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Reconceptualizing harms and benefits in the genomic age

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Abstract

As new, high-powered sequencing technologies are increasingly incorporated into genomics research, we believe that there has been a break point in how risks and benefits associated with genetic information are being characterized and understood. Genomic sequencing provides the potential benefit of a wealth of information, but also has the potential to alter how we conceptualize risks of sequencing. Until now, our conceptions of risks and benefits have been generally static, arising out of the early ethical, legal and social implications studies conducted in the context of targeted genetics. This paper investigates how the increasing availability of genetic information is changing views about risks and benefits, particularly examining our evolving understanding of psychosocial harms and our expanding conception of benefit. We argue that the lack of robust empirical evidence of psychosocial harms and the expanding view that benefits of genomic research include indirect familial benefit necessitate continued ethical, legal and social implications research.

Keywords

ELSI; genomics research; next-generation sequencing; research ethics; risks and benefits

The advent of next generation sequencing, such as massively parallel sequencing technology, has greatly altered the ease of gathering significant amounts of information about individuals tested [1]. This has ushered in a new era of expansive testing for a wide variety of genetic information, ending the earlier era of targeted genetic testing primarily for severe, highly penetrant conditions. As these sequencing technologies have increasingly been incorporated into genomics research projects, we believe that their introduction marks a break point in the way that the risks and benefits associated with genetic information are being characterized and understood. While targeted genomic sequencing, filtering and panel testing are currently utilized in research to minimize the flood of information, we believe that the amount of information tested for and potentially returned to research participants will only continue to grow and that conceptions of benefits and harms have already begun to morph given the growing amount of available information. Testing individuals across a vast portion of one's genetic code carries the potential benefit of providing a wealth of information to individuals [1]. But this new technology also has the potential to alter the way

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that we conceptualize risks of genomic sequencing since it represents such a radical shift away from the medical principle that you should only order the minimum number of necessary tests. Up to this point, our conceptions of potential risks and benefits of genetic testing have been generally static, arising out of the early psychosocial studies conducted in the context of targeted genetics that were part of the larger ethical, legal and social implications (ELSI) literature [2–4]. In a genomic age, however, it is worth re-evaluating the extent to which original predictions about or conceptions of risks and benefits have held up over time and with changes in technology. Indeed, ELSI literature provides helpful insight for researchers assessing potential harms and benefits of genomics studies and provides an opportunity to assess how the increasing availability of genetic information is slowly changing views about risks and benefits in the field of genetics. While single gene testing will continue to be utilized in certain research settings, a consideration of how harms and benefits may change for sequencing studies provides insight for researchers and Institutional Review Boards (IRBs) assessing potential genomic studies. In this paper, we particularly examine our evolving understanding of psychosocial harms and our expanding conception of the potential clinical benefits of research, through a literature review of ELSI publications in these areas. We examine this changing landscape through a US lens, although we note throughout the article European literature that is consistent with the themes found in the US.

An evolving understanding of psychosocial harms

For most of the ELSI era, when researchers assessed potential harms of genetic information, a primary concern was its risk of causing psychosocial harms. These kinds of harms can be thought of as adverse events flowing from the generation of genetic information about an individual and can be divided into psychological harms and economic harms. Under the earlier, targeted genetic testing paradigm, the ELSI community was worried that negative (i.e., unfortunate) genetic information could lead research subjects or patients to experience adverse psychological effects like depression and anxiety [2–4]. A classic example was a condition like Huntington’s disease, where extensive research demonstrated that people were very reluctant to get tested because of fears about how the information would impact their psychological wellbeing [5]. Similar arguments were made about other conditions, particularly breast cancer and Alzheimer’s disease [6]. Throughout the literature, commentators regularly cite to these conditions as evidence that people face significance risk of psychosocial harm when presented with genetic information indicating increased risk (or certainty) of manifesting a serious disease [7]. Given the hereditary nature of genetic information, there were also serious concerns about the risk of stigmatization and the social impact that the findings could have on relationships with relatives [8].

In addition to the risk of psychosocial harms, there was also substantial research into the risk of economic harms, primarily focusing on discrimination in a range of contexts. Specifically, there was considerable worry about discrimination in health insurance, wherein insurers would deny coverage or charge higher premiums for people with increased genetic risk of disease [9]. Similar concerns were explored about discrimination in the long-term care, disability and life insurance industries [10]. Employment discrimination was also a frequently explored topic [10].

