Published in final edited form as:

J Law Med Ethics. 2012 ; 40(4): 1008–1024. doi:10.1111/j.1748-720X.2012.00728.x.

What Research Ethics Should Learn from Genomics and Society Research: Lessons from the ELSI Congress of 2011

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Introduction

In much the same way that genomic technologies are changing the complexion of biomedical research, the issues they generate are changing the agenda of IRBs and research ethics. Many of the biggest challenges facing traditional research ethics today — privacy and confidentiality of research subjects; ownership, control, and sharing of research data; return of results and incidental findings; the relevance of group interests and harms; the scope of informed consent; and the relative importance of the therapeutic misconception — have become important policy issues over the last 20 years because of the ways they have been magnified by genomic research efforts. Research that examines the ethical, legal, and social implications (ELSI) of human genomics research has become a burgeoning international field of scholarship over the last 20 years, thanks in part to its support first by the genome research funding bodies in the U.S. and then by national science agencies in other countries. A large part of the intellectual effort in this field has been devoted to identifying, highlighting, and analyzing critical issues in genomic research as it moves through the translational process. Given the prominence of these issues in today's debates

over the state of research ethics overall, these studies are well positioned to contribute important data, contextual considerations, and policy arguments to the wider research ethics community's deliberations, and ultimately to develop a research ethics that can help guide biomedicine's future.

In this essay, we illustrate this thesis through an analytic summary of the research presented at the 2011 ELSI Congress, an international meeting of genomics and society researchers. The Congress[1] was supported by the National Human Genome Research Institute (NHGRI), and hosted by the Center for Genomics and Society at the University of North Carolina at Chapel Hill, one of six Centers of Excellence in ELSI Research.[2] It was the third such conference since the ELSI program was established in 1990.[3] Featuring current and recent ELSI research, the Congress provided a slice-of-time perspective through which to consider a set of pivotal factors that characterize genomic research today, and that promise to increase in significance as genomic research and practice continue to evolve.

ELSI Congress announcements to recruit paper and panel submissions were sent to multiple national and international scholars, organizations, and institutions in the fall of 2010. Themes were defined broadly. Applicants were asked to consider how ELSI research has expanded since 2008, and how it has changed through links to other sciences and disciplines, increased specialization, and internationalization. In October 2010, an international planning committee[4] was formed to review submissions and develop the Congress agenda. Based on their particular expertise, committee members were assigned in groups to conduct reviews, using criteria of relevance, clarity, significance, and originality. A total of 35 Congress sessions were scheduled: 18 panels and 17 themed sessions, comprising 79 papers overall. The Congress also featured invited plenary speakers and workshops, but we focus here on the submitted research, as it offers a unique opportunity to inductively assess the state of the field in ELSI research and to offer insights about research ethics that are drawn from a wide variety of presentations.

Drawing on submitted abstracts, presentation slides, notes taken during each session by volunteer rapporteurs,[5] and the ELSI issues generated by advances in genomic research,[6] we identify three pivotal factors currently shaping genomic research, its clinical translation, and its societal implications — each of which, in addition, represents contested concepts in research ethics generally, and lessons for contemporary issues in research ethics. These factors are: (1) the increasingly blurred boundary between research and treatment; (2) uncertainty — that is, the indefinite, indeterminate, and incomplete nature of much genomic information and the challenges that arise from making meaning and use of it; and (3) the role of negotiations between multiple scientific and non-scientific stakeholders in setting the priorities for and direction of biomedical research, as it is increasingly conducted "in the public square." In our discussion, we refer to individual and panel presentations from the Congress with letters and numbers corresponding to the listing in the Appendix, and the names of first authors when individual presentations in a session are cited. Additional information about Congress presentations is available upon request.

(1) Blurring the Boundary between Research and Treatment

Both the Belmont Report and the Common Rule emphasize the importance of the distinction between research and treatment. An essential requirement of informed consent to research has always been that patients recruited into studies must understand that the researcher-subject relationship and its attendant rights and responsibilities are fundamentally different from the relationship between physician and patient. In fact, since 1982, much empirical work has been devoted to assessing the danger that patient-subjects (not to mention other stakeholders) might misunderstand this critical distinction; that is, that they might fall prey to the "therapeutic misconception."[7] At the same time, a lively conceptual debate has developed regarding the relationship between research and treatment, primarily but not exclusively in the context of clinical trials.[8] ELSI researchers have made significant contributions to these literatures, beginning by questioning the term "gene therapy" as applied to early-phase gene transfer research.[9]

It is noteworthy, then, that an impressive number of papers and panels in the Congress focused on aspects of a powerful shift that seems to be accompanying the genomic revolution and concomitant attempts to move research toward personalized medicine as quickly as possible. The issue of providing to research participants individual "results" related to the aims of a study, or even findings that were uncovered "incidentally," has become increasingly controversial, generating heated debates regarding the norms and the justifications for relaxing the strict boundary between research and treatment.[10] Far from receding as an issue largely settled by better conceptual clarity about the goals of clinical research, the work presented at the Congress demonstrated that the blurriness of the boundary between research and treatment has only been increased by the advent of genomic tools and methods, in several respects.

The debate over whether — and if so, which, when, and how — results and incidental findings from gene-finding and other genomic research should be provided to individual subjects has been a long-standing focus of attention for ELSI researchers. Importantly, the question itself exemplifies the blurring of research and practice in two ways. First, the very expectation that any data arising from a research project will have meaning and value for individual research subjects arises from the belief that the research will have direct and immediate clinical significance. Second, the failure to distinguish between "research results" and "incidental findings" — a blurring that, although not ubiquitous, is far from uncommon — compounds the problem.

Genomics researchers struggle with the issue of returning individual research results to participants because, in many if not most cases, the results are of uncertain meaning or significance and thus may lead to misunderstanding, confusion, and harm when participants attempt to make clinical sense of them. Return of incidental findings poses similar but not identical problems. The provision to an individual participant of data that pertain to him or her but are not directly related to the objectives of the study may not raise uncertainty issues when deemed important enough to return. Nonetheless, the expectation that some clinically meaningful information will be identified in genomic research contributes to the blurring of research and clinical care.

(a) Returning Incidental Findings

For example, a panel session [A-4] previewed the 2011 revision of the National Cancer Institute Best Practices for Biospecimen Resources, examining (a) appropriate handling of diagnostic discrepancies and incidental findings discovered during pathology review of biospecimens; (b) return of results to individual research subjects in biospecimen research; and (c) disclosure of aggregate research findings. The return of diagnostic discrepancies and incidental findings with potential clinical significance most obviously blur the research-treatment boundary, in the same way that this boundary is blurred in the context of other research. Imaging studies, or for that matter screening or diagnostic studies in any clinical trial, may uncover information of potential clinical importance that would not otherwise have been found. The return of incidental findings in any research study thus raises questions about the nature and scope of investigators' duties of nonmaleficence and beneficence to research subjects — questions that move research toward treatment by virtue of the clinical significance of the findings at issue.

In a panel [D-1] that examined the ELSI implications for genomics of issues arising in neuroscience, a paper by Judy Illes discussed the treatment of incidental findings in neuroimaging and considered the similar issues arising from incidental findings in genomics research. The familiar problem of incidental findings in clinical research more generally is increased greatly in scope in biospecimen research, owing to its much greater magnitude and scale. The collection of large numbers of biospecimens, and the technologies that permit identification of multiple mutations potentially associated with common complex disorders like cancer, make the identification of genetic variants that are not being looked for but that may have clinical meaning far more likely. Thus there is both (1) a need to determine in advance appropriate protocols for handling a high volume of incidental findings, and (2) an expectation on the part of research subjects that information of potential clinical significance is likely to be found.

Janet Williams and colleagues [E-6] documented this shifting terrain with research that presented contrasting views held by IRB chairs compared to genomic researchers regarding the return of incidental findings. While both groups agreed that the rapid development of extensive genomic sequencing techniques is creating some urgency in addressing the issue, they differed on whether research participants should be notified when an incidental finding emerged. Researchers believed such notification goes beyond the scope of their responsibilities, and thus there was little need to address incidental findings in consent processes, but expected to look to IRBs for guidance when such findings appeared. In contrast, IRB chairs believed that notification should be a concrete option, out of respect for participants and acting in their best interests; that a wide range of information should be included in consent forms; and that researchers had a duty to initiate the process of responsible management of incidental findings.

Unless clinicians and researchers work hard to clarify the difference, returning individual results may be viewed by potential subjects as essentially the same as handling incidental findings, at least in part because the key question — What information obtained in research has meaning for individual subjects? — is the same. The difference, of course, lies not in the

question but in the answer, since the purpose of genomic research is precisely to gather information whose meaning and value is yet to be determined.

