Reproductive Genetic Testing and Human Genetic Variation in the Era of Genomic Medicine

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New genetic technologies are increasingly being used in the clinical setting, necessitating an open and pragmatic discourse on their ethical use. The greatest urgency applies to preimplantation and prenatal genetic testing, particularly with the commercialization and expanding scope of noninvasive prenatal testing (NIPT) (Hayden 2014). Sparrow (2015) has made another important contribution to the ongoing debate about the value of, and possible threats to, disability and genetic diversity. Often missing from this debate are clinicians and researchers with expertise in genetics. Although Sparrow (2015) acknowledges the "dangers of oversimplification" in his hypothetical scenarios, we have a social responsibility to address herein common misconceptions about the human genome and about the capabilities of some reproductive genetic technologies (Scully 2008).

GENETIC UNCERTAINTY, AND THE BLURRED LINE BETWEEN DIAGNOSIS AND SCREENING FOR RISK

The pathway from genotype (the genetic makeup of an individual) to phenotype (their observable characteristics) is largely unpredictable. Genetic uncertainty is the result of incomplete knowledge and random processes operating at all levels of biological organization (Ruvinsky 2009). The rapid pace of advances in our understanding of the human genome, especially in the last decade, has fueled a common deterministic misperception that "genetic information objectively and unambiguously draws the contours of normality and abnormality for genotypes, phenotypes, and ultimately, people" (Scully 2008). Instead, new knowledge is challenging our views of even the "simplest" genetic conditions: single-gene disorders like sickle cell disease and cystic fibrosis. For example, since the first mutation for cystic fibrosis was identified in the *CFTR* gene, hundreds of other rare mutations in that gene have been reported in individuals with the illness (Sosnay et al. 2013). The degree to which the specific mutations influence the severity of the clinical presentation is largely unknown. Also, different individuals with the same mutations, even within a family, can have major differences in illness severity (Fanen, Wohlhuter-Haddad, and Hinzpeter 2014). Therefore, in spite of continued improvements in analytical validity of NIPT and other genetic tests (Hill et al. 2015), our ability to make definitive statements about outcomes to couples undergoing reproductive genetic testing for these conditions is limited.

For most common conditions (e.g., congenital malformations, neuropsychiatric disorders, cancer, autoimmune diseases), focus is shifting from individual genes to genetic pathways. The familiar phrase "*the* gene for . . ." is often misleading. Moreover, genetic findings in these conditions are almost all characterized by reduced penetrance (i.e., where the mutation does not always lead to disease) and variable expression (i.e., where the mutation leads to different diseases or degrees of severity in different individuals). Even the best established and most clinically significant genetic findings in diseases like autism or schizophrenia, for example, seem to bestow a risk well below 50% and have a wide spectrum of possible expression (Fung et al. 2015; Lowther et al. 2015; Marshall and Scherer, 2012). Many of these findings are not new (de novo) mutations; instead, they can be inherited from a parent in whom there was an attenuated or imperceptible effect (Costain 2015; Lowther et al. 2015). Attempts to better understand these phenomena, with the goal of improving the predictive ability of genetic testing, will be a major undertaking in the coming decades. Ultimately, however, even if all the modifying genetic and nongenetic factors were known, the stochasticity inherent in development is unavoidable (Ruvinsky 2009). When faced with such uncertainty, different couples will make different reproductive decisions on the basis of the same information.

GENE–GENE INTERACTIONS, INTERCONNECTED NETWORKS, AND QUANTITATIVE TRAITS

Our continued study of the human genome, and of its impact on health and disease, has revealed unexpected complexity. Just as disability exists along a continuum, so

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too do common quantitative traits, including some of the "cosmetic" traits alluded to by Sparrow (2015). These are largely the result of multifactorial effects on highly dynamic, interdependent, nonlinear biological networks (Mackay 2014). Taking IQ and height as two examples, there is a natural genetic distinction between the rare high penetrance mutations that lead to extremes (e.g., those resulting in Fragile X syndrome [for IQ] and achondroplasia [for height]) and the hundreds to thousands of individual genetic factors that influence these traits in the general population. Reproductive genetic technologies are, in general terms, capable of influencing the former but not the latter.

Avoiding rare high-penetrance mutations is fundamentally different from attempting to improve on evolution by inducing new beneficial changes. Even in a hypothetical scenario in which germline genetic engineering (i.e., introducing targeted mutations at conception) in humans was possible, attempts to modify common risk variants and subtly influence quantitative traits would be expected to perturb a delicate interconnected network. As selective forces have brought most genetic functions to local maxima (Ruvinsky 2009), any minor "tinkering" is likely to result in a worse outcome. Purported risk variants for one trait or condition may have other direct or indirect benefits, and/or a vanishingly small effect on the resulting phenotype. Personal trade-offs would be a certainty—for example, a variant that has a subjectively positive effect on height may have a subjectively negative effect on IQ. A separate issue is the necessity of genetic variation to the survival of the species, which precludes the idea of a single "perfect" human genome (Savulescu 2007; Sparrow 2015), as discussed elsewhere (Gyngell 2012).

DECISION MAKING IN THE ERA OF GENOMIC MEDICINE

The relationship between disability and genetics is complicated, and the possibility that advances in genetics might be put to unethical use is a legitimate concern. Although we have taken this opportunity to infuse the debate with additional practical and technical considerations, we are conscious of the common assumption of scientists that, "understanding lay people's concerns about a technology means identifying what they misunderstand, and correcting it" (Scully 2008). Putting aside the issue of what outcomes are desirable, we emphasize that most decision making in the context of new reproductive genetic technologies will be influenced by both practical and immutable uncertainties. This makes "a world of striking uniformity" (Sparrow