The ELSI focus on informational harms (a term which we are using to encompass both psychosocial and economic harms) is understandable because the advent of genetic testing represented such a paradigm shift. As genetic testing emerged, it was viewed with caution and concern because genetic information had unique characteristics that differed from extant medical information [11]. Specifically, genetic information was seen as special because it was predictive rather than diagnostic [12], and because it could have an impact on family members as well as the proband [13]. Genetic information is also an immutable part of one's self, unlike behaviorally or environmentally mediated health traits, further explaining the early exceptionalist view that argued for treating genetic information differently than other kinds of medical information.

The existence of an exceptionalist view and the accompanying focus on informational harms is understandable from a historical context, but after two and a half decades of ELSI research, it is fair to ask about the extent to which the available evidence continues to support such a position. We are enthusiastically supportive of the continued evolution of genomic testing technology and its adoption into a more personalized iteration of medical practice. Yet, despite this promising future, it appears that the primary focus of the psychosocial portion of the ELSI discourse remains fixated on speculative informational harms [14], and we question whether this focus remains justified. Take, as an example, the recent discussion about whether patients have a right not to know ('RNTK') genetic information about themselves. In 2013, the American College of Medical Genetics and Genomics (ACMG) issued a recommendation regarding the incidental findings, arguing that whenever a patient's genome was sequenced, a specific set of high-value genetic variants should always be interrogated and returned (if positive), regardless of patient preference [15]. This suggestion set off a vigorously contested debate about the RNTK, wherein RNTK proponents regularly appealed to fears about informational harms as justification for requiring that patients be given an opportunity to choose whether or not to learn this information, despite the fact that other important medical information is not given similar treatment, and that much of the research on which fears of informational harms are based was published in the 1990s when genetic testing was still novel [16]. As one of the authors has argued, this reliance on informational harms suggests that strong conceptions of the RNTK are difficult to support [6].

As genomic sequencing is incorporated into medical care, and as we get closer to reaching the promise of personalized medicine, it is worth assessing what the past two plus decades of research have revealed about the psychosocial and economic risks associated with genetic information. On the one hand, it is clear that many people persistently remain concerned about informational harms [17]. Fear of discrimination is often cited as a reason why people forgo potentially beneficial genetic testing [18,19]. In one study, researchers found that 4.5% of doctors who order genetic tests take measures to disguise results in response to such fears. One systematic review found 21 articles documenting the patients' pervasive fears about genetic informational harms and discrimination in particular [20].

Despite this persistent concern, there is a clear gap between fears of informational harms and actual evidence of economic or psychosocial harms [20]. Studies about the actual psychosocial effects of genetic information have demonstrated much lower than expected

levels of concern. While one should be cautious in evaluating these data because these studies have some significant methodological limitations, they point toward exercising a measure of prudence before making broad claims about the risk of informational harms. One review of the literature on the psychosocial impact of cancer testing found that while several studies did show some increase in anxiety after learning about genetic risk, the anxiety was generally transient and minimal [21]. A 2008 systematic review of the then existing literature on the psychological impact of genetic information across all conditions took an even more definitive stance, concluding that “overall genetic testing had no impact of psychological outcomes such as general and specific distress, anxiety or depression [22].” Even when patients are given genetic risk information devastating neurodegenerative conditions like Huntington’s disease and Alzheimer’s disease, where there are no available treatments, it appears that any psychosocial impact is minimal, and that long-term distress is similar to that of noncarriers [23–25]. In fact, a number of studies demonstrate that patients actually report substantial benefit rather than anxiety after learning genetic information about neurodegenerative disease [26]. Specific vulnerable populations who might be at particular risk for psychological risks, such as children [27] and high-risk minority population [28], were also only minimally adversely impacted by genetic testing.

Perhaps the lack of evidence about pervasive psychosocial harms, and the persistent gap between perceived worry and actual harms, should not be surprising given increased understanding of the psychological concept of affective forecasting. Affective forecasting is the notion that people are not terribly adept at predicting their future emotional reaction to negative events. Generally, people have a tendency to overestimate the adverse impact that a given unfortunate event will have on them [29]. This is primarily attributed to the concepts of immune neglect and focal illusion. Immune neglect describes the phenomenon where people fail to account for their ability to adapt to future events. Focal illusion captures our tendency to emphasize the impact of the specific bad event we are actively thinking about, while discounting any positive influences that might mitigate the adverse emotional effects of that event [29].