(b) Returning Results

To classify any research results as worthy of returning to individual subjects requires the establishment of criteria by which to assess their significance. Thus, criteria relevant to answering the question include not only professional characterization of the findings (e.g., scientific validity or clinical utility), but also whether, and if so how, the possibility of returning results to individuals is addressed in the research consent form — an inclusion that may itself heighten public expectations about the direct clinical relevance of research results. Importantly, NHGRI has recently funded research on these topics through several grant mechanisms.[11]

Return of results has been examined in a wide range of studies of new genomic technologies, such as whole genome sequencing, microarrays, and exome sequencing. These new technologies have been utilized in conditions as diverse as breast cancer, Miller's syndrome, and coronary artery disease. A panel [G-1] examining these emerging analytical technologies addressed patients' and providers' perceptions about the significance of information derived from novel technologies for a range of research subjects: asymptomatic individuals, families with extremely rare disorders, and individuals testing negative for well-proven genetic associations.

Other Congress papers described variation in attitudes, practices, and assessments of this boundary-blurring. Reed Pyeritz [E-6] addressed the "Duty to Recontact in the Genomics Age," outlining a broad spectrum of situations that might affect views about the criteria for returning results and/or incidental findings, including: whether genetic variation is likely to be pathogenic; whether a new gene is discovered that either causes or predisposes to a condition for which evaluation was originally sought; whether potentially clinically actionable information is to be returned to the research subjects; and whether abnormalities that were outside the original indication for performing the study are identified. A survey of attitudes and practices of GWAS investigators regarding return of individual results [E-6, Ramoni] documented significant barriers, including uncertain clinical utility, the possibility that participants might misunderstand the information, the potential for causing emotional harm, and the need for access to a trained clinician. While two-thirds of the investigators surveyed believed the return of individual results was justified under certain circumstances, particularly to benefit participants' health, the vast majority reported that they had no plans to return results.

More specific contexts were also explored, providing evidence of complexity in assessing the issue. For example, research on pharmacogenomics, which evaluates genetic variations in an individual's genome to predict how a patient may respond to a particular therapy or dose, may involve fewer risks and more benefits (with likely high clinical utility) compared to returning results from research on disease susceptibility studies [E-6, Dressler]. A very different context for the debate on return of results was described by Laura Beskow [E-6], in her work on ethical challenges in genotype-driven research recruitment. This type of research design is a powerful tool for understanding human genetic variation. However,

opinions differ regarding whether and how to provide the genetic findings that prompted recruitment of an individual participant. Researchers and IRBs must consider the potential harms of not disclosing to an individual the genetic variation that has prompted their recruitment into a genotype-driven study, and compare these with the potential harms that arise from offering to disclose information about the individual subject's genetic make-up that is of uncertain significance and, often, ultimately meaningless.

(c) Biobanking and Blurring

ELSI research examining biobanking also often highlights the issue of research-treatment blurring. On the one hand, many biospecimen contributors are expected to donate without anticipation of individual benefits, thus exemplifying "genetic citizenship." Some biobanks created from newborn blood spots, or as a result of collection and storage of biospecimens and associated data from hospital inpatients, or even national biobanks, may espouse this perspective. In contrast, other biobanks, including some of those maintained by disease advocacy organizations, are created specifically for the benefit of contributors, with the return of individual results as one goal [D-4, Thiel].

Pediatric biobanking complicates this picture in interesting ways. In one panel [E-2], Ellen Clayton argued that pediatric biobanks are "Not Just Biobanks for Little Adults" — indeed, that the return of results for children raises unique implications that have not been extensively discussed. In the same panel, Holly Tabor used several examples from whole exome sequencing studies to illustrate the challenges that arise in biobanking research with biospecimens from children, including: the right not to know; results that may be clinically actionable for family members but not necessarily for the child research subject; and the dynamic nature of the meaning of genetic information over time. A second panel that addressed pediatric biobanking included a paper on "The Gene Partnership: Implementing the Informed Cohort in a Pediatric Setting" [B-4, Clinton], which described an innovative way to include parents and children in ongoing consent and engagement of families: in partnership they decide (1) how much information they would like to share about a particular topic and (2) what information they would like to receive from the Gene Partnership.

Thus, many presentations in the Congress helped to demonstrate a lively ongoing theoretical discussion of the nature and scope of researcher obligations and benefit-sharing in genomic research [A-2; A-5, Caga-Anan; A-5, Lehmann]. Findings presented at the ELSI Congress play an important role in animating this theoretical discourse, and document perceptions that the boundary between research and clinical care is increasingly blurred in the context of translational genomic research [A-5, Whitener; A-8, McDonald; D-5, Cappella; G-5, Frank]. It is noteworthy that the scientific complexity of genomic research and the high degree of public interest it attracts has highlighted the need to increase scientific literacy by means of public education. Despite the recognition of this need, the blurriness of the research-treatment distinction itself, as perceived by many genomic research subjects and potential subjects, represents the primary challenge to efforts aimed at improving public understanding of and dialogue about genomic research [B-3; E-1].

In contrast, making aggregate results of genomic research available poses few blurring problems, and may help to educate the public at large by virtue of educating increasing numbers of biospecimen-providing research subjects. Thus, if biospecimen resources undertake conscientious development of websitebased documents and plain language summaries, return of aggregate results may contribute to public education about the limits of genomic knowledge [A-4]. Similarly, direct-to-consumer genetic testing, which is focused not on research but on return of individual test results, may itself be used as an additional type of educational tool, as outlined by another Congress panel [D-2].

In sum, current ELSI research suggests that, despite a history of work in research ethics attempting to clarify distinctions between research and treatment, problems fueled by the uncertain boundaries of these concepts will continue to haunt biomedical research. These conceptual uncertainties will be compounded by the scientific and clinical uncertainties of much of the information that genomic research could propel across this boundary. These uncertainties constituted the second major recurrent theme at the ELSI Congress, and seem certain to animate research ethics debates even more widely in the future.

(2) The Varieties of Uncertainty

Uncertainty arises in the course of making meaning and use of information from genomic research. As genomics illustrates, biomedical research is increasingly making massive amounts of data about individual patients and research participants readily available long before the clinical significance of that information can be established. Presentations at the Congress [e.g., D-3] provided a wealth of insights about the impact of genomic information, good ways to provide that information, counsel people about its meaning, and educate clinicians and the general public about its limits, given a high degree of uncertainty. What is learned from ELSI research can inform a reflexive, iterative developmental process, whereby research moves from description to prescription and back again, in response to what has been learned about how patients and the public understand and use genomic information.

(a) Clinical Uncertainty

It was the rare presentation in the Congress that did *not* mention uncertainty as a critical feature of the understanding and use of genomic information in all contexts. A wide range of genetic screening and testing services, especially direct-to-consumer genetic screening/testing, attempts to make use of new information about genetic associations, variations, susceptibilities, and the like as predictive information for prevention and other decision-making purposes, seeking to translate data of uncertain meaning rapidly into practice. The ambiguities of understanding surrounding research into novel genomic technologies like exome and whole genome sequencing and high-resolution microarrays [G-1] exemplify this problem. A panel addressing non-invasive prenatal genetic testing [G-3] likewise considered the ways in which ease of implementation of a new technology can lead to unconsidered, even unfettered use without regard to genuine usefulness — in this instance, uncertainty about how this more readily available but still ambiguous information should be used in decisions about pregnancy and birth.

A paper describing the detection of copy number variants in autism spectrum disorder noted that the genetic test at issue, array comparative genomic hybridization, was quickly becoming routine in clinical practice, even though the lack of diagnostic certainty arising from test results caused many insurance providers to label the test investigational [B-7, Shutske]. Similar challenges arise with prenatal microarray testing, which is newly available clinically and has recently been recommended by the American College of Obstetricians and Gynecologists for use in prenatal diagnosis when abnormal anatomic findings on prenatal imaging are accompanied by a normal karyotype. Perhaps unsurprisingly, microarray testing itself often provides uncertain results [E-7, Bernhardt]. Uncertainty also played a significant role in papers addressing how cancer genetic risk assessment and cancer pharmacogenomics are viewed by stakeholders outside academic medical centers, for whom advanced diagnostics are newly accessible [D-7].

The translation of recently discovered genetic information into clinical care was addressed by a panel [E-4] presenting the results of a project examining the implications of identifying mutations associated with Long QT syndrome, a cause of sudden unexpected cardiac death. Family decision-making has particular significance in Long QT syndrome, especially regarding questions of whether and how to involve potentially affected adolescents or young adults who may be particularly distressed by uncertainty of information about at-risk status and risk-reducing interventions.

