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On What We Have Learned and Still Need to Learn about the Psychosocial Impacts of Genetic Testing

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The introduction of genomic technologies into medicine has already had a significant impact on medical care (1). Cancer patients routinely undergo genomic analysis of their tumors to identify potential therapeutic targets (2); prenatal ultrasound abnormalities lead to microarray testing of the fetal genome (3); and genome sequencing is the diagnostic tool of choice for newborns with serious, undiagnosable conditions (4). Given the extensive research now underway applying genomic technologies to predictive and diagnostic testing for a multitude of conditions, the role of genomics in medicine is likely to continue its exponential growth. Indeed, one leader in genomic medicine suggested recently that we are on “the path to routine genomic screening in health care” (5).

Since the start of the program to investigate the Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project in 1990, however, many ELSI scholars have maintained that genetic testing should be used with caution, because of the potential for negative psychosocial effects associated with receiving genetic information (6). They have argued that the potential for negative effects such as depression and anxiety, heightened stigmatization and discrimination makes it essential to engage patients in a sustained informed consent process to help them decide if they really want access to their genetic information. More recently, however, some ELSI scholars have produced evidence that suggests that the original ELSI concerns were unfounded, exaggerated, or at a minimum misdirected. At least in the contexts that have been most studied—single-gene disorders such as Huntington’s and hereditary cancers such as those associated with mutations in BRCA genes, and single gene testing for more complex conditions such as Alzheimer’s disease—large negative impacts have not been found in the vast majority of people studied (7).

If it were true across most contexts that there are no large negative psychosocial effects to worry about, one would indeed have reason no longer to consider genetic testing as different from other medical tests. It is difficult for us to identify any other type of medical tests for which patients are routinely told about the kinds of probabilistic or uncertain information they may receive, the sorts of choices they might face, or the potential psychosocial consequences of the results. Negating the special status of genetic testing would entail a reduction in, if not jettisoning of, the notion that informed consent should include education

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about these issues. No one expects clinicians to engage in such an informed consent process before, for example, taking a blood sample to assess electrolyte levels. Indeed, in daily practice, many medical tests are simply ordered by the treating clinician, with no consent process at all. *If* the psychosocial risks of genetic testing are largely chimeric, to insist on a special variety of informed consent is arguably to succumb to "genetic exceptionalism" (8).

As we tried to come to grips with the evolving literature on the psychosocial impacts of genetic testing, we began to wonder what might explain the discrepancy between the original hypothesized outcomes and the growing impression that large negative effects appear to be few and far between. Did those who predicted large negative effects just make a mistake about the size of the effects? That is, were they right that there would be effects but wrong about their magnitude? Did those who looked for effects use the wrong methods? Would, for example, qualitative methods, which entail listening carefully to recipients of the genomic information, detect larger effects than the quantitative survey methods that primarily have been used? Did the predicted large effects actually appear in a minority of individuals—perhaps due to predisposing factors—but fail to be recognized in final analyses that reported average effects across a population?

Or was the hypothesis that there would be large negative psychosocial effects simply wrong? Did the scholars who predicted them fail to appreciate the insight from affective forecasting research, which shows that human beings tend to overestimate the impact of negative experiences (from receiving difficult genomic news to being in a car accident) and tend to underestimate the speed with which we return to our original psychological set point (9)? And if the original predictions of large negative psychosocial effects were simply wrong, is it time for ELSI researchers to move on, confident in the view that whatever negative psychosocial impacts exist, they are too small or appear in too few people to warrant additional attention? Again, if the original predictions were indeed wrong, full stop, are we at the moment when genetic testing should be normalized, and would it be appropriate to relax or abandon the practice of engaging patients in a process of detailed informed consent before they receive genetic information?

To confront those questions, we convened a conference, entitled "Looking for the Psychosocial Impacts of Genomic Information." At the conference, we sought to review what is known about the negative impacts of genetic information on a variety of populations and in multiple medical and social contexts, to explore the implications of the findings, and to consider whether future research might benefit from different methods than have been used to date. We left the question concerning what is known about the positive impacts of genetic information (especially regarding improved health behaviors) for another occasion. The conference was held at Columbia University in February 2018 and co-sponsored by Columbia's Center for Research on Ethical, Legal & Social Implications (ELSI) of Psychiatric, Neurologic & Behavioral Genetics and The Hastings Center.

