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Psychological Implications of Genetic Testing, Both Past and Present

Overview of psychological implications in single-disease genetic testing:

In order to consider what the implications of genome-wide genetic screening may have, it is important to look backwards historically. Prior to the explosion of genetic data caused by major breakthroughs in genome-sequencing technologies, genetic testing for specific diseases such as Parkinson's breast cancer, colon cancer, etc were readily available. In theory, these genetic tests allowed for early detection, target surveillance, and perhaps most importantly, behavioral changes in affected individuals. In a review article published in *Nature* an extensive literature was done to identify studies that measured the psychological and behavioral impact of genetic testing on persons. For affective outcomes, the majority of genetic screens (for a single disease such as Parkinson's or breast cancer) found a short-term negative effect on carriers versus non-carriers of the disease of interest. In regard to behavioral changes, a notable increase in screening behavior of varying degrees of intensity was demonstrated in carriers versus non-carriers. That said, this increase was lower than expected. Risk perception tapered over time with carriers and non-carriers having no statistically significant risk beyond the 12 month mark. Overall, genetic testing to determine the predisposition of a person to a specific disease appeared to have no significant long-term impact on psychological outcomes, behavior, and risk perception [1, 2].

Having said that, this conclusions is very generalized and spread over greater than 35 studies. In another review which also considered multiple single-disease genetic tests but looked at each disease type discretely showed subtle results in the psychological of genetic testing. For example, for Huntington's disease (HD), only 10-20% of at-risk individuals chose to be tested and broadly speaking, people with a predisposition for HD were more interested in a theoretical predictive test than one which was immediately available. Furthermore, people who declined the test had a more pessimistic outlook for the future. Considering the behavior of persons at-risk for HD relative to those with cancer showed that people with a predisposition for cancer are more likely to agree to a genetic test than those for HD. However, the levels of interest were still lower than anticipated. Upon the

analysis of breast cancer specifically, factors which had a positive correlate with opting for testing included a.) being female, b.) having a higher-level of education, c.) possessing health insurance, and d.) awareness of genetic testing for breast cancer. Interestingly, women who perceived themselves as being low-risk for cancer who declined testing tended to have higher levels of spiritual faith whereas no such correlation existed for patients who saw themselves as high-risk [3].

Among each discrete disease group, subgroups appeared to exist which have a more apparently psychological vulnerability. For example. among those tested for breast cancer, women with higher stress-levels showed the greatest tendency towards depression *without* actually having been tested. Another sub-group indication which predicted a poor reaction to tested was the subset of individuals who did not consider the emotional impact of the test [3].

Across all testing domains, decisions about whether or not to agree to a genetic test was more a function of perceived risk than actual risk. Again, considering the discrepancies between cancer-specific testing and disease-specific testing (such as HD) were significant. People are far more likely to opt for a cancer screen than an HD screen. This is likely a function of the fact that there is no treatment for a HD and thus, little agency is gained through the acquisition of knowledge. Finally anecdotal evidence suggests that most individuals commit to a genetic test long before being involved in any kind of genetic counseling. The minds of those who had decided against it were not easily swayed. Ultimately, the conclusion reached by Lerman *et al* was the same as those found by Heshka *et al* and Christiansen *et al* -- genetic testing appears to have little to no influence on long-term emotional distress [3].

Contradictory attitudes towards genetic testing:

In the general public:

To discern the attitudes of the general population to genetic testing, one Finnish group conducted an extensive survey on the issue. Many contradictory findings evolved in the results. Firstly, almost all (94%) of people

surveyed approved of the availability of genetic testing. That said, there were a number of underlying contradictions and caveats to this "approval". Only 52% of correspondents approved absolutely of genetic testing and did not mark and contradictory statements. The remaining 33% agreed with one or more of the following ideas in conjunction to approving of genetic testing:

1. Genetic testing is not acceptable because there are a number of current health issues with are more pressing (10%)
2. Genetic testing is not acceptable because it disrupts the natural order of things (7%)
3. Genetic testing is not acceptable because it could lead to the discrimination of individuals based on their results (23%)
4. Genetic testing is not acceptable because it will make abortions more common (17%)

In many regards agreement with any of the previous statements are not unfounded. For example, in 1992, it was reported that genetic testing resulted in the discrimination of those tested in regards to obtaining health insurance, finding and retaining employment, and interacting with adoption agencies [4].