Other examples focused on adaptation to uncertainty. One paper [A-7, Biesecker] described the development and use of an adaptation scale assessing how individuals affected by and at risk of being affected by a genetic condition understand and come to terms with health threats. Several panel sessions reported on survey and interview studies of patients' and families' interpretation and use of genomic screening and testing results. One panel [B-1] presented empirical evidence to inform practice and policy in personal genomics based on responses to risk information. Such information includes, in the case of the REVEAL Study, return of results from APOE testing, which signals risk for the development of Alzheimer's disease.

It is noteworthy that few observations about uncertainty in genetic screening and testing are unique to genomic research or practice. One exception may be found in the possibility that expansion of newborn screening may identify maternal disease [B-7, Buchbinder]. However, genomics often simply makes more ambiguous information more readily available, thus highlighting the need for expert professional understanding and the professional time and talent to undertake the necessary education and counseling for patients and families. For example, variants of unknown significance (VUS) have long presented very similar challenges when they are identified in imaging studies. Today, VUS are frequently seen in microarray testing, even when it is employed in the hope of making a more definitive identification of as-yet-unexplained anomalies [B-7, Reiff; E-7, Bernhardt]. Another type of VUS that is unique to genomics is copy number variants (CNVs), which are now detected with some frequency in patients with autism spectrum disorder through array comparative genomic hybridization [B-7, Shutske]. While, as noted above, this is becoming routine in clinical care, newly identified CNVs do not provide definitive confirmation of etiology; this

therefore may simply compound the uncertainty that parents already feel about the potential severity and management challenges facing their children with autism spectrum disorder.

Another important arena of uncertainty is the longstanding controversy over whether children should be tested to determine whether they are at genetic risk for adult-onset disease. Even when the identified risk is relatively high, as in BRCA1 and 2, the balancing of harms and benefits arising from early identification of uncertain risk and the assignment of meaning to probabilistic information is significant for families [E-7, Bradbury].

Uncertainty also arises in novel ways in expanded newborn screening. It is well-recognized that the expansion of newborn screening has resulted in identification of some disorders for which little or no effective treatment is available, and in other instances, early identification of disorders for which the timing and severity of manifestation are uncertain — both of which give rise to concerns about labeling and stigmatization.[12] Newborn screening for Krabbe disease appears to combine these two concerns, as it detects both a treatable, early-onset version of the disorder, which fits the paradigmatic phenylketonuria model for newborn screening, and also a late-onset form, which is not treatable and thus fits the Huntington's Disease paradigm for strongly discouraging early diagnosis [D-6, Dees]. Newborn screening for common complex disorders raises similar challenges with respect to uncertainty, because of the multiple genetic contributions each common complex disorder represents. Type 1 diabetes is such a disorder, one which is currently not preventable but which presents considerable uncertainty with respect to its likelihood and severity when identified via expanded newborn screening [D-6, Kerruish].

(b) Conceptual Uncertainty

As genomics research delves into the uniqueness of individual bodies in search of individualized health interventions, it has also shed new light on old uncertainties about humans as individual bodies and about diseases as problems of those individual bodies. The discovery of the human microbiome has called into question our very concepts of what it means to be human by revealing the vast communities of microorganisms that not only live in our bodies, but play an essential part in the functions of these bodies that we once thought of as solely our own.[13]

In the case of research on the human microbiome, concerns about uncertainty have entered at an early stage: in the very selection of research subjects. Because the Human Microbiome Project has sought to sequence the microbiomes of "normal," "healthy" subjects, researchers have begun to question the very meanings of these terms, and the narrow range of potential participants these criteria have yielded [A-3; G-5].

Genomic science has also brought us back, again and again, to long-standing debates about the nature of illness — questioning how much of an individual's risk of developing diseases lies with the family, the community, and the society, and thus weighing interventions focused solely on the individual against interventions that include or primarily target social factors. Newborn screening debates bring these questions to the fore, as genetic risk factors discovered in screening an individual infant may point to risk factors for the parents or other family members [B-7]. The search for genetic factors in addictions has also highlighted the

problems of solely individualistic conceptions of disease. Recent examination of media representations of addiction has revealed a dichotomy between genetic determinism, on the one hand, and simple "willpower" on the other [G-5]. Yet, despite the proven success of social interventions such as indoor smoking bans and restrictions on tobacco sales, the role of social factors has been largely ignored in public, media, and policy discourses, which focus mainly on individual genetic susceptibilities and individual pharmaceutical interventions.

Finally, genomics has brought new clarity to our understanding of racial groupings, but has also intensified persistent uncertainties about the use of race as a category in research and clinical care.[14] One ELSI Congress panel highlighted several facets of race as a contested category in biomedicine [A-8]. While self-reported race may be a useful point of entry for clinicians seeking genetically targeted interventions for their patients, the social category "race" does not necessarily capture the genomic complexity of populations and ancestry groups. In fact, as one paper argued, there is a well-documented tendency to turn to racial categories as proxies for population risk in the context of clinical uncertainty [A-8, Cunningham].[15] Current patenting regulations tend to reify "race" as a genetic category in the development, testing, and marketing of new pharmaceuticals, a trend that has serious implications for the design of clinical trials and the marketing of new drugs [A-8, Kahn]. This conflation of race with genetic ancestry is exacerbated by NIH policies on the inclusion of underrepresented minorities in research, since these minority groups are defined by self-reported race and ethnicity, rather than genetically defined ancestry groups [B-6].

Many genetic association studies use ancestry estimation in order to identify genetic contributions to disease while mitigating the confounding effects of social stratification by race or ethnicity. Yet this practice may bring up new uncertainties for communities whose social identities depend upon an understanding of shared ancestry that may be challenged by genetic testing. Interdisciplinary perspectives on the use of genetic ancestry estimation in research must balance concerns about the entrenchment of ideas about race as a biological category with a commitment to addressing health disparities that are caused more by social differences than genetic ones [B-6].

While they are brought into dramatic focus by the lens of human genome research, conceptual uncertainties about how we should understand health, illness, individual human identity, and the connections between these ideas and the human groups into which we sort ourselves for social, political, and scientific reasons, are important challenges for all biomedical research. They are important because they implicate the goals of the research enterprise, its foundational assumptions, and its driving hypotheses. Moreover, the ELSI research presented at the 2011 Congress suggests that they are not uncertainties that can be resolved through science alone. Rather, as critical as they are to scientific priority-setting and direction, they ultimately are uncertainties that can only be resolved socially, through negotiation between the many different parties they implicate.

(3) Negotiating Genomics in the Public Square[16]

A significant part of ELSI research has always been looking beyond the challenges that genomic technology can raise for scientists and clinicians to the larger questions it raises for the public. During the tool-building era of the Human Genome Project itself, most ELSI research looked ahead to anticipate the effects that increased genomic information would have on society at large, through studies of its implications for insurance, employment, privacy, and the justice system, as well as its potential impact on cultural notions of personal and group identity, and concepts of normality and health. While these studies set the stage for important policy developments like the Genetic Information Non-Discrimination Act, they were also criticized by some for looking too far downstream from genomics, as if the design and conduct of genome research itself required no discussion by societal stakeholders beyond the scientific community. Indeed, the "Genomes to Society" portion of the ELSI research agenda is sometimes still portrayed as operating at a distance from genome research itself, as referring to "broader" or "downstream" considerations "beyond" the lab or clinic, with the lowered urgency that distance connotes.

In the years since the completion of the Human Genome Project, however, it has become obvious that in order to realize any translational goals for genomic research, a variety of public interests, perceptions, and voices must be engaged in conducting the science itself. In order to acquire the population samples and data that large scale genomics requires, the scientific community must leave the academic lab to negotiate with other social institutions — hospitals, public health agencies, communities, governments — that bring quite different agendas and interests to the table. As the scientific community has made its way across this crowded public square, ELSI researchers have accompanied them, to try to understand those agendas and interests, and what their implications might be for science policy.

As a result, it is noteworthy that, despite the linear metaphor of a "translational pipeline" that is often used to explain the classification of ELSI research projects addressing "genome research issues," "clinical integration issues," and "societal impact issues," one recurrent theme that cuts across contemporary ELSI research is increased attention to the ways in which societal interests and concerns and clinical realities and goals loop back to affect the design and conduct of genome research itself. The amount of research currently addressing public concerns and social agendas in conducting large scale and translational genomic research is itself a testament to the way in which placing societal issues at the downstream or distal end of the translational pipeline for genome research has both the distance and direction wrong. ELSI research today is not really captured by a heading like "Genomes to Society": in fact, much of it might be more accurately called "Society to Genomics," or even "Genomics Through Society" research, because it proceeds on the assumption that genome research can only make progress by coming to terms with the many different stakeholders it needs to enlist in its efforts.