The essays you are about to read derive from that conference. As you will see, a clear answer did emerge to the background question regarding whether it is now time to jettison the commitment to an informed consent in the genetics context that includes psychosocial risks: no. Regarding most of the other questions we asked, however, the answers are less

crisp. The good news is that in these essays you will discover that ELSI scholars are making incremental progress in understanding the other issues we convened to address, including the impact of genetic testing on psychosocial outcomes and how best to advance the research agenda. Just coming better to understand why one-size-fits-all answers will not be forthcoming is itself progress.

We have organized this collection into 3 major parts, each of which includes 3 essays. The first part steps back to provide historical and social context for the current debates about empirical research into the impacts of communicating genetic information to patients. In particular, it introduces the original, foundational ELSI concern about "genetic essentialism," the idea that genes are the essence of humans, and thus genetic knowledge is not only crucial for improving our health, but for understanding who we are. More precisely, the first part reveals a disagreement within the contemporary ELSI community about genetic essentialism. Whereas one camp of ELSI scholars points to evidence consistent with the worry that genetic information will be essentialized and thereby produce an array of psychosocial harms, the other points to evidence that most people avoid genetic essentialist thinking, making the hypothesized harms less likely to accrue. The second part of the collection focuses on empirical studies that support the second camp's skepticism about the existence of large, negative psychosocial harms associated with the communication of genomic information. And the third part focuses on empirical studies that support the first camp's claim that reasons for concern about psychosocial harms are as relevant today as ever. The concluding essay explains why generalizing across contexts is difficult. Before inviting you to read the essays for yourself, however, we will offer a slightly more detailed tour of what you are in for.

Part 1. Disagreement about the prevalence of genetic essentialism.

The first essay is by Maya Sabatello, a political theorist and lawyer, and Eric Juengst, who is a philosopher and was the first Chief of the ELSI Office at NIH when the Human Genome Project began. In defense of their claim that genetic essentialism remains a problem today, Sabatello and Juengst explain its intellectual history and place it within a network of closely related concepts. After showing how genetic essentialism is related to genetic determinism and genetic reductionism, they draw connections between those 3 "isms" and 3 more that implicate the world of medical practice, what they refer to as "genetic fatalism," "genetic meliorism," and "genetic imperialism." Next, they draw connections between those first 3 "isms" and yet 3 more that implicate the wider social and political world: "genetic racism," "genetic sexism," and "genetic ableism." They suggest that this network of isms constitutes a vicious circle, which we won't escape as long as we indulge in what they take to be hyperbole about the power of genes to improve our health and to deepen our self-understanding. Until that overstatement abates, they argue, this set of concepts remains as relevant today as when the ELSI program was created.

Whereas Sabatello and Juengst come at genetic essentialism from traditional bioethics, Steven Heine, Benjamin Cheung, and Anita Schmalor come at it from social psychology. They argue that, across ages and cultures, human beings have developed a suite of biases and heuristics that help us to manage a complex world. Among the ways that we simplify and

manage the world is by attributing "essences" to things, which we imagine to be the result of "deep, hidden, and internal forces" below the surface of what we observe. Heine, Cheung, and Schmalor argue that, because of our inadequate educations in genetics, it is especially easy for us to imagine that *genes* are "deep, hidden, and internal." That is, genes are, as it were, an especially effective hook on which to hang our essentialist intuitions. The problem, on their account, is that genetic essentialism can be an especially powerful tool for doing social harm. They offer results from myriad social-psychology experiments, which suggest that genetic information can, for example, undermine people's sense of themselves as agents, exacerbate their tendencies to discriminate against others, and make them more punitive in criminal sentencing decisions. They grant that genetic information does not always cut in only one direction or even always in what they take to be a harmful direction (they discuss, for example, how genetic information has been recruited to advance gay rights), but their strong emphasis is on the harmful outcomes. They end, nonetheless, on an optimistic note: with better education about the complexity of the relationship between genes and complex behaviors and traits, lay people will get over being genetic essentialists.