In addition to a lack of evidence for psychosocial harms, there has also been increasing skepticism about the extent of actual risk for genetic discrimination. While some early commentators have argued that fears of genetic discrimination are overstated [30,31], it is difficult to prove a negative. Nevertheless, there seems to be little available evidence of pervasive discrimination on the basis of genetic information. The Genetic Information Non-Discrimination Act (GINA) was passed in 2008 with the goal of pre-emptively prohibiting employers and health insurers from using genetic information to make employment or actuarial decisions. Interestingly, the enforcement numbers seem to suggest that genetic discrimination might not currently be the problem it was thought to be. For example, in 2016 there were 238 complaints filed with only 38 (15.3%) resulting in actual merit resolution in favor of the charging party [32]. Similar numbers were reported in the six previous years for which data are available. While it is possible that the law’s mere existence staved off a potential epidemic of genetic discrimination, a plausible explanation for these enforcement numbers is that such widespread genetic discrimination is not rampant. Other literature reviews in the context of insurance and employment bolster this theory [20], finding only rare cases of genetic discrimination [33] most of which occur in the fairly narrow context of

untreatable single gene disorders like Huntington's disease [34]. In the health insurance context, the passage of the Affordable Care Act (ACA) just 2 years after GINA has muted any potential effect or evidence of GINA's effect on health insurance. Taken as a whole, though sporadic individual cases of genetic discrimination can be identified, the available literature suggests that there is a lack of evidence to suggest that genetic discrimination currently represents a pervasive societal problem, although the fear of genetic discrimination is pervasive in society [34].

It is certainly plausible that genetic discrimination could eventually become a problem, and more research is required to ensure that pernicious practices are not proliferating, particularly in countries with less robust legal protections. But based on the weight of the available evidence, we believe that it seems warranted to start drawing the normative conclusion that perhaps a continued emphasis on nonphysical harms is not justified. Though the academic literature still appears to maintain such a focus, there is some evidence that, at least at the actual policy level, the focus on informational harms might be abating. For example, after researchers in 2013 demonstrated that it is possible to reidentify genomic data, concerns about genetic privacy and informational harms prompted policymakers to restrict access to DbGaP (a US database that aggregates genotype and phenotype data from publicly funded studies for the purpose of facilitating secondary research use) [35]. Yet, after reassessing the informational risk that genomic databases pose [36], National Institutes of Health is currently proposing to reduce the requirement for controlled access to summary genomic data residing in public databases [37].

Similarly, it appears that there is increasing attention being paid to physical harms that might flow from genetic testing. These are not physical harms in the traditional sense; the procedure itself is not a risk since most genetic testing only involves a blood draw. Rather, there has been increased interest in physical harms in the sense that inaccurate or uncertain genetic information could lead to unnecessary procedures that carry their own physical risks. For example, the US FDA has recently begun exploring the regulation of whole-genome sequencing as an investigational device, prominently citing the proximal risk of unnecessary interventions [38].

Finally, it appears that people evaluating research risks are increasingly open to the notion that genetic research can be a minimal risk activity. In one survey of genetic researchers and IRB professionals, the authors found that a majority of all respondents were not worried about the prospect of harm associated with participating in genetic research, although IRB professionals were more concerned on average [39]. This diversity of opinions is also reflected in IRB guidance and policy, with some institutions and commentators arguing that genetic studies are generally minimal risk, while others suggest they are more than minimal risk [40]. Similarly, some commentators have begun arguing that genetic research is typically minimal risk [40], but that view is far from universal [41].

Even though the psychosocial portion of the ELSI literature continues to explore informational harms, it appears that there are at least early signs of moving beyond that focus. As the field continues to evolve, the gap between fears of informational risks and actual evidence of widespread harms suggests that we should be cautious about continuing

to be unduly concerned about theoretical harms. This is especially true as technologies move away from testing for highly penetrant single gene mutations, to testing for a broader range of genetic information. Under this new technological framework, it could be prudent to accept a default wherein genetic research is deemed to be minimal risk, unless there is specific evidence to the contrary in a particular case. The worry is that by ignoring existing evidence and focusing on looking for psychosocial harms associated with genetic testing, we are creating a “culture of risk-aversion in which patients may be opting out of potentially beneficial diagnostic and treatment regimes [29].” Of course, ELSI researchers should continue to monitor social conditions to ensure that genetic informational risks do not begin to significantly emerge as genomic knowledge expands and regulations and norms shift. Furthermore, ELSI researchers should work to develop educational strategies to shrink the gap between the public’s fear of harm and the actual incidence of such harm.