Differences in what research subjects want and expect and what researchers are prepared to provide, as well as in what patients and the public want and what clinical genetic testing is able to provide, were frequently highlighted in Congress presentations. A broad spectrum of scientists, clinicians, patients, families, policymakers, and the public at large are

participating in ELSI research and helping to shape how genetic information is explained and applied. Newborn screening represents one such area, as does personalized genomics in general (in direct-to-consumer genetic testing and other forms). Critiques of the usefulness and cost of data acquisition and the uncertainty of analysis reflect the input of the public square, as do debates about what is considered useful and by whom. For instance, one panel session involved Congress attendees in a dramatic reading addressing different perspectives on enrollment in gene-finding research within a family affected by a genetic disorder [E-3].

Research reports that illustrate this cross-cutting theme at the ELSI Congress can be clustered into four overlapping sets of social/scientific negotiations, each focusing on a different aspect of translational genomic research: its *orienting goals*, its *driving hypotheses*, its *methods for acquiring human genetic material*, and the *rules governing its transactions* with the human sources of that material. This is not surprising, since each of these features is critical to the progress of the research, and each involves important normative choices: that is, value judgments about what directions the research should take and how it should proceed. In the case of translational genomic research, however, the questions raised by each of these four features are particularly vexing.

(a) Negotiating Genomics' Orienting Goals

In the promotional rhetoric of the scientific community, the success of much translational genomics research is measured in terms of how fast and well it can realize the orienting goal of personalized genomic medicine (PGM)[17] in health care. But as ELSI researchers point out, adopting PGM as the orienting goal for translational genomic research is not a value-neutral choice: it puts our money on the virtues of this model for health care instead of alternatives [A-2; D-2]. For biomedical research planners and their public funders, embracing this goal responsibly means reconciling any health care trade-offs involved.

One way this challenge was illuminated at the ELSI Congress was by explorations of benefit sharing and the reduction of health disparities as goals of translational genomic research [A-1; A-2; B-6, Courtwright]. Genomics research now takes place in an era when the potential beneficiaries of biomedical research have unprecedented knowledge of and advocacy regarding research agendas and the translation of findings into health benefits. Proponents of integrating stakeholders at every stage of the translational pathway argue that translation is less a linear than a cyclical process, and that integrating the assessments of multiple stakeholders into initial research design not only facilitates more democratic or "just" translation, but produces better science from the outset [A-1]. Another angle on these tensions was explored by several presenters for a panel examining the nature and limits of researcher obligations to participants [A-5, Caga-anan; A-5, Lehmann; A-5, Marsden]. In many instances, perhaps best exemplified by the return of results controversy [A-4], consensus conferences and similar efforts demonstrate the attempt to incorporate the views of stakeholder groups; without good empirical data, however, the value of consensus documents can remain an open question.

For clinicians, health care institutions, and research participants, defining the goals of translational genomic research also means ensuring that such research can yield meaningful health benefits in practical contexts. This again involves taking seriously the perspectives of

the different stakeholders who are involved in the health care system and are presumed to benefit from outcomes of the research. Examples at the Congress include surveys and interviews uncovering: differences between clinicians and insurance providers regarding whether genetic testing should be regarded as standard or investigational [B-7, Shutske]; differences between genetic counselors' evolving understanding of risk and the perceptions of their clients [B-7, Stern]; the range of health conditions for which the general public would seek genetic testing [B-7, Biesecker]; differences across jurisdictions and across the citizenry in views about newborn screening, including conditions tested for and views about consent [D-6, Grob]; views of the acceptability of newly available cancer genetic risk assessment technologies among hospital administrators, clinicians, and at-risk individuals [D-7, Miesfeldt]; and adoption of cancer pharmacogenomic testing among oncologists [D-7, Dressler]. The introduction of novel genomic technologies like non-invasive prenatal testing [G-3], exome sequencing, whole genome sequencing, and microarrays [G-1] similarly demonstrates a diversity of perspectives between generalist and specialist clinicians, scientists, patients, advocacy groups, and insurers.

(b) Negotiating the Driving Hypotheses of Translational Genomic Research

Proponents of genomic medicine assume that the best way to improve health care is to understand human genomic variation and the regulation of human gene expression at as high a level of resolution as possible. Translational genomic research priorities are set in terms of these assumptions. But depending on the assumptions they make and the questions they address, studies of the relevance of human genomic variation and gene expression to human health can implicate the social, political, and economic interests of many stakeholders, from individuals and families to communities and populations. For both genome scientists and these other stakeholders, these competing interests raise normative questions about who should be involved in the framing of particular translational genomic research hypotheses and how genomic research results should be publicly interpreted, commercially developed, and clinically applied, if we are to avoid disadvantaging those the research is intended to help.

Genomic research has encountered and intensified social and political uncertainties for some minority groups that are underrepresented in biomedical research. Addressing this challenge was repeatedly marked as urgent by presenters because of the scientific, conceptual, and political uncertainties that can get eclipsed in the process of moving too quickly from one sphere to the next. One ELSI Congress panel detailed the creation of an international Indigenous Genomics Alliance (IGA), which facilitates connections between indigenous groups worldwide and the development of research frameworks that respect indigenous values and self-determination [G-4]. Organizations like the IGA serve an important function in the wake of past misunderstandings and exploitations of indigenous groups by genomics researchers, and echo a wider call for community partnerships in genomics research that can facilitate mutually beneficial research relationships.

While the Latino community has historically been poorly represented in biomedical research, recent projects designed to increase Latino participation in research on autism spectrum disorders have built community partnerships through trusted community-based

organizations [B-3]. Ethical and social issues must be carefully addressed in using community members and organizations as gatekeepers who assist researchers in accessing potential research participants, but this exploratory research suggested that this model could be implemented at other sites to help achieve more balanced representation of Latinos in genetic research. Similarly, another ELSI Congress panel discussed the development of community partnerships with marginalized and indigenous communities in the U.S. and Peru, addressing community perceptions of genomics research and researchers and seeking a better understanding of community needs that can lead to collaborative research relationships [E-1].

In this respect, assumptions about what should count as legitimate risks for genome research also come up in deciding how to frame the genomic research agenda. Should genomics be concerned with social and cultural beliefs that might be challenged by scientific findings, or let the "chips fall where they may" in terms of the social sequelae of genomic variation research for group identity claims, values, and social coherence? Here, examinations of the risks to cultural beliefs constitutive of our social fabric were discussed in the context of microbiome research [G-5, Frank], ancestry studies [D-8, Ossorio], and population structure and reputation [G-4].

(c) Negotiating Procurement Methods in Translational Genomic Research

Translational genomic research capable of illuminating genomic variation and gene expression in ways that can lead to health benefits is only possible if researchers have access to the raw materials they need: large numbers of DNA samples from genetically diverse sets of people with relevant phenotypic traits. The design of any specific translational genomic research project is shaped by the need to procure these annotated samples. But procuring the raw materials for translational genomic research is not as straightforward as ordering chemical reagents from a scientific supply house. In order to acquire the volume and kinds of human DNA samples they require, genome scientists must build or turn to existing collections of stored tissue from human beings. For these scientists, the managers of these collections, and the people from whom biospecimens are obtained, this need raises normative questions about dispositional authority over samples, ownership of intellectual property [B-5], the privacy of the information that biospecimens yield, and how best to share the benefits of research among those involved.

As a result, ELSI researchers are devoting significant effort to empirical studies of attitudes and experiences of different populations about being involved in large scale or translational research, including African Americans [A-8, McDonald], Native Americans and other indigenous peoples [G-4; D-8, Ossorio], Latino families [B-3], technological elites [D-4, Thiel; D-5, Cappella], and persons with low socioeconomic status, from both the urban north [E-1] and the rural south [D-4, Mitchell]. Research on biobanking presented at the ELSI Congress addressed community and public perceptions of biobanking and related research, revealing the complexities of relationships between biospecimen providers and researchers and the challenges these raise [B-4; D-4; E-2].

Nowhere are these ethical and practical questions more contentious than in pediatric biobanking. Research on the policies and practices of organizations banking pediatric

samples has revealed a wide range of decisions about the return of research results and incidental findings, study withdrawal, consent/assent, and re-consent of minors when they reach adulthood [B-4]. Pediatric biobanks must consider the unique features of consent in the pediatric context, and address the amount of influence parents should exert to encourage children's participation. The disclosure of information during consent and of results discovered during research also present challenges, especially because such information may have equal or even greater implications for parents and other genetic relatives than for the pediatric donor [E-2]. Equally thorny issues arise in the context of banking umbilical cord blood and residual newborn screening samples for future research, since both of these types of samples are collected immediately after childbirth, a context in which informed consent is difficult at best [B-4]. As several panels discussed [B-4; D-4], recent legal battles in Texas and Minnesota have highlighted the "gap between law and ethics" when newborn screening samples are used for research without informed consent by parents. One panel reported that efforts to engage the public on the issue of research using newborn screening samples have resulted, on the one hand, in a recognition of the public's desire for explicit requests for consent when such samples are used for new research, and, on the other, in greater public understanding and support of the value of such research [D-4].