Celeste Condit, who has long studied public understanding of genetics and who resides in a communication studies department, presents a view that stands in stark contrast to the first two essays. She argues that lay people are *strategic*—not *genetic*—essentialists. Whereas Heine, Cheung, and Schmalor explicitly rely on a strand of social psychology literature about heuristics and biases (and how they lead to simplifications like the assumption that genes are the essence of humans), Condit's point is consistent with another strand of work in social psychology, which shows that most of the time, most of us have a conclusion in mind first and then search for justifications to support it (10). Yes, she observes, people with a racist agenda can try to use genetic evidence to advance their agenda, but (as we mentioned above) people with a pro-gay-rights agenda can use genetic findings to advance their goals as well. There isn't, Condit argues, anything about genetic information that determines the strategic purpose to which any given individual will put it. Moreover, her research suggests that lay people do not have simplistic, essentialist views of how genes cause complex traits and behaviors. On her account, lay people tend to believe that genes can play an important explanatory role (think Huntington's), but that environmental forces can also play an important role (think smoking and lung cancer), and, usually, that genetic and environmental variables both play a role (think social success).

It may be that we don't need to choose between the point emphasized in the first two essays (genetic information can be an especially effective hook on which to hang essentialist impulses that tend to conduce to social harm) and the point emphasized in the third essay (genetic information can be used "strategically" to advance whatever agenda we hold from the outset). Seeing those two points juxtaposed, however, can help us notice how difficult it can be to generalize about the psychosocial impacts of genetic information.

Part 2. Three essays that emphasize reassuring news about psychosocial impacts.

Scott Roberts is a psychologist with expertise in public health genetics and genetic counseling, and is a coprincipal investigator on the widely discussed Risk Evaluation & Education for Alzheimer's Disease (REVEAL) study. The REVEAL study, which explored the consequences of returning information about testing for the ApoE4 allele—a polymorphism that increases the risk for Alzheimer's Disease (AD)—reported that, on average, persons who were found to have one or two ApoE4 variants, and hence elevated risk for developing AD, did not show significant elevation on measures of depression or anxiety after receiving their results (11). REVEAL is often invoked by those who are skeptical of the claim that genetic testing can have large negative psychosocial impacts. In his essay for this collection, in keeping with the thrust of the REVEAL findings, Roberts discusses other findings, which suggest that, if people decide to get susceptibility testing after a process of informed consent, any psychological distress that occurs tends to be "generally mild and transient." He is, however, at pains to recognize that the REVEAL study should not be viewed as the final word on the impacts even of ApoE4 testing, much less genetic testing altogether. Roberts describes, for example, the study by Lineweaver and colleagues, who compared two groups of older adults who tested positive for the ApoE4 allele (12). One group was aware of their results, while the other group was not. People in the first group not only reported more memory problems, but showed worse performance on objective measures of memory. These effects—far more subtle than the ones anticipated in the early literature on genetic testing—could nonetheless have a significant impact on the quality of life and functioning of people who learn of their risk for AD. Roberts outlines a number of directions for future, more refined approaches to investigating the impacts of genetic susceptibility testing, and he is careful to emphasize that the pattern he describes—if there is psychological distress it is generally mild and transient—is pertinent for people who have undergone pre-test (and where applicable, post-test) education and counseling. No matter the average psychological impacts of genetic testing results, his commitment to the importance of engaging patients in a process of informed consent remains strong.

Jada Hamilton is a clinical psychologist who studies the psychosocial impact of genetic testing for susceptibility to hereditary cancers and Mark Robson is a medical oncologist. Hamilton and Robson begin their essay by describing a finding similar to the pattern described by Scott Roberts: when patients receive results regarding high-penetrance variants (that is, changes in the DNA sequence that are highly likely to result in disease) such as common mutations in BRCA1/2, they do not appear to experience an increase in their levels of general anxiety, and in fact have "decreased cancer-specific distress over time." And they also urge the reader to distinguish between traditional (Sanger) testing for single genes and what is now coming on line: multigene panel testing, which uses next generation sequencing technology to determine the sequence of multiple cancer susceptibility genes at once. Because multigene testing is not necessarily limited to genes indicated by the patient's personal characteristics and family history, the certainty associated with the results may be less than the certainty associated with traditional single-gene testing, and the psychological impacts might not be the same. Moreover, Hamilton and Robson observe, with new

sequencing technology come variants of unknown significance (VUS). Because uncertainty regarding the meaning of a genetic (or any other test) can be accompanied by psychological distress, Hamilton and Robson are, like Roberts, careful about extrapolating from what we've learned so far to what we can expect in the future. It is one thing to receive information about a test for a single gene that has relatively well understood significance; it is another to receive information about a test for many genes that are less well understood or to receive results of altogether unknown significance.

