll consider that, but at this point that’s not really something that we’re actively pursuing or thinking about.”

Most adult patients emphasized that their negative result was an indication that the science of genomic medicine had not progressed enough to find the genetic cause for them, but hoped that it would be found in time to benefit their children and other relatives. An older man with a neurological condition recounted what he took away from the clinic visit:

> They told me in the beginning just like [the neurologist] had said, “You know, there’s no guarantee on what we’re doing. We’re looking, and you’ve given us permission to look and respond to what we find on you.” I said “That’s what I want, and if we can find something that will help me, that’s great, but I understand. I understand this is a very slim, slim thing that’ll be to help me, but my grandchildren, great grandchildren, or somebody else – if you find something that can help them, excuse me, I’ve done my deed.”

As these examples indicate, participants shared hope for a future genetic explanation. For many, a negative result was interpreted as a “for now” resting point on the diagnostic odyssey. They were willing to place the responsibility for finding this explanation with the clinical geneticists. Also, although participants may have felt some disappointment at not getting a definitive genetic diagnosis, the uncertainty of a negative result left open the possibility for an answer in the future when genomic medicine advances. Clinicians promised to “keep looking” for a genetic explanation, and pointed to the progress that will be made. Adult patients invoked the potential for ES to provide answers, if not for themselves, then for future generations; and parents held dearly to hopes that ES would result in diagnosis and treatment for their children in the (near) future. In the realm of an uncertain and contingent genetic finding, these promises and potentialities provided reassurance and optimism for participants beyond the clinic visit.

Discussion

Sociological studies of the impact of massive parallel sequencing on medical and diagnostic practice are just beginning as these technologies have only recently become adopted for clinical purposes. In our examination of the nuanced negative, we contribute to studies of clinical genomics and to the negative result as a meaningful category of inquiry. Our focus has been on the performance of the clinical use of exome sequencing for diagnosis of suspected Mendelian conditions, specifically the meanings clinicians and patients construct around the negative ES result in the moment of the clinical encounter and beyond. We found that clinicians and patients turned the nuanced negative into a nuanced optimism that either a genetic diagnosis will be found in the future or that there is none to find.

In other situations of medical uncertainty, patients and parents sometimes disagree with medical opinion and construct alternative meanings of disease etiology and treatment (e.g. autism—see Hebert and Koulouglioti 2010, Kaufman 2010). In this study, we found all but two participants agreed with the clinicians' judgment on whether the negative result was more or less likely to rule out a genetic cause for their condition. This agreement was possibly due to clinicians' qualifying the result within the contexts of current limitations of ES, the patient's medical and family history, and the potential for finding the answer in the future. Also, most participants did not have an ease or expertise with the language of sequencing, target genes, or deleterious variants. In this situation, participants may have been more inclined to trust and adopt the interpretations of the medical geneticists and genomic researchers (see also Jutel and Nettleson 2011).

We frame our discussion of these findings in light of scholarly work on potentiality and on the place of the clinic in the age of molecular diagnosis and emerging diagnostic biocollectives. First, the call for an anthropology of potentiality (Taussig et al. 2013) as an analytic device and as a discourse for examination requires a closer analysis of how funders, researchers, clinicians and patients both talk about the potentiality of ES and live with its implications. In NCGENES, researcher-clinicians and participant-patients understood and discussed the uncertainty of a negative result within a temporal context of potentiality—it is a "for now" result, not conclusive or decisive. They voiced optimism for the potential of ES to lead to diagnosis in the future when as yet unknown pathological genetic variants and gene-disease associations would be found, and to the creation of disease cohorts around these variants. An important implication of this future narrative for participants was relinquishing their responsibility to search for a diagnosis. Parents especially expressed relief about turning this task over to the researcher-clinicians who possessed their child's sequence data and the necessary expertise for further exploration. Our previous work in pediatric genetics, in contrast, found that parents continued to feel responsible for searching for a genetic diagnosis when their child received a negative result from standard genetic tests (Raspberry and Skinner, 2007). We suggest that the reason for this difference lies in the powerful and pervasive discourse that imbues ES with a kind of potentiality to produce an answer in the future that other genetic testing contexts (e.g., single-gene, microarrays) do not hold.

Studies by Latimer (2013) and Rabeharisoa (2006) are especially relevant for thinking about the implications of the performance of the potentiality of the nuanced negative. Similar to Rabeharisoa's (2006) observations of a clinical collective engaged in diagnosis of children with conditions of uncertain etiology, NCGENES may be viewed as an "emerging therapeutic project" as clinicians hold out the possibility that the genomic enterprise will lead to new discoveries of gene-disease associations and perhaps treatments that could change the patient's care. Rabeharisoa notes that genomic medicine has been criticized for not producing cures or treatments for patients, but she argues that searching for a diagnosis is a form of care. In our study, participants valued a diagnosis, even if it did not change treatment, and viewed the clinicians as the best chance of finding a diagnosis through their continued efforts. Latimer (2013) refers to this dynamic as a process of deferral. She reported in her study of a dysmorphology clinic that a lack of diagnosis did not end clinicians' relationships with families, rather, it fostered continued contact through promises

of diagnosis and discovery. Similarly, the ways in which NCGENES clinicians performed uncertainty, optimism, and potentiality in their communication of the negative result worked to maintain a clinical relationship with families in their promise to "keep looking" for the answer; and this concern constituted a type of care.