(d) Negotiating Genomics' Social Contract

Finally, translational genomic research takes place within a framework of moral norms, professional codes, institutional procedures, and public policies that govern research with human beings. This framework influences the ways in which human DNA samples can be obtained and used in translational genomic research projects, potentially affecting their ability to illuminate human genomic variation and expression. But abiding by the rules that govern the approval and regulation of translational genomic research is not straightforward. For the institutional committees that oversee this research and the scientists who design and conduct it, the interpretation of our research ethics conventions, codes, and regulations poses an array of specific normative questions about how best to proceed with research recruitment, obtain informed consent, protect data confidentiality, and address the disclosure and publication of results.

For example, one of the distinctive norms of basic genome research has been a commitment to broad data sharing. Now that communities and advocacy groups exert influence alongside funders and data producers as stakeholders in genomics research, new compromises and guidelines are being considered with respect to data sharing [E-5]. Recent research has shown that research participants and community members often approve of wide data sharing for research purposes, but concerns remain regarding commercial use, retention of donor/community choices about sharing and secondary uses, and potential loss of privacy [D-5; E-5; G-2]. Loss of privacy is a particular danger for genomic data, which is potentially identifiable given enough SNPs; and identifiability is especially problematic in the case of rare genetic traits [B-5; D-5; G-2]. Researchers have voiced additional concerns about data sharing, including the risks it poses to the assignment of credit for breakthrough discoveries, which is crucial for career advancement and future funding through grants or patent revenue [E-5]. On a broader scale, questions have emerged as to the feasibility, for current hypothesis-driven research, of applying the rapid data-sharing principles that were designed

to facilitate the generation of raw sequence data for the Human Genome Project [E-5]. This model fits well with recommendations on genomic data sharing proposed by recent expert groups, which advocate for longitudinal partnership with participants [G-2].

But if genomic data are to be shared, the governance of this "commons" must be decided. ELSI Congress presentations reported on the NIH's decision to restrict access to genomic research data shared through dbGap, and on data governance policies that have altered scientific practice in the U.S., in Mexico, and in the U.K. [B-5; E-5; G-2]. International collaborations bring particular challenges, and one presenter elaborated on these challenges, suggesting that some can be met through establishing shared values among members of these consortia [E-5, Knoppers].

Another major topic of negotiation in the conduct of genomic research is how best to respect the interests of communities when they are recruited to represent larger populations. Projects were presented testing and proposing methods for building trust between the public and the scientific community, by improving the dialogue between them about the risks, benefits, and meaning of participating in translational research, such as Anderson's study of methods for promoting dialogue on the research uses of residual newborn screening bloodspots [B-4]; Whitener's proposal for engaging American Indian communities in research through community-based system development [A-5]; or West's project on developing common language for cross-cultural genetic research [A-5].

Similarly, panels at the ELSI Congress suggested various approaches to addressing the issues raised by biobanking, the research it facilitates, and its public implications. One presentation offered a multi-method approach to engaging parents in dialogue and policy-making efforts on the use of residual newborn screening samples [B-4, Anderson]. Given the challenges of informed consent in the biobanking context, where it is impossible to know all possible future research uses for samples at the time they are donated, one paper suggested an alternative model based on clinical advance directives, which bestow the ethical authority for future decision-making on a surrogate [D-4, Solomon]. Another panel discussed Vanderbilt University's model of "human non-subjects research" using de-identified samples from clinical treatment [E-2]. Under this model, risks are minimized through governance, while patients are offered annual opportunities to opt out of future research. Alternately, as described above, the "Informed Cohort" model provides a particularly collaborative approach in which "personally controlled health records" facilitate communication and the return of individual research results [B4, Clinton].

Finally, whether or not studies or sample storage are "large-scale" in the sense of drawing on a large number of participants, the speed at which genomic science has advanced means that genomic information is increasingly "large-scale" in its quantity, scope, and implications. Several ELSI Congress panels addressed issues related to ownership, sharing, and identifiability of genomic data. Although researchers regard samples and information as valuable resources, their understanding of who owns these resources and what is entailed by that ownership is often vague [B-5]. Researchers have also expressed concern that patenting practices are creating "patent thickets" that inhibit the development of new genetic diagnostic tools [B-5].

By illuminating the ways in which all four critical elements of translational genomic research — its goals, hypotheses, methods, and social constraints — are dependent on trade-offs between scientific and non-scientific considerations, the 2011 ELSI Congress raises a much broader question for research ethics. If biomedicine's flagship research movement is shot through with negotiations involving parties with different values and priorities, surely the larger clinical research enterprise is subject to the same social forces. Should these forces be embraced as the "democratization of science," or resisted as the distortion of science by social agendas? If such negotiations are inevitable and ubiquitous, how should they be managed if they are to be dealt with responsibly?

Conclusion

Our review of presentations at the 2011 ELSI Congress identified three major, interrelated themes for contemporary research ethics. First, new forces are reshaping the boundaries between research and treatment, threatening to erase the dividing line initially set forth in the Belmont Report. This challenge, which dates back to the early, problematic distinction between "therapeutic" and "nontherapeutic" research,[18] has long been recognized in oncology research,[19] and has more recently become pervasive. Contributing trends in clinical research generally include the media's role in promoting research results;[20] the increasing roles that patients and communities now often take in research design and implementation; and communication of research results and incidental findings in studies of all sorts. Whether these changes are ultimately appropriate and beneficial is as yet unclear.

Second, the unprecedented and often uncontrolled translation of genomic research into commercial genetic testing and into clinical settings highlights ongoing controversy over the nature and meaning of genomic information, for different populations, in different contexts. Uncertainty has always been a key characteristic of scientific knowledge, but avoidance of its implications is no longer so easy, now that large data sets and information-sharing have become pervasive throughout clinical trials. As other areas of biomedical research increasingly exploit the wealth of data made available by the new interoperability of biobanks, databases, and electronic medical records, these issues of uncertainty promise to become ubiquitous.

Third, ELSI research presented at the Congress drew attention to broader issues at play whenever basic scientific research requires the participation of non-research institutions, the private sector, and diverse communities in order to achieve its translational goals. Just as genomics must juggle multiple agendas in crafting its large-scale translational projects, biomedical research generally will increasingly face the ethical challenges involved in such negotiations. The relationship between science and society has rarely before been the subject of such comprehensive scrutiny.[21]

It is not a coincidence that the most prominent policy initiatives related to research ethics today, such as the ongoing effort to revise the Common Rule[22] and the recent research ethics report by the Presidential Commission for the Study of Bioethical Issues,[23] focus in no small part on challenges that have been thrust into the limelight by human genome research. Issues such as those raised by gene-hunting research with banked human tissue samples, by family

studies involving potent informational risks, or by genomic variation studies of human populations challenge our current views about the rights and interests of individual research participants. As the tools and strategies of genome research spread across the biomedical landscape, these challenges are becoming unavoidable. Fortunately, the ongoing work of the ELSI research community can provide the larger research ethics community an important head start on ensuring that its deliberations are well-informed and forward-looking.

Appendix

Presentation List from the "2011 ELSI Congress: Exploring the ELSI Universe"

A-1 **Panel:** Justice in Translation: Achieving Benefit for All from Genomic Science

Suzanne Holland, Helene Starks, S. Malia Fullerton, Wylie Burke

A-2 **Panel:** Research on the Genetics of Antisocial Behavior and Violence: Implications for Social Control and Criminal Justice

Henry Greely, Megan Allyse, Paul Appelbaum, Nita Faraheny

A-3 **Panel:** A Next Generation of ELSI Research: The Human Microbiome Project

Pilar Ossorio, Amy McGuire, Richard Sharp, Cecil Lewis, Pamela Sankar

A-4 **Panel:** Ethical and Legal Implications of Return of Research Results to Participants in Biospecimen Studies

Nicole Lockhart, Carol Weil, Rihab Yassin

A-5 Themed Papers: Community Issues

- Positive Obligations in Genetics/Genomics Research: Are There Lessons to Be Learned from International Health Research Ethics?

