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Preventive Genomic Sequencing in the General Population: Do PGS Fly?

Mildred K. Cho

Stanford University

Twelve years after the National Human Genome Research Institute and the Department of Energy announced the completion of the Human Genome Project, the technological capabilities that grew from the project have now led to a debate about the ethical uses of the vast amounts of genomic data that can be collected and analyzed from individuals. These new capabilities have raised the possibility of “population-based preventive genomic sequencing (PGS) programs with the goal of identifying genetic health risks in adults without known risk factors,” which is the topic of the target article in this issue of *AJOB* (Lázaro-Muñoz et al. 2015). In other words, we are now debating *genomic screening*. Lázaro-Muñoz and colleagues present a detailed argument for a “menu approach” to screening, which would allow individuals to selectively opt out of sequencing or analysis of specific genes, as opposed to an all-or-none “panel approach.”

The detailed arguments presented by Lázaro-Muñoz and colleagues are from the multiple perspectives of ethics, law, public health, family studies, and technology. Nevertheless, the accompanying commentaries still identify gaps to be filled that would be necessary to construct a comprehensive rationale for population-based genomic screening, by any approach. For example, both Appelbaum and Sabatello, and Hens and Dierickx point out the specific challenges of such screening in minors. Bertier and colleagues and Hurst question the current costs and benefits of PGS, given the large amount of uncertainty around the meaning of many genomic variants and the reality of the expenditures of personnel time to interpret genome sequence. The lack of infrastructure and broad data sharing to interpret rare variants and variants of unknown clinical significance is still a significant barrier to efficient and effective medical uses of genome sequences (Angrist and Cook-Degan 2014).

These contextual issues are critically important to evaluating the validity of the argument about the limits of autonomy in the use of genomics. However, Trinidad and colleagues get closer to the core of the ethical question when they hone in on the purpose of the activity as the key determinant of the terms of the debate. If this discussion is about public health screening, principles such as autonomy play a vastly different role in this context than in medical diagnosis. As an example, Char points out the possibility of distinct impacts of whole genome sequencing in the critical care setting.

Thus, framing is everything. Although Lázaro-Muñoz and colleagues initially present PGS as a public health screening activity, there is slippage into medical care, as noted by Trinidad and colleagues. There is a well-established, decades-old set of criteria for implementation of public health screening programs (Wilson and Jungner 1968) that still serves as the basis of program implementation today. However, these criteria were not considered in any analysis except by Holm and Pluog. Principles of disease screening have been revisited in recent years specifically with the emergence of genomic technologies in mind, but even a cursory review of updated criteria indicates that they have not yet been met. For example, it is unlikely that the requirement for scientific evidence for program effectiveness (Andermann et al. 2008) or the requirement for availability of adequate pretesting information or counseling (Petros 2012) has been fulfilled in the context of genomic screening.

The relatively limited scope of these arguments and counterarguments, however, brings to mind an incisive analysis by Buchanan (2007), which examined the moral criticisms of the eugenics movement. His major insight was that the conventional “ethical autopsy” of eugenics in the early to mid 20th century erroneously pitted autonomy, rights, and justice against consequentialism because the conventional view of ethics focused too narrowly on moral principles. He also argued that the misdiagnosis of the “moral pathology” of negative eugenics (“more Kant, less Bentham!”) therefore “fails to provide moral guidance for us today.” While the specifics of his analysis of coercive negative eugenics do not necessarily apply to the current debate about public health genomic screening, the broader implications of his exposure of the shortcomings of conventional ethics and its relationship to science, medicine, and public policy bear consideration because the stakes for public health and for bioethics are potentially high.

Buchanan’s analysis led him to call for a broader view of the aims of ethical analysis to include consideration of the effects of institutions and social practices on the “proper functioning of moral powers” to incorporate and evaluate factual claims, in an inquiry of social moral epistemology. He observed that policies driven by the eugenics movement were made possible by epistemic deference to scientific experts in the face of inadequate evidence and epistemic asymmetries that predisposed the public to believe certain false factual claims.

The commentaries on the target article in this issue by Lázaro-Muñoz and colleagues suggest that such a broadening of scope might be necessary. Many of these critiques target assumptions on which factual claims are based, such as the presumption that the financial costs of genetic testing are the price tags attached by the companies that sell the tests, when it is clear that real-world analysis of genome sequences requires significant infrastructure and personnel time (Dewey et al. 2014) that are not typically included in the accounting. Thus, robust ethical inquiry should question not only principles but factual claims and the role of social practices and institutions in framing the arguments. For example, why is it that when even medical geneticists admit that there is little evidence to suggest that “simply informing individuals of their genetic risks of disease will induce beneficial behavioral changes” and that “at first blush, the notion of deriving public health benefit from a focus on rare diseases seems counterintuitive” (Evans et al. 2013), whole-genome screening of asymptomatic individuals seems to be accepted as inevitable? Why is it assumed that the analytic validity of genome sequencing is adequate for clinical and public health purposes

when there is evidence to the contrary (Lam et al. 2011)? Perhaps we should question the logic that rationalizes expanding “the focus of public health genomics in a way that its promise can be realized” (Evans et al. 2013) as a new opportunity afforded by technological advances rather than creating a problem in search of a solution—that is, asking *why* are we looking for trouble.

The bioethics community should take up the challenge put forth by Buchanan and examine the role of commercial interests, the institutionalization of genome sequencing, and the operation of public health programs as part of the ethical analysis of the application of genomic technologies to screening of asymptomatic individuals. This debate should be far more wide-ranging than about the relative role of patients and clinicians in managing genomic information. We should be critically examining the forces that have led to the generation of massive amounts of genome sequence data in the first place, as well as the justifications for it. We should also evaluate the role of epistemology, moral epistemology, and social moral epistemology in shaping policy decisions. Namely, we should question how it is that, in recommendations for reporting incidental findings in clinical exome and genome sequencing (which was characterized as opportunistic screening), a medical professional society can recognize the lack of empirical data about the clinical validity of genomic findings (especially for those without symptoms or family history of disease) as a critical limitation, yet “nonetheless determined that an initial set of recommendations was appropriate at this time” (Green 2013). How is it that such recommendations were developed and endorsed, seemingly oblivious to established practices for development of both screening and clinical guidelines (Committee on Standards for Developing Trustworthy Clinical Practice Guidelines 2011)? Bioethicists should also independently evaluate the factual evidence about genomics—we cannot afford to commit errors of epistemic deference again with regard to genetics and public health.

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