An expanded conception of benefit in the genomic era

The concept of benefit has also begun to evolve in the past decade. Research has traditionally asked participants to assume a range of risks in order to benefit society at large. Indeed, personal benefit is neither an integral nor necessary component of a research endeavor. However, research including genomics research, is moving toward translational applications and is increasingly focused on individual results and their implications. Through return of results, personal benefits are now integrated into the research ethics calculus. Ethical debates regarding duties to return individualized results rest in large part on the potential clinical benefits and personal usefulness of genomic results [42–45].

There is an emerging majority view among US commentators that results with clinical utility should be returned to research participants and that other results may be returned [45]. Clinical utility of genetic results, however, is generally discussed at the abstract condition, gene or variant level, not in the specific context of an individual. For example, *BRCA1* and 2 are considered medically actionable (a concept that closely parallels concepts of clinical utility [46–48]) because there are preventive measures, such as prophylactic surgeries or cancer screenings, that are available to asymptomatic individuals who carry a genetic predisposition. In reality, however, the availability and advisability of undertaking preventive measures with a positive *BRCA* test is quite relational. It depends on a variety of individualized factors, including personal health history, gender, extent of family history, genetic variant and age. This is true beyond just the *BRCA* example, as Foster and colleagues note, ‘No genetic test has unqualified clinical utility. Genetic tests have utility for specific purposes, in particular clinical settings, for appropriate patient populations [49].’

Given that research protocols often develop a plan for returning results related to medically actionable genetic conditions prior to enrolment of participants, they do not tailor considerations to specific individual criteria. For example, an analysis of nine studies funded under the Clinical Sequencing Exploratory Research (CSER) program did not indicate that the informed consent documents discussed in detail that clinical utility of results in the preventable/treatable category could be variable depending on individual factors [1].

However, although the individual participant may not gain clinical benefit, due to the shared familial implications of genetics, the information may have clinical utility for a family member. Indeed, there are many scenarios where a test result may not have clinically utility for the participant, but would for a relative. For example, an individual may be too young to begin taking any recommended medical action, but their genetic information may provide helpful information for their parents and other older generations. Similarly, a pathogenic *BRCA1/2* result would provide limited clinical utility for a male participant, but could lead to significant disease prevention for his female relatives. In another context, a carrier status result might not provide any clinical information for the individual, but have implications for a sibling or for reproductive decision-making. This potential indirect familial benefit has morphed conceptions of the benefits of genetic testing, beyond direct clinical benefit for the research participant. There are, of course, the potential for familial harms and other ethical considerations surrounding familial obligations, but we focus here on the question of potential clinical benefit. In the remainder of the section, we discuss how this potential clinical utility to family members fits into traditional IRB calculations of the benefits of research.

Providing relatives information regarding predisposition to serious, but preventable genetic conditions is by no means a bad thing. However, as the concept of benefit has expanded to include familial benefit, the distinction between personal benefit and familial benefit has sometimes been lost. We argue that it is best to conceptualize clinical benefits to the individual research participant and familial benefits as distinct concepts – one having direct clinical utility and the other having indirect clinical utility [48].

The question then becomes, how researchers and IRBs should weigh the value of indirect familial benefits as compared with direct benefits and risks. The common rule requires that “risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects. [50]” The common rule requires informed consent to include a description of benefits ‘to the subject or to others’ [51]. Even when the recent revised updates to the common rule are implemented, the newly published rule did not change these portions of the regulation.

While much has been written on ways to conceptualize harm in research, relatively little has been written about conceptualizing benefit [52,53]. In her discussion of benefit in clinical trials, Nancy King identifies three types of benefit – direct, collateral or aspirational [52]. King defines direct benefits as ‘benefit arising from receiving the intervention being studied’ that run directly to the subject [52]. As discussed above, familial benefits are not direct benefits, but rather indirect benefits since the clinical benefit is mediated through the passage of information rather than a direct result of participation.