  E. Charlisse Caga-anan

- Partnering with Research Participants: What Researchers Owe Participants

  Lisa Lehmann

- Linking In: Patient Networks and Genetic Research

  Wendy Marsden

- "Passed Down Through Our Blood": Developing Common Language for a Cross-Cultural Genetic Research Partnership

  Kathleen West

- Engaging American Indian Communities in Research through Community Based System Development

  Ron Whitener

A-6 Themed Papers: The ELSI Enterprise

- The Ethical Corporation?: Exploring the Ways the Private Sector Engages ELSI

  Jenny Dyck Brian

- Expanding ELSI- Challenges and Implications of Conducting ELSI Research in the Critical Care Environment

  Bradley Freeman

- ELSI Programs Across NIH: An Achievable Goal

  Jennifer McCormick

- Mapping the ELSI Universe: Taking Stock of the Field

  Clair Morrissey

- The “E” in “ELSI”

  Rebecca Walker

A-7 Themed Papers: Public Rhetoric

- Development and Evaluation of an Adaptation scale: Use in Six Studies on Living With or Being at Risk for a Genetic Condition

  Barbara Biesecker

- Problem Solved?: Media Representations of iPS Cell Research

  Timothy Caulfield

- Personalized Genomic Medicine and the Rhetoric of Patient Empowerment: Implications for Research and Practice

  Eric Juengst

- Framing Attitudes Toward Direct-to-Consumer Genetic Testing

  Jocelyn Landau

- Geneticization of Race in the News Media

  Jo C. Phelan

A-8 Themed Papers: Concept of Race

- “Clinical Uncertainty and the Use of Race as a Proxy for Genetics”

  Brooke Cunningham

- Mandating Race: How the PTO is Forcing Race into Biotechnology Patents

  Jonathan Kahn

- Attitudes About Genetically Targeted Care Among African Americans

  Jasmine A. McDonald

- Race as a Genetic Category: Challenging Conventional Wisdom

  John Moskop

B-1 **Panel:** Empirical Research to Inform Practice and Policy in Personal Genomics: Lessons from the REVEAL Study, Multiplex Initiative, and Coriell Personalized Medicine Collaborative

Robert Green, J. Scott Roberts, Colleen McBride, Eryn Gordon

B-2 **Panel:** The “Geneticization” of Food: ELSl lmplications of Genetically-Modified Probiotics

Richard Sharp, Ruth Farrell, Patricia Marshall, Gail Geller

B-3 **Panel:** Ethical, Social, and Scientific Implications of Activities to Increase the Representation of Latino Families in Bio-Medical/Genetics

Barbara Wheeler, Clara Lajonchere, Irene Martinez

B-4 Themed Papers: Pediatric Biobanking

- Methods for Promoting Public Dialogue on the Use of Residual NBS

  Rebecca Anderson

- The Gene Partnership: Implementing the Informed Cohort in a Pediatric Setting

  Catherine Clinton

- Legal Regulation of Banking Newborn Blood Spots for Research: What Can We Learn from State Approaches to Consent?

  Katherine Drabiak-Syed

- Who’s Cutting the Cord? Social and Ethical Implications of Using Publicly Banked Umbilical Cord Blood for Genetic Research

  Aaron Goldenberg

- Evaluating the Landscape of Pediatric Biobanks

  Danielle Soucier

B-5 Themed Papers: Ownership

- Examining University Researchers’ Views on Retention and Ownership of Human Genetic Specimens

  R. Jean Cadigan

- Intellectual Property Challenges for the Development of Novel Genomic Diagnostics- An Emerging Picture

  Subhashini Chandrasekharan

- An Investigation of Women’s Experiences of an IVF Egg Sharing Scheme for Somatic Cell Nuclear Transfer Research.

Erica Haimes

- Governing Data: A Study of Institutional Processes and Scientists' Experiences with Genomic Data Sharing

  Pilar Ossorio

B-6 Themed Papers: Race and Policy

- eMERGE-ing Complications: Race in the Era of Genomic Data Linked to the EMR

  Patrick Blackburn

- Trickle Down Breakthroughs: Can We Prevent Advances in Translational Therapeutics from Worsening Health Disparities?

  Andrew Courtwright

- Re-examining Inclusion in the Genome Era: Researchers' Views of the National Institutes of Health Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

  Sarah Knerr

- What Are Our AIMs? Interdisciplinary Perspectives on the Use of Ancestry Estimation in Genetics Epidemiology Research

  Joon-Ho Yu

B-7 Themed Papers: Genetic Testing-Clinical Understanding

- Do People Distinguish Between Diseases When Offered Genetic Testing for Multiple Common Health Conditions? Findings from an Ancillary Study of the Multiplex Initiative

  Barbara Biesecker

- Newborn Screening and Maternal Disease: A Case of Mistaken (Patient) Identity

  Mara Buchbinder

- Dealing with Uncertainty in Microarray Testing: Seeking Understanding and the Need for Clarity

  Marian Reiff

- aCGH Testing for Patients with Autism Spectrum Disorder: Is It Research or Clinical Practice?

  Krysta Shutske

- "Calculating Uncertainty: Genetic Counseling and the Development of Genetic Risk in the United States"

  Alexandra Stern

D-1 **Panel:** "The Challenging Ethical, Legal, Policy, and Social Considerations in Neuroscience Research: Intersections with Genetics"

Jennifer McCormick, Henry Greely, Judy Illes, Paul Appelbaum, Jonathan Moreno

D-2 **Panel:** "Personal Genomic Testing as an Educational Tool: Legal Standards, Ethical Questions, and Empirical Data"

Shawneequa Callier, Kelly Ormond, Reed Pyeritz, Richard Sharp

D-3 **Panel:** "Innovative Approaches to Qualitative Data"

Marsha Michie, Martha King, Rachel Haase, John Conley, Nancy Press

D-4 Themed Papers: Biobanking

- "Community Understanding of the MURDOCK Study"

  Robert Mitchell

- "Mind the Gap: An Advance Directive/Surrogacy Model for the Relationship Between Biobanks and Tissue Donors"

  Stephanie Solomon

- "Town Hall and Online Responses to Informed Consent Models for Public Health Biobanks"

  Daniel Thiel

- "Reconsent in Genome-Scale Research: Implications for Engagement"

  Susan Brown Trinidad

- "Biobanking Cancer Tissue: Patients Consider Excised (Tumour) Tissue to Be 'Connective Tissue'"

  Eric Vermeulen

D-5 Themed Papers: Identifiability/Confidentiality

- Ethical Issues Regarding the Potential for Identifiability of Information in a Public Genotype-Phenotype Database

  Michelle Huckaby Lewis

- The Use and Understanding of Certificate of Confidentiality

  Lauren Dame

- Non-Welfare Interests in the Uses of De-Identified Materials

  Tom Tomlinson

- Public Opinion and Deliberation About Ethical Issues in Genetic Testing: Comparing Qualitative, Quantitative and Elite Views

  Joseph Cappella

D-6 Themed Papers: Newborn Screening

- Ethical Paradigms of Genetic Screening

  Richard Dees

- Citizens' Values Regarding Expanded Newborn Screening and the Role of Parental Consent: A Public Engagement Study

  Yvonne Bombard

- Pausing for Reflection: Governance Challenges in the Age of "New" Newborn Screening

  Rachel Grob

- Parents' Experiences of NBS for Type 1 Diabetes

  Nikki Kerruish

- Notes from the Front Lines: Psychosocial Follow-up of Newborn Screening

  Joanna Fanos

D-7 Themed Papers: Genetic Testing- Modes of Delivery

- Delivery of Cancer Genetic Services: Acceptability of Models of Care in a Geographically Remote Setting

  Susan Miesfeldt

- Cancer Pharmacogenomic Testing, Clinician Adoption and Patient Benefit

  Lynn G. Dressler

- Gaps in Oversight of Nonmedical Genetic Testing

  Sara Huston Katsanis

- Navigating a Research Partnership between Academics and Industry: Collaborations with Personalized Genomic Testing Companies

  Lisa Soleymani Lehmann

D-8 Themed Papers: Group Membership Concerns

- Does Specific Consent Cause People to Act Selfishly?: A Conjoint Analysis of Privacy and Biobanks

  Daryl Pullman

- Lessons From the Havasupai

  Pilar Ossorio

- Impact of the Havasupai Lawsuit on Genetic Research Studies

  Nanibaa' Garrison

- Genetic Testing in Immigration for Family Reunification: A Comparison of US and Canadian Policies

  Llida Barata

E-1 **Panel:** National and International Perspectives on Community-Based and Community Engaged ELSI Research

Patricia Marshall, Cecil Lewis, Aaron Goldenberg, Nanibaa' Garrison, Jodyn Platt

E-2 **Panel:** Pediatric Biobanks: Not Just Biobanks for Little Adults

Ellen Clayton, Benjamin Wilfond, Holly Tabor, Kyle Brothers

E-3 **Panel:** Genes and Plays: Exploring New Approaches and New Perspectives

Karen Rothenberg, Lynn Bush

E-4 **Panel:** Ethical, Legal and Social Issues in Genetic Testing Following Unexpected Deaths: Translation of Cardiogenetic Knowledge to Clinical Practice

Siobhan Dolan, Marina Stolerman, David Wasserman

E-5 Themed Papers: Data-Sharing

- Stakeholder Views on Data Sharing Policies: Who Wins, Who Loses, and Why?