The primary motivator dictating whether or not a person approved or disapproved of genetic testing whatsoever (disregarding the aforementioned discrepancies) stemmed from the concept of right-to-choose, which essentially argues that a person has a right to understand their own body to the extent to which they are comfortable but the choice of genetic testing must, in fact, be a *choice* and reflect the moral and ethical beliefs of the person being tested and no one else. Unsurprisingly, the right-to-choose premise comes with it's own problems. Critics of this mode of thought have argued that a couple's right to prenatal gene testing and potentially abortion may conflict with the fetus' future choice to live. Beyond this, the concept of whether or not right-to-choose is an absolute necessity conflicts with the desires of some subset of people who have undergone genetic testing. For example, in certain instances, women undergoing genetic counseling for an unborn fetus have wanted to defer the decision of how to interpret the genetic results and plan a future course of action regarding the child to the genetic counsellor. In contradiction to this (yet again), many correspondences reported a strong distrust of what would happen to their genetic data and the motivations of genetic counsellors.

87% of those surveyed were fearful of their results being used without their knowledge or would some how contribute to an implicit end-goal of eugenics [4].

The latter observation regarding the desire of some cohort to push the decision-making element of genomic testing interpretation into their physician and/or counsellor raises a fundamental question as to the role of the physician in guiding (and/or deciding) decision-making given a specific set of genetic predispositions. In some ways, this idea plays into broadening the gap in knowledge and "authority" within the physician-patient dynamic. In an effort to glean the expectations of a contemporary audience with regard to the level of which a physician should be involved in the genetic testing process, a survey was conducted in 2009 on a cohort of 1,087 social networking users. One dimension of the survey, assessing interest and attitude towards personal genomic testing (PGT) had the same findings as the previous paper with the vast majority of people either having had or being interested in genetic testing for the same primary reason as previously mentioned - to better understand and take control over their health and inform future medical decision-making. The new dimension of PGT introduced by the survey highlights the degree to which people expect guidance throughout the process. 34% of those surveyed would consider their genetic results to be *a medical diagnosis* as opposed to a predisposition or increased risk. 78% of people would ask their primary care physician for assistance in interpreting their genetic results and 61% of people believe that physicians have *a professional obligation* to to do. Most people surveyed feel insecure in their understanding of the risk/benefit analysis of their PGT results and do not feel that they know enough about genetics to trust their own judgement. 76% of people believe that PGT companies should provide a medical professional to help read results and 51% believe that PGT should be regulated at the level of government and policy. Among those who have been sequenced, there is a statistically significant association between believing the test result to be a medical diagnosis and desiring to speak to a physician [5].

Having said this, there are contradictory concerns regarding whether physicians have the necessary understanding to be maximally useful. Only 47% of participants believed that the physician's knowledge is sufficient for helpful interpretation [5].

Despite claims that PGT companies are not providing diagnostic information, many respondents (34%) see their genomic results as a medical diagnosis which will affect their future health choices. Although companies tend to provide information of genetic associations from the scientific literature, genetic testing for most association has not been integrated into active clinical care due to the early stage of research, lack of evidence, concerns over the validity of certain findings, and the uncertain or weak penetrance of specific variants for disorders. This clearly points to a fundamental question -- is the support system necessary to interpret genetic results appropriately in place and furthermore, is it ethical for PGT companies to be providing data (despite their claims of what the data truly means) to an audience which is taking this data very literally and potentially making life-long decisions on the basis of it [5]. Perhaps the best indication of the communication mismatch between PGT companies and consumers is the government-forced shutdown of the medical indication component of 23&me's genomic analysis [6].

Within the medical community - the physician's perspective:

The next factor to consider seems obvious - what is the physician's opinion in all of this? In many ways genetic testing perturbs the patient-physician relationship in a completely novel way and forces a longitudinal perspective on an oftentimes temporal relationship. According to a study conducted in 2003, physicians in the United States feel a great deal of uncertainty regarding the lack of genetic testing practice guidelines, patient confidentiality (in specific reference to insurance discrimination), the usefulness of genomic testing, and the degree to which they feel qualified to provide counseling and order genetic testing. Results of the survey show that the majority of physicians feel that proper guidelines outlining how to manage patients with positive genetic testing results for inherited cancer susceptibility. This fact again underscores the idea that the proper measures to cope with genetic testing are not publically available not just for patients but for physicians. Less than a third of all physicians considered themselves qualified to provide adequate counselling. Unsurprisingly, a primary concern for physicians (just as with patients) was the potential for insurance discrimination. Fear of insurance discrimination is the primary reason patients opt out of genetic testing and is a fear shared by the medical

community at large. More than half of physicians surveyed said that it is difficult and unlikely that a patient's genetic results will remain confidential. Proper guidelines for physicians regarding genetic testing management should certainly address the implications of maintaining confidentiality. Finally, many physicians are even unsure whether genetic testing has true clinical utility [7]. Therein lies another question - can the clinical effectiveness of genetic testing be properly valued by physicians? Or is it more inline with a statistician or a genetic counsellor?