Yet indirect benefits do not squarely fit under the remainder of King’s taxonomy. Improved health of family members could perhaps be labeled an aspirational benefit of genomic research. King defines aspirational benefits as those that benefit society and future patients [52]. However, whether we should consider return of results relevant to family members as a benefit of the research project is dependent upon whether the results returned are part of the research aims of the project or arise incidentally. If improved health of family members is highlighted as an aspirational benefit of a research project, this begins to shift the clinical

utility of genomic research from a clinical perspective to a public health perspective [54]. Too much focus on the potential health benefits to family members from incidental findings could conceivably increase the burden and time pressure on researchers and therefore actually diminish the express aspirational benefits of the research protocol.

Finally, clinical utility for family members or the personal utility of gaining information relevant to relatives is perhaps best characterized as a collateral benefit of the research project. King defines these as benefits ‘arising from being a subject, even if one does not receive the experimental intervention’, such as a free physical exam or altruism [52]. Here, the indirect familial benefits do require that the individual receive the intervention. Others conceptualize collateral benefits a little more broadly. That is, they are benefits that arise from participation in the research project, but are not related to the intervention or goals of the research [53]. This definition most directly ties into the concept of indirect benefits. Collateral benefits, however, should not be considered as part of the harm/benefit calculus in IRB deliberations [53].

Given that indirect clinical benefits do not squarely fit into traditional discussions of research benefits, it is perhaps no surprise that research recommendations have differed in the handling of return of results to a participant specifically for the benefit of their family members [48]. For example, early on in the return of results debate, a National Heart, Lung, and Blood Institute Working Group, recommended that results with proven therapeutic or preventive interventions be returned. They added that ‘research results on genetic diseases or traits that do not affect the participants’ health but carry significant reproductive risks for disease among offspring should be considered for reporting to study subjects’ [55]. Just 4 years later, the Working Group provided updated recommendations that noted that researchers should return results that have ‘important health implications for the participant’ and may return a broader array of results, such as those related to reproductive risks or have personal utility [42].

In ‘Return of genomic results to research participants: the floor, the ceiling and the choices in between’, Jarvik *et al.* summarized consensus principles between the return of results committees of the CSER Consortium and the Electronic Medical Records and Genomics (eMERGE) Network [45]. One of their leading principles was that results that provide options to ‘protect the participant’s health’ should be returned. They questioned, however, whether returning medically actionable results that had no current clinical implications for the study participant, but that were relevant for family members should be returned.

Recommendations regarding return of results differ in their approach to addressing results that could benefit family members. Several recommendations focus specifically on whether a previously unknown familial mutation associated with an adult-onset disease should be returned in a pediatric study because of the clinical importance to the parents. Jarvik *et al.* noted that this practice had been recommended in the clinical context because “the prevention of potential harm to the transmitting parent and other family members is a benefit to the child” [45]. However, in their recommendations, the P³G International Paediatrics Platform members argued that such decisions should be assessed on a case-by-case basis [56].

Although this paper focuses on research, given that the benefits relate to direct and indirect clinical benefits, it is helpful to see how recommendations regarding benefit to family members have been discussed in the clinical context. Two notable recommendations argue for returning of results in part due to the benefit for family members. First, in 2013, the ACMG recommended that their list of medically actionable genes be returned whenever clinical whole exome or whole genome sequencing was completed, regardless of patient choice. Notably, the ACMG discussed in some depth the tension highlighted in the P³G. “The ACMG working group also felt that the ethical concerns about providing children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child’s parent of discovering an incidental finding where intervention might be possible.” [15]. Throughout the rest of the report, it is clear that the working group considered both benefits to the individual and their family in their recommendations. Although these recommendations were updated a year later to allow for a patient to opt out of returns, the guiding principles remained [57].

Second, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group recently recommended that individuals with newly diagnosed colorectal cancer have their tumors sequenced for Lynch Syndrome [58]. Upon review of the evidence, they found that there was not sufficient findings to recommend a change in clinical management for the proband, but that testing was still recommended due to the clinical utility for family members [58]. The EGAPP and ACMG recommendations both arise in the clinical context, but given the translational nature of much genomic research, provide insight into how researchers may continue to think about clinical utility of genetic testing with regards to individuals versus their family members.

