Published in final edited form as:

Am J Bioeth. 2016 December ; 16(12): 41–43. doi:10.1080/15265161.2016.1240261.

No Panacea: Next-Gen Sequencing Will Not Mitigate Adoptees' Lack of Genetic Family Health History

Stephanie M. Fullerton

University of Washington

There are currently more than 2 million adopted children under the age of 18 years living in the United States (Kreider and Lofquist 2010) and many other adults who were themselves adopted as children. While open adoptions, that is, arrangements where adoptive parents have some degree of contact with an adoptee's birth family, have become more common, it remains the case that many adopted individuals have little or no information about their families of origin. It cannot be overstated how profound a loss this is for many adoptees, who will spend much of their lives wondering both about the specific circumstances of their placement and about the biological relatives (parents, grandparents, siblings, etc.) they will never know. As May and colleagues (2016) note, this state of affairs is also of practical significance when it comes to current norms of individual health risk assessment: Without access to the details of the genetic-relative family health history (GRFHx), adoptees and their health care providers are effectively blinded to a subset of information of potential relevance to disease predisposition and hence may not be able to take appropriate steps (e.g., behavioral modification, enhanced screening) to prevent or delay the onset of disease.

I leave it to others to comment on whether adoptees' lack of access to their GRFHx is appropriately viewed as an unfair healthcare disadvantage; it may, in fact, be neither unfair nor a disadvantage, especially considering that so many important nongenetic determinants contribute to health status. Instead, I would like to address the other claim made by May and colleagues, namely, that this presumed injustice can be mitigated with the use of next generation sequencing (NGS) aimed at identifying “rare but highly penetrant and pathogenic gene–disease associations” of relevance to long-term planning and reproductive decision making. NGS does not currently constitute a “plausible, effective mechanism” to address this informational absence, nor are potential gains associated with participation in genetic testing likely to offset risks associated with inconclusive or inaccurate results. In short, NGS does not now, nor will it likely ever be fully able to, “stand in” for GRFHx, and we risk both disappointing and misleading adoptees in the suggestion that it will.

Perhaps the strongest argument against the routine use of NGS in lieu of GRFHx is the very low likelihood of identifying rare but highly penetrant and pathogenic gene–disease associations that might suggest something about future disease predisposition. For example, one recent review of 112 genes associated with medically actionable genetic disorders (e.g., breast/ovarian cancer, cardiomyopathy) in individuals sequenced by the National Heart,

Lung, and Blood Institute's Exome Sequencing Project found that only 88 of 4,300 European-ancestry participants (2.0%) and 25 of 2,203 African-ancestry participants (1.1%) had variants known or suspected to be pathogenic, such as might be returned from a targeted gene panel or exome (Amendola et al. 2015). Similarly, among 3,296 participants in the Clinical Sequencing Exploratory Research (CSER) network for whom the 56 genes recommended for secondary result return by the American College of Medical Genetics and Genomics (ACMG) were examined, only 68 (2.1%) were found to have a pathogenic or likely pathogenic variant related to their primary indication for testing (Green et al. 2016). These and related results suggest that only a very small proportion of adoptees would receive a genetic test result that would be directly informative with regard to future disease risk. NGS, in other words, would not remedy the lack of access to the GRFHx in most cases.

Even if the potential yield of medically actionable results from NGS were higher, there would still be the nontrivial problem of predicting the clinical consequences of a specific genetic finding for a given individual. The assessment of variant pathogenicity is complex and involves weighing diverse forms of evidence, including the co-inheritance of the variant with disease among biological relatives (Quintans et al. 2014). Despite concerted efforts on the part of ACMG and the Association for Molecular Pathology (AMP) to establish transparent standards for classifying variant pathogenicity, however, nine molecular diagnostic laboratories applying the ACMG–AMP framework to the evaluation of a common collection of variants still reported discordant classifications in 30% of cases (Amendola et al. 2016). In the absence of information about associations with disease outcomes in genetic relatives, uncertainty would likely be even higher. Therefore, rather than providing a solution to the lack of access to GRFHx experienced by many adoptees, NGS interpretation would be hampered because of the absence of family history information.

Beyond complications of variant classification, there are related concerns surrounding the interpretation of variant penetrance, that is, the proportion of individuals who carry a specific variant who express the trait associated with the variant. As researchers have begun to collect DNA sequence information for a wider variety of individuals, it has become possible to assess the clinical consequences of variants in populations unselected for specific disease outcomes. In one recent study (Van Driest et al. 2016), investigators observed that the majority of the patients found to have putatively pathogenic variants in one of two genes associated with cardiac arrhythmia disorders had no evidence of the associated phenotype(s) in their electronic medical records. This suggests that the penetrance of these variants may be lower than previously supposed and, accordingly, that it would be risky to return such findings to otherwise healthy individuals who might elect to pursue unnecessary testing and/or invasive clinical interventions in response. While variant penetrance can differ among family members, for adoptees even such limited clues about potential clinical outcomes would be unavailable, making it impossible to assess the risks and benefits of acting on putative predispositions.

Finally, there is also the matter of uncertainties that derive not from the lack of corroboratory evidence of close relatives but instead from inequities in relevant genomic reference databases. Slightly less than 50% of adopted children in the United States are non-Hispanic whites, with a higher proportion of Blacks and Asians among adoptees as compared to

biological children under 18 years (Kreider and Lofquist 2010). Therefore, a higher proportion of adoptees seeking information from NGS may hail from non-European ancestral genetic backgrounds. The reason this matters is because the rare but highly penetrant variants that May and colleagues expect NGS to identify among adoptees are not well captured by current databases, which woefully underrepresent non-European genetic diversity. The specific consequences of such underlying inequities have only recently begun to be clarified. In some cases, a suspicious variant will not have been previously observed in patients with disease, and—in the absence of additional information about clinical impact—will be conservatively classed as a variant of uncertain significance (VUS) and hence inconclusive finding (Dorschner et al. 2013). Alternatively, and arguably more problematically, a suspicious variant may be erroneously assumed to be pathogenic because disease-free reference controls are drawn from a population that has a lower frequency of the variant as a function of a distinct ancestral heritage rather than a lack of association with disease (Manrai et al. 2016). Either way, biases in reference databases mean that interpretation of NGS test results will often be more time-consuming and uncertain for minority ethnicity patients (Petrovski and Goldstein 2016), including many adoptees.

In summary, emerging data suggest that NGS should not be regarded as a panacea for the lack of GRFHx experienced by many adoptees. The genetic results most likely to be immediately informative with regard to future health status are infrequent, and significant uncertainties accompany their interpretation, even in “best-case” scenarios where complete family health history information is available and genetic testing of biological relatives is feasible. Rather than viewing NGS as a plausible surrogate for GRFHx, it would be better to use current advances in genomic medicine to undermine deterministic assumptions and to work to identify ways of promoting health and wellbeing among adoptees (and others) that do not rely primarily on knowledge of family health history.

Acknowledgments

Funding: This work was supported by the National Human Genome Research Institute of the National Institutes of Health under award numbers P50HG003374 and U01HG006507.

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