Prenatal genetic screening and eugenics:

Likely the most ethically precarious area regarding genetic sequencing is not the risk-assessment of grown individuals and constructing and implementing the appropriate method of coping with the data, but rather prenatal screening. Prenatal genetic screening lends itself to a number of ethically challenging situations such as abortion (previously mentioned) and opens up the possibility of genetic engineering. In a recent publication in *CNN*, it was announced that US health officials are trying to decide whether to approve trials involving using the DNA of 3 people (the mother, father, and a de-nucleated embryo from another female with healthy mitochondrial DNA) to prevent mitochondrial diseases. The treatment, as it is presented, would allow a woman afflicted with mitochondrial disorders such as muscular dystrophy or respiratory problems, to birth a child without the disease [8]. While in many ways, mitochondrial disease is, ethically, a much simpler consideration relative to other genetic disorders in that the mother's DNA is unchanged and in vitro fertilization has been around for more than four decades, there is a natural question that follows - why stop there? The ethical line as far as preventative measures regarding children with genetic disorders is concerned is extremely vague and will likely continue to be in the foreseeable future.

While disease screening in the prenatal stage has been done for decades (consider, for example, karyotyping for down syndrome), genome-wide molecular sequencing offers the new opportunity to detect abnormalities which are fairly minute and extending far beyond early-onset disorders such as small interstitial or telomeric deletions or duplications which could lead to late-onset cancer. Therein lies this question - to what extent is harnessing the

information gain of sequencing actually beneficial to advocating for the quality of life of the unborn fetus? What are the ethics involved in this question? One solution that has been proposed has been using very specific targeted testing which will avoid the detection of clinically unclear findings. Another issue which arises is what information a physician should withhold from a mother, in particular when considering SNP analysis. Giving too much information of too fine granularity could result in the trivialization of abortion. Giving too much information could also result in overloading the mother and in some way impeding her right-to-choose, frustrating rather than serving the aim of autonomous choice. Finally, the issue which has been touched on again and again in this paper, but is incredibly socially relevant specifically in regard to making a judgement call on late-onset disorders in fetuses is the concept of the child's "anticipatory autonomy rights." Terminating a pregnancy due to a predisposition or certainty of late-onset disorders for a child deprives that child of his or her right to self-determination. It is easy to compare this to the legal changes which happen when a child turns 18 though it does underscore, in some sense, how arbitrarily a person comes into their rights of self-determination [9].

Much of the problem with treating mitochondrial DNA disorders or any disorder discovered in a fetus whatsoever is the degree of *uncertainty* to which a diagnosis is known. Studies have shown that couples who decide to terminate pregnancy based on the existence of some uncertainty about the severity of the defect in the fetus or the accuracy of the test are at risk for prolonged periods of grieving. In these cases, the couples' doubts about the moral rightness of the decision also increased. Unfortunately for mitochondrial DNA disorders and others, both the expression and penetrance of the disease are uncertain and almost impossible to predict. In the worst case, a healthy fetus is aborted based on sub-optimal data. While some may accept this as an unavoidable side-effect of imperfect technology, there is a significant group of people which are unwilling to take such risks. Tying back to a disorder mentioned at the beginning of this paper - Huntington's Disease - it is actually possible for a prenatal exclusion test to be performed on an unborn fetus. The test is applicable when a potential carrier wants to exclude transmission of the mutation to their children *and* they themselves do not want to know their genetic status. This exclusion test results in 50% of healthy fetuses being aborted [10]. Herein lies another question - is it ethically acceptable for a parent to make an extreme decision about an unborn child

(who may not actually have HD) while avoiding confronting the reality of the disease in the context of their own life? Is there a need for ethical consistency between the parent's treatment of their own genetics and their treatment of their potential offspring's?

Conclusion:

Given the explosion of sequencing data in the last few decades and the seeming inevitability of the pervasiveness of genome sequencing, specifically in reference to genetic predispositions for disease, it is important to consider the ethical implications of sequencing. While instinctively, the situation which comes mind when considering whether or not to get tested seem purely practical (i.e. will getting tested result in my struggling to get health insurance or change my long-term life plans), there are a number of more far-reaching considerations to make. For example, should my behavior change because of my knowledge of a specific predisposition, and if so, to what extent? What is statistically significant for me and what role does my physician play in this process? Is there a system in place to guide me through navigating my own genetics? Furthermore, and perhaps sticker still, is the prospect of highly ubiquitous prenatal genetic screening. At what point does disease-prevention muddle into eugenics and how can we advocate for the unborn fetus, factor in the statistical reality of not just false positives but varying degrees of disease penetrance, while respecting the life-choices and autonomy of the parents? Instinctively, I want to argue that the intricate contradictions in genetic testing are fundamentally irreconcilable; yet, as a scientist and someone who believes strongly in generating the resources and educational materials necessary to enable people to live the highest quality of life possible, I want to push for sequencing on all accounts. To me, more knowledge is always superior to less knowledge, but whether or not more knowledge truly leads to a more ethical, well-thought out, and ultimately better decision is hard to say. Only time will tell.

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