The concept of familial benefit has begun to seep into discussions of the risk/benefit calculus of research; however, these benefits do not easily conform to traditional research ethics norms. Without clear, conceptually different categories of direct and indirect benefit, there may be detrimental consequences in research studies. First, when the concepts are conflated, individual research participants may overinterpret the clinical benefit for themselves versus the clinical benefit for family members [59]. If taken to an extreme, this could lead to potential overtreatment in some circumstances.

Second, conflation of indirect and direct clinical benefits in research studies may create detrimental consequences for resource allocation in study budgets and the focus of research studies. Inclusion of return of results with indirect clinical benefits has not only positive sequela, but also runs the risk of pulling valuable resources away from the primary goals of a research study and weakening the altruistic focus of participation and the aspirational goals of the researchers. This creates both a challenge and opportunity for ELSI researchers to consider the implications on the growing reliance on familial benefit in the research context.

Conclusion & future perspective

Recognizing the moral complexity associated with sequencing the first complete human genome, leaders of the human genome project had the foresight to allocate funds to establish a research program to study the ELSI of genetic and genomic science. Later rooted as a

legislatively mandated 5% carve out from the National Human Genome Research Institute (NHGRI) budget, the ELSI program has led the way in examining the profound impact that rapidly advancing genetic and genomic knowledge is having on society [60]. In one area of ELSI focus, researchers have spent the past few decades exploring how to think about the risks and benefits associated with genetic information. But in such a rapidly moving scientific field, there is a risk that the way that ELSI concerns are framed become entrenched and lags behind the existing evidence and available technology. In this paper, we highlight two areas where thinking has begun to stray from principles and norms long established in the ELSI community. We say this not as a critique of ELSI, but view this as an opportunity to incorporate ELSI scholarship back into the field in an iterative manner. These shifting realities challenge us to reassess how we weigh and communicate the potential risks and benefits of genomics research studies and provide future opportunities for robust empirical ELSI study, so that the ELSI field can continue to evolve.

In the future, the percentage of individuals who have undergone next generation sequencing will continue to grow. This vast growth in the amount of data and information provided to each individual will result in a range of benefits and risks observed across the population. The ELSI community should continue to assess potential harms and benefits and understand how changing conceptions alter research ethics and design.

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Executive summary

- New sequencing technology provides significant amounts of information for each individual tested.
- Traditional conceptions of risk and benefits of genetic research arose out of early ethical, legal and social implications (ELSI) studies focused on targeted genetic testing.
- An evolving understanding of psychosocial harms.
 - Early ELSI literature focused on information harms, including psychological concerns, such as depression and anxiety, and economic concerns of discrimination.
 - While this historical position is understandable, empirical evidence for the most part has not supported these wide-spread concerns.
 - Evidence does show that people are concerned about such harms, but there is not as much evidence that harm has occurred, both psychological and economic.
 - Continued focus on nonphysical harms may no longer be justified, although ELSI researchers should continue to monitor if these risks materialize in the future.
- An expanded conception of benefit in the genomic era.
 - The move toward translational genomic research has led to increased focus on individual research participant results.
 - There is a growing view that results with clinical utility should be returned to research participants.
 - Clinical utility is dependent on individual factors, such as age, gender, ethnicity and medical history, yet research protocols often provide results for variants in genes that could be clinically useful.
 - Thus, a participant may receive a result that is not clinically beneficial for themselves, but clinically beneficial for a family member.
 - This is not necessarily a problem, but it is expanding the concept of benefit in the research context to include familial benefit in addition to personal benefit.
 - These should be viewed as two conceptually different things – one with direct clinical utility and the other with indirect clinical utility.
 - This will have implications for how researchers and institutional review boards weigh the value of indirect familial benefit, but is essential so that limited research resources are not pulled away from the express aspirational benefits of the research.

- Conflation of personal and familial benefit may also lead to potential confusion and overinterpretation of individual clinical benefit for research participants.
- Recommendations
 - ELSI researchers should continue to monitor the potential for psychosocial harms in the future, but should recognize the current status of empirical evidence of harms in genomic research.
 - Familial benefit and personal clinical benefit of genomics research should be viewed as conceptually distinct. Institutional review boards reviewing genomic studies should carefully assess how much emphasis is being placed on each and avoid limited research resources being pulled away from the aspirational benefits of the research project as a whole.