Barbara Biesecker, a health psychologist and genetic counselor, reviews the literatures that investigate how women and their partners psychologically manage the experience of receiving genetic results from prenatal screening and testing. She acknowledges that in some cases women can experience anxiety around prenatal screening, which so often entails false positives. But she emphasizes that this anxiety is usually the result of insufficient knowledge around what screening is, and that better education about screening could remedy that problem. She also acknowledges that waiting for prenatal test results can produce anxiety and that discovering the presence of an atypical genetic result can be enormously anxiety provoking. Nonetheless, the data suggest to her that those negative psychological impacts are transient; as one might well expect from the affective forecasting literature, most people appear to return to their baseline sense of well-being. Moreover, she observes that the women who choose to get testing would rather endure those negative psychological impacts than discover that their child has a genetic disorder after the child is born. As Biesecker emphasizes, however, prenatal genetic testing is a "preference-based health care option." No woman is required to undergo such testing, and every woman who gets it must receive pre-test (and where applicable, post-test) education and counseling. As a genetic counselor, Biesecker is acutely aware of the many demands already placed on Ob-Gyns and of the dearth of trained genetic counselors, but she is committed to finding new computer-based platforms that can help to promote pre- and (where applicable) post-test patient education.

Part 3. Three essays that emphasize less reassuring news.

Allison Werner-Lin, Judith McCoyd, and Barbara Bernhardt have backgrounds in social work and genetic counseling, and all have considerable experience doing research on the experience of pregnant women who have received genetic information about their fetus. Different from Barbara Biesecker, who reviews the empirical literature on the *average* experience of pregnant women who have received genetic information of relatively certain clinical significance regarding their fetus, Werner-Lin, et al. listen carefully to the experience of women who have received genetic information that is of unknown clinical significance. Although some women decide to terminate a pregnancy on the basis of such information, Werner-Lin and colleagues studied women who decided to continue their pregnancies without knowing if the genetic variant brought to their attention would turn out to be of clinical significance. When they listened carefully to individual women, they found that variants of unknown clinical significance can cause considerable anxiety for some women during the pregnancy and after, even if the child has no signs of a disorder. According to Werner-Lin, et al., the uncertain information can remain on parents' minds, creating the perception that their child is especially vulnerable and adversely affecting the child's development. Even though the sorts of anxiety that they observe subsides over time, Werner-

Lin and colleagues find that, if parents had had a better appreciation of what they were in for, at least some of them would have declined to receive data of uncertain significance. Once again, then, we see the importance of providing better pre- and post-test education and counseling. Prospective parents who do not think that all data is empowering could be helped to understand what sorts of information they should avoid.

Rachel Grob is a sociologist whose work has focused on the lived experience of people who encounter the medical system as prospective or new parents. Like Werner-Lin and colleagues, Grob champions qualitative research. In particular, she uses "interpretive qualitative research," which gives the researcher even more opportunity to hear and learn with the research subject than does "traditional" qualitative research. Whereas, Grob observes, quantitative research seeks to understand average or typical patient responses, qualitative research—especially of the interpretive variety—aims to understand individual differences. And she offers evidence that a non-trivial number of people whose experience falls far from the mean of the normal distribution, have significantly negative psychological experiences in the context of prenatal and newborn screening and testing. She explicates several notable and repeated findings, including: disruptions to the experience of pregnancy or of early parenthood that cause lasting regret; the creation of a new class of "patients in waiting" who do not currently and may never have a symptom associated with the genetic finding of concern; and the creation of preventive health regimes, which can be difficult, if not overwhelming, for some families to implement. As Grob explains, even if the negative psychosocial experiences that interpretive qualitative methods describe are not common within a population, they are deeply important to the individuals who have them. And she argues that excitement about the declining cost and increasing power of genetic technology, combined with ardent enthusiasm from some families who believe that the technology has been or could be good for their families, should not keep us from noticing the "inconvenient complexities" that arise when we consider the diversity of experiences within a population.