  Helene Starks

- Examining the History and Implications of the 'Bermuda Principles' for Data Sharing

  Rachel Ankeny

- Bermuda's Legacy: The Future of Pre-Publication Data Release in the Post-Genome World

  Jorge L. Contreras

- Complexity, Genomics and Science Regulation

  Jesus Siqueiros

- International Governance for International Consortia?

  Bartha Knoppers

E-6 Themed Papers: Return of Results

- Ethical Challenges in Genotype-Driven Research Recruitment

  Laura Beskow

- Return of Individual Research Results from Pharmacogenomic Versus Disease Susceptibility Studies

Lynn G. Dressler

- Duty to Recontact in the Genomic Age

  Reed Pyeritz

- Attitudes and Practices of Genome Investigators Regarding Return of Individual Genetic Test Results

  Rachel Ramoni

- IRB Chair and Researcher Perspectives on the Emergence of Genomic Incidental Findings

  Janet Williams

E-7 Themed Papers: Pediatric Genetic Testing

- "It's a Little Bit of a Black Box"; Patient and Provider Experiences with the Uncertainties of Prenatal Microarray Testing

  Barbara Bernhardt

- Considering the Genetic Testing of Minors for Adult-Onset Disease. Parent Opinions and Experiences with Early Communication.

  Angela R. Bradbury

- Informed Consent Process in Alpha-1 Testing of At-Risk Children: Views of Parents and Adults Tested as Children

  Marilyn Coors

- Assessment of Parental Attitudes About Genetics and Congenital Hearing Loss

  Cynthia Powell

- Diagnosis Down Syndrome: Parental Perceptions of the Informing Process

  Marcia Van Riper

G-1 **Panel:** Ethical Challenges and Sociocultural Dimensions of Emerging Genomic Analyses: Data from Recent Studies of ExomelWGS

Holly Tabor, Barbara Bernhardt, Debra Skinner, Flavia Facio, Richard Sharp

G-2 **Panel:** Genomic Data Sharing: Perspectives on Building a Community Resource in the US and Abroad

Amy McGuire, Naomi Hawkins, Jill Oliver, Susan Trinidad

G-3 **Panel:** Conceiving Future Generations: Ethical, Legal, and Social Issues Surrounding Non-Invasive Prenatal Genetic Testing

Mildred Cho, Lauren Sayres, Mark Nunes, Susan Kelly, Jaime King

G-4 **Panel:** Rebuilding Our Nations: Strategies of Indigenous People to Navigate the Ethical, Legal and Social Landscape of Genomic Research

Rosalina James, Nanibaa' Garrison, Maui Hudson, Maile Taualii, Ron Whitener

G-5 Themed Papers: Gene-Environment/Microbiome

- Media Representations of Gene-Environment Interaction in Addiction Research: Implications for Substance-Use Policy

  Molly Dingel

- Gene by Environment Interaction in the Context of Behavioral Genetics: Public Understanding of Eating Disorder Causation

  Michele Easter

- Human Microbiome Research and the Social Fabric

  Lily Frank

- Imagining and Defining Who Will Be "Normal" Volunteers for Human Microbiome Research

  Sheryl McCurdy

- "Snake-Oil," "Quack Medicine," and "Industrially Cultured Organisms." Investigators' Perspectives on the Commodification and Commercialization of the Human Microbiome

  Melody Slashinski

References

1. The "2011 ELSI Congress: Expanding the ELSI Universe" was held in Chapel Hill, NC, from April 12–14, hosted by the Center for Genomics and Society at the University of North Carolina at Chapel Hill, an NHGRI-funded Center of Excellence in ELSI Research (P50 HG004488, Gail Henderson, PI). The Congress was funded by a supplement to this center grant. Other sponsors included the Carolina Center for Genome Sciences; the UNC School of Medicine, Department of Social Medicine; the UNC Center for Bioethics; the Wake Forest University Center for Bioethics, Health and Society; and the North Carolina Translational and Clinical Sciences Institute.
2. In the fall of 2003, the NHGRI in collaboration with U.S. Department of Energy (DOE) and the National Institute of Child Health and Human Development (NICHD) launched a new initiative to create interdisciplinary Centers of Excellence in ELSI Research (CEER). The CEERs are designed to bring investigators from multiple disciplines together to work in innovative ways to address important new, or particularly persistent, ethical, legal, and social issues related to advances in genetics and genomics. In addition, the centers will support the growth of the next generation of researchers on the ethical, legal and social implications of genomic research. Special efforts will be made to recruit potential researchers from under-represented groups. See <http://www.genome.gov/ELSI/#al-4> (last visited December 7, 2012).
3. In January, 1990, the ELSI Working Group issued its first report and defined the function and purpose of the ELSI program as follows: "1. To anticipate and address the implications for individuals and society of mapping and sequencing the human genome; 2. To examine the ethical, legal and social consequences of mapping and sequencing the human genome; 3. To stimulate public discussion of the issues; 4. To develop policy options that would assure that the information be used to benefit individuals and society." The ELSI Working Group envisioned a program that would anticipate problems and identify possible solutions and suggested a number of means to

accomplish these goals. Specifically, it encouraged the research community to explore and gather data on a wide range of issues pertinent to the Human Genome Project that could be used to develop education programs, policy recommendations or possible legislative solutions. A number of focus areas were identified, including: fairness in the use of genetic information; the impact of knowledge of genetic variation on individuals; and privacy and confidentiality of genetic information. See <https://www.genome.gov/10001754#al-2 accessed 12/14/2012> (last visited December 14, 2012).

4. The Planning Committee was composed of ELSI researchers, both CEER and non-CEER affiliated. It also included two individuals from outside the U.S. and members of the ELSI program staff. The following were members: Barbara Bernhardt, Joy Boyer, Tim Caulfield, Wendy Chung, Bob Cook-Deegan, Aaron Goldenberg, Gail Henderson, Eric Juengst, Jane Kaye, Nancy King, Sandra Lee, Jean McEwen, Nancy Press, Charmaine Royal, Elizabeth Thomson, and Marcia Van Riper.
5. Volunteer note takers for the Congress included: Astrid Ertola, Brooke Cunningham, Charlisse Caga-Anan, Cheryl Brewer, Colleen Clarke, Dragana Lassiter, Greg Guzaukas, Jane Peace, Jessica Erickson, Joon-Ho Yu, Karey Sutton, Kate McGlone West, Kathryn Maxson, Katie Byerly, Kelly Hogan, Krysta Shutske, Laura Wagner, Lauren Milner, Lauryn Sayres, Leila Jamal, Llida Barata, Marsha Michie, Martha King, Megan Allyse, Michele Easter, Michelle Montgomery, Nanibaaa' Garrison, Rachel Haase, Sarah Knerr, Sondra Smolek, Sony Tuteja-Stevens, and Wendell Fortson.
6. On February 10, 2011, *Nature* magazine published NHGRI's strategic plan for the future of human genome research: "Charting a course for genomic medicine from base pairs to bedside." This plan includes a section on Genomics and Society that outlines four areas that will need to be addressed as genomic science and medicine move forward. Based on these areas, the NHGRI has developed the following broad research priorities: 1. **Genomic Research**. The issues that arise in the design and conduct of genomic research, particularly as it increasingly involves the production, analysis and broad sharing of individual genomic information that is frequently coupled with detailed health information. 2. **Genomic Health Care**. How rapid advances in genomic technologies and the availability of increasing amounts of genomic information influence how health care is provided and how it affects the health of individuals, families and communities. 3. **Broader Societal Issues**. The normative underpinnings of beliefs, practices and policies regarding genomic information and technologies, as well as the implications of genomics for how we conceptualize and understand such issues as health, disease, and individual responsibility. 4. **Legal, Regulatory and Public Policy Issues**. The effects of existing genomic research, health and public policies and regulations and the development of new policies and regulatory approaches. See <http://www.genome.gov/10001618#al-2> (last visited December 7, 2012).
7. Appelbaum and colleagues coined the term "therapeutic misconception" in 1982.Appelbaum PS, Roth LH, Lidz C. The Therapeutic Misconception: Informed Consent in Psychiatric Research. International Journal of Law and Psychiatry. 1982; 5(3–4):319–329. [PubMed: 6135666] See also subsequent work on assessment of informed consent, perceptions of benefit in research, and the therapeutic misconception:Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False Hopes and Best Data: Consent to Research and the Therapeutic Misconception. Hastings Center Report. 1987; 17(2):20–24. [PubMed: 3294743] King NMP. Defining and Describing Benefit Appropriately in Clinical Trials. Journal of Law, Medicine & Ethics. 2000; 28(4):332–343.Miller M. Phase I Cancer Trials: A Collusion of Misunderstanding. Hastings Center Report. 2000; 30(4): 34–43. [PubMed: 10971892] Joffe S, Weeks JC. Views of American Oncologists about the Purposes of Clinical Trials. Journal of the National Cancer Institute. 2002; 94(24):1847–1853. [PubMed: 12488478] Dresser R. The Ubiquity and Utility of the Therapeutic Misconception. Social Philosophy and Policy. 2002; 19:271–294. [PubMed: 12678090] Horng S, Grady C. Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, and Therapeutic Optimism. IRB. 2003; 25(1):11–16. [PubMed: 12833900] Sankar P. Communication and Miscommunication in Informed Consent to Research. Medical Anthropology Quarterly. 2004; 18(4):429–446. [PubMed: 15612409] Brody BA, McCullough LB, Sharp RR. Consensus and Controversy in Clinical Research Ethics. JAMA. 2005; 294(11):1411–1414. [PubMed: 16174704] Miller FG, Joffe S. Evaluating the Therapeutic Misconception. Kennedy Institute of Ethics Journal. 2006; 16(4):353–366. [PubMed: 17847601] Appelbaum PS, Lidz C. Re-evaluating the Therapeutic Misconception: Response to Miller and Joffe. Kennedy Institute of Ethics Journal. 2006; 16(4):367–373. [PubMed: 17847602]