Such optimism for clinical genomic research, as Haase et al. (2015) described for a project similar to NCGENES, fuels the development of promissory bioeconomies where participants are willing to invest time, emotion, and DNA. Latimer (2013) too noted that relations of exchange are established as families gift their genetic and medical information to the clinic in exchange for receiving information that may have personal and clinical utility. Even if they do not receive a diagnosis, by participating in the research enterprise, they can contribute to their vision of an abstract "good". Participants in our study did not share the critical view of genomic research and the "regimes of hope" tied up in its production as commented on by others (e.g., Brown 2003, Taussig *et al.* 2013). Rather they expressed belief in the scientific enterprise and valued their contribution to it. By sharing their genotypic and phenotypic information, as we discuss below, they became part of an emerging genomic diagnostic biocollective.

Although a full sociological analysis of the impact of ES on diagnosis and clinical practice is beyond the scope of this paper, we offer some thoughts for further exploration. We expect that exome sequencing will very likely become a first-tier diagnostic test for conditions suspected to have a genetic etiology (van Zelst-Stams et al. 2015). How this and other MPS technologies may impact clinical practice and judgment is a topic of debate, with some accounts suggesting that the lab will supplant the diagnostic authority of the clinic (though as part of a larger collective), displacing clinical judgment and relegating clinicians to being mere conveyors of the lab report (e.g., Bourret *et al.* 2011). Further evidence for this comes from studies that show how new diagnostic categories and diseases are produced not by clinical judgment but by molecular technologies. For example, Navon & Shwed (2012) chronicle how discovery of a microdeletion at a particular locus consolidated clinically diffuse conditions under a new diagnostic category (22q11.2 Deletion Syndrome), and in turn produced a new community of patients.

Although Latimer's (2013) ethnography of a dysmorphology clinic preceded the use of MPS, our work supports her argument that the clinic retains a central place in diagnosis, even as genome sequencing threatens to redefine diagnostic classifications and diseases at the molecular level and to emphasize genotypes over phenotypes. Large-scale genomic sequencing is a prime example of "big data" as it produces massive amounts of genetic information and presents enormous complexities in capturing, curating, and interpreting which of the hundreds or thousands of genetic variants are of clinical importance. To translate these data for clinical use requires the biomedical platforms described by Keating and Cambrosio (2006) that bring together dispersed expertise, technology and regulations to produce new knowledge. In this vein, we would argue that clinicians, along with families, are central to these platforms and to an emerging genomic diagnostic biocollective that is being built on a global scale.

In this current age, advances in genomic diagnostics depends on collaborative work between the lab and clinic in producing evidence for gene-disease associations and the pathogenicity of variants from the genotypic and phenotypic data donated by individuals, evidence which is compiled and adjudicated on a global level through shared databases (e.g., Landrum *et al.* 2014, Rehm *et al.* 2015). The expertise of clinicians is essential in this process, but it is their key role in interpreting what genomic results mean for individual patients that we have focused on here. As Timmermans and Buchbinder (2012) described in another context of genetic diagnostic uncertainty, NCGENES clinicians were actively involved in performing a type of "bridging work", interpreting results with their patients to contextualize and moderate the uncertainties associated with the ES negative result while promoting optimism for potential certainty in the future.

While the role of the clinician is not likely to be usurped, with initiatives like the 100,000 Genomes Project in the UK (http://www.genomicsengland.co.uk/the-100000-genomes-project/), the Precision Medicine Initiative® in the U.S. (https://www.nih.gov/precision-medicine-initiative-cohort-program), and the creation of innumerable university and hospital-based centers for personalized medicine, clinical practice is likely to change. As Jutel and Nettleson (2011) outline in their call for a sociology of genomic diagnosis, research will continue to be needed on whether and how clinicians are pressured to provide genetic diagnoses for a wide range of conditions as well as how the formation of new diagnostic categories may affect health care providers and patients. We have provided one example of the complexities and uncertainties that ES presents. As sequencing becomes more prevalent in clinical care, including its use by clinicians who are not geneticists, the authority of diagnosis may come to reside more in the molecular lab. We argue, however, that that even with such changes in clinical practice, clinicians will still play a key role in interpreting and communicating the nuances of negative and uncertain results, and work with their patients to navigate what these uncertainties mean for their continued care.

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