Matthew Lebowitz is a psychologist who studies the impact that genetic and other biological information about the causation of psychiatric disorders can have on patients and on how others perceive those patients. According to Lebowitz, there is some reassuring news in this context: genetic information can attenuate the tendency to blame patients for their mental illnesses. But the less reassuring news is that such information can also promote "prognostic pessimism" in people with mental illness. As he explains in his essay, he and his colleagues showed that when people are told that their depression is genetically caused, they are more likely to report experiencing depressive symptoms and to be pessimistic about their chances for recovery. As he puts it, "Genetics can mean less blame, but also less sense of agency." His finding regarding depressive symptoms resembles Lineweaver's finding regarding Alzheimer's symptoms (which we mentioned earlier). In fact, as we prepared this set of essays for publication, we saw the first paper of which we are aware suggesting that learning one's genetic risk for diseases such as Alzheimer's, cancer, and obesity can change one's physiology—independent of the actual genetic risk (13). An important conclusion from these findings appears to be that, as Lebowitz puts it, "pronouncements about the supposed failure to find negative psychosocial effects of personalized genetic health information seem premature."

Painting a large swath of a complex, evolving landscape.

In the final contribution to the collection, Christopher Wade, who uses social science research methods to study health behavior, especially as it relates to genetics, offers a review of systematic reviews concerned with the impacts of genetic testing. Specifically, he discusses 8 systematic reviews, each of which focuses on the genomic testing space from a very different angle: (1) the psychosocial impact of Huntington's disease testing; (2) the decision to decline testing; (3) testing for hereditary cancers; (4) testing of symptomatic individuals; (5) carrier testing; (6) direct-to-consumer testing; (7) pediatric testing; and (8) familial communication of risks. Similar to Roberts, Hamilton and Robson, and Biesecker, Wade emphasizes that, on average, when people receive genetic information of relatively certain significance or they have requested access to that information, any negative psychosocial impacts are minor and temporary. As he puts it, "the quantitative findings in the systematic reviews do not appear to support the idea that there is a major statistically significant and sustained negative psychological impact of genetic and genomic testing."

Although Wade was asked to—and does—deliver a general impression of a large literature, he also issues a strong warning against generalizing across contexts. As he puts it,

> Generalizing across areas of scholarship as broad as the psychosocial impact of [genetic and genomic testing] is perhaps unwise, particularly given the heterogeneity of the scholarship and types of testing. *Any blanket statements of this type should rightfully be viewed with suspicion. Indeed, most of the literature reviews that have been summarized were careful to emphasize that the limited quantity and quality of their source literature prohibited strong conclusions* (italics added).

Based on what Wade and others say in their contributions to this collection, as we move forward, it will be important to notice the myriad variables that we need to consider as we investigate the psychosocial impacts of genomic information. For a list of variables that will make it difficult to interpret, and generalize about, results in such a complex and evolving landscape, please see Table 1.

Coda.

We know now that, when the Human Genome Project launched, ELSI scholars exaggerated the magnitude of the negative psychosocial effects that receiving a single piece of highly certain genomic information about a single disorder would have on most individuals. They simplified terribly when they imagined that the same piece of genomic information would have consistent psychosocial effects on different people. Individual psychological differences are crucially important, no less so than individual genetic differences.

We should not forget, however, the ways in which the exaggeration and simplification that transpired in those years among ELSI scholars resembled similar trends among geneticists themselves. In the early 1990s, many geneticists exaggerated the likely effect sizes of single genes, especially in complex traits, in large part because of what today we know to have been a terribly simplified view of how genes work. Just as we are no longer surprised by the

fact that single genes usually have small impacts on most complex diseases and traits, we should not be surprised by the fact that single pieces of genomic information have smaller impacts on psychosocial functioning than ELSI scholars originally predicted. Like geneticists have had to do, ELSI scholars now need to develop more complex pictures of how single pieces of genomic information can be of different kinds and have different impacts, depending on the context—and how many pieces of genomic information may also have different aggregate effects.