8. See, e.g.,Jansen LA. A Closer Look at the Bad Deal Trial: Beyond Clinical Equipoise. Hastings Center Report. 2005; 35(5):29–36. [PubMed: 16295262] Largent EA, Joffe S, Miller FG. Can Research and Care Be Ethically Integrated? Hastings Center Report. 2011; 41(4):37–46. [PubMed: 21845922]
9. The following articles present findings from a study (R01 HG 02087, Gail Henderson, PI) of perceptions of benefit in gene transfer trials:Churchill LR, Nelson DK, Henderson GE, et al. Assessing Benefits in Clinical Research: Why Diversity in Benefit Assessment Can Be Risky. IRB: Ethics and Human Research. 2003; 25(3):1–8. [PubMed: 14569987] Henderson GE, Davis AM, King NMP, et al. Uncertain Benefit: Investigators' Views and Communications in Early Phase Gene Transfer Trials. Molecular Therapy. 2004; 10(2):225–231. [PubMed: 15294169] King NMP, Henderson GE, Churchill LR, et al. Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research. IRB: Ethics and Human Research. 2005; 27(1):1–8. [PubMed: 15835063] Henderson GE, Easter ME, Zimmer CR, et al. Therapeutic Misconception in Early Phase Gene Transfer Trials. Social Science and Medicine. 2006; 62(1):239–53. [PubMed: 16000230] Henderson GE, Churchill LR, Davis AM, et al. Clinical Trials and Medical Care: Defining the Therapeutic Misconception. Public Library of Science-Medicine. 2007; 4(11):1735–1738.
10. See, for example,Wolf SM, et al. Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations. Journal of Law, Medicine & Ethics. 2008; 38(2):216–435.Wolf has argued that clinical researchers have an obligation to return incidental findings, while E. Clayton, among others, has argued for caution; seeClayton EW. Incidental Findings in Genetics Research Using Archived DNA. Journal of Law, Medicine & Ethics. 2008; 38(2):286–291.
11. NHGRI issued a press release on September 26, 2011, announcing seven grants awarded under a new call for research on return of results in genomic research: The National Human Genome Research Institute (NHGRI) today awarded seven grants, totaling $5.7 million, aimed at untangling one of the knottiest ethical issues facing genomic researchers. Under the microscope are issues around if, when and how researchers should return to study participants information about their risk for diseases or conditions discovered during studies of their genomes... Researchers have widely varying opinions on the 'return of results' issue. Some believe that they have an ethical or legal obligation to reveal to study participants their genomic information – especially if it is medically significant and interventions can prevent or reduce the risk of a disorder. Others consider sharing such information unethical – especially if the research participant was told he or she would not be re-contacted, if the information relates to a disorder for which there is no known intervention, or if the precise medical significance of the information is unclear. Researchers on both sides of the question must also consider regulatory and policy issues related to bringing genome sequencing to clinical applications. Until now, researchers have had very little data to guide their decisions, except for research that asks people hypothetically whether they want incidental findings returned to them. An incidental finding is a health finding about a research participant that is discovered in the course of conducting research but is not the central aim of the study. What people want in the abstract may be very different from what they want in an actual genomic research setting. See <http://www.genome.gov/27545526> (last visited December 7, 2012). On December 6, 2011, they issued a press release for *Clinical Sequencing Exploratory Research Projects*. To help speed up the application of genomic science to medical care, NHGRI will invest $40 million over four years to support five Clinical Sequencing Exploratory Research Projects, in which new multi-disciplinary research teams will explore the ways in which healthcare professionals may use genome sequencing information in a medical care setting. Physicians, ethicists, genomic scientists, patients and families will work together to learn important lessons about the use of genome sequencing in medical care and to develop methods to improve its use in the future…Clinical Exploratory Research Projects will answer questions such as how to incorporate genomic data into medical records, what tools are needed to extract relevant information from a patient's genome sequence, and how the availability of genome sequence data affects a physician's recommendations regarding treatment. The research will include important ethical and psycho-social elements, such as how patients should be counseled and educated before having their genome analyzed, the best way to acquire patient consent to participate in a study, and when to return findings to patients that are not related to the primary medical condition for which the test was done. The program will also provide a forum for the development and dissemination

of innovative and best practices for clinical genome sequencing. At <http://www.nih.gov/news/health/dec2011/nhgri-06.htm> (last visited December 7, 2012).

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13. Juengst, E. Metagenomic Metaphors: New Images of the Human from 'Translational' Genomic Research. In: Drenthen, M.; Keulartz, J.; Proctor, J., editors. New Visions of Nature: Complexity and Authenticity. New York: Springer; 2009. p. 128-153.
14. Burchard E, Ziv E, Coyle N, et al. The Importance of Race and Ethnic Background in Biomedical Research and Clinical Practice. New England Journal of Medicine. 2003; 348(12):1170–1175. [PubMed: 12646676] Cooper R, Kaufman J, Ward R. Race and Genomics. New England Journal of Medicine. 2003; 348(12):1166. [PubMed: 12646675] Foster MW, Sharp RR. Race, Ethnicity, and Genomics: Social Classifications as Proxies of Biological Heterogeneity. Genome Research. 2002; 12(6):844–850. [PubMed: 12045138] Lee SS, Mountain J, Koenig B, et al. Open Letter, "The Ethics of Characterizing Difference: Guiding Principles on Using Racial Categories in Human Genetics". Genome Biology. 2008; 9(7):404. [PubMed: 18638359] Ossorio P, Duster T. Race and Genetics: Controversies in Biomedical, Behavioral, and Forensic Sciences. American Psychologist. 2005; 60(1):115–128. [PubMed: 15641926] The Race, Ethnicity, and Genetics Working Group, National Human Genome Research Institute. The Use of Racial, Ethnic, and Ancestral Categories in Human Genetics Research. American Journal of Human Genetics. 2005; 77(4):519–532. [PubMed: 16175499]
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16. A phrase coined by Eric Juengst to illustrate our point on behalf of the Center for Genetic Research Ethics and Law (CGREAL) at Case Western Reserve University. E. Juengst, NIH Grant Application # 2 P50-HG003390-06, "Center for Genetic Research Ethics and Law," April 15, 2009.
17. A typology also anticipated by the research plan that currently frames the work of our CGREAL colleagues at Case Western Reserve University. E. Juengst, NIH Grant Application # 2 P50-HG003390-06, "Center for Genetic Research Ethics and Law," April 15, 2009.
18. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. available at <http://www.wma.net/en/30publications/10policies/b3/> (last visited December 7, 2012)Levine RJ. The Need to Revise the Declaration of Helsinki. New England Journal of Medicine. 1999; 341(7):531–534. [PubMed: 10441613]
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23. Presidential Commission for the Study of Bioethical Issues, *Moral Science: Protecting Participants in Human Subjects Research* (December 15, 2011).