It is reassuring that, on average, the receipt of genomic information about single genes does not have large, negative psychosocial effects on those who choose to receive that information. And it is true that the many people going to private companies to sequence their genomes, who receive little or no information before pursuing testing, do not seem to be negatively impacted by the results they receive (15). But it is crucial to remember that these people are self-selected. It is surely not the case that, because we see few negative psychosocial impacts in people who choose testing for informational purposes, that we should expect to see equally few impacts among all people.

Again, a careful consideration of what we have learned from empirical studies suggests that we are not nearly ready to revoke the special status of genetic testing, nor jettison the commitment to truly informed consent. These studies do suggest that ELSI scholars need to guard against some of the exaggeration and simplification we were guilty of at the start of the Human Genome Project. And they suggest that we have an extraordinary amount more to learn about the psychosocial implications of sharing genomic information.

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Table 1:

Nature and Purpose of the Testing

- *Purpose of seeking the information*. Does testing aim to diagnose an already existing set of symptoms? To assess an individual's risk for future disease? To facilitate an intervention to prevent or treat disease? To facilitate a decision about pre-implantation genetic diagnosis or use of other reproductive technologies?
- *The number of disorders tested for*. Similarly, it would be rash to extrapolate from research into the impacts of learning about single conditions like Huntington's, Alzheimer's, and heredita0072y cancers (which patients will likely be familiar with, based on family history) to learning at once about the probabilities of developing multiple conditions.
- *Character of the disorders (or traits) being investigated*. It is one thing to test for what are regarded as diseases or disorders like cancer and another to test for predisposition to traits that are not so regarded, including conditions like autism spectrum disorder (which can be viewed as a difference rather than a disease) and outcomes like educational attainment (a recent target of genomic research (14)).

Characteristics of the Test Results

- The level of certainty associated with a test result. Most of the literature surveyed in this collection regards testing for completely or highly penetrant genes associated with a single disorder (such as Huntington's, Alzheimer's, or breast/ovarian cancer). But many of the results produced by the new sequencing technologies will yield findings that are of low- or mid-level penetrance or even of entirely unknown significance. As polygenic risk scores for complex disorders become more common, patients may receive information about risks for multiple disorders with limited predictive power. Insofar as managing probabilities and uncertainty is difficult for most of us, it would be a mistake to extrapolate too hastily, from the finding that, on average, negative impacts of testing for highly penetrant alleles are mild or transitory, to what will become the much more common case as exome or genome sequencing becomes the norm.
- Method of delivering the results. Were the test results conveyed by letter or email, on online web portal or electronic health record, or the person's primary care physician (who may have little sophistication about genetics) or a genetic counselor or clinical geneticist? How much time was taken and how much context provided? Was the patient provided with educational materials or decision aids?

Context for the Testing

- Age at which testing occurs. Testing adults, children, newborns, fetuses, and embryos can raise different issues. When, for example, parents give consent for children or fetuses to be tested, more complicated relationship issues arise than when adults choose for themselves.
- Social context in which testing is done. Is the test being conducted in a clinical setting for a specific indication or is it part of a public health screening program? Is testing the result of concern about a family history of disease, another family member being identified as carrier (so-called cascade testing), or planned or actual pregnancy?
- Population in which testing is done. None of the pieces in this collection attends to whether different demographic groups are affected differently by the receipt of genomic information. There may turn out not to be significant differences, but one can't know that from the literature surveyed here.

Methodologic Issues

- The impacts measured. Are the outcomes assessed readily identifiable symptoms (such as anxiety and depression) or are they more subtler symptoms (such as a decreased sense of agency)? Are objective outcomes assessed (for example, test performance) or are the measures entirely subjective? Are they measured in the short or long term (for example, six months or six years)?
- Method(s) used to investigate the impacts. Quantitative studies, traditional and interpretive qualitative studies, and mixed approaches all have different strengths and weaknesses. It is one thing for public health researchers to want to know average impacts across a population and another for clinician-researchers to want to know what the impact can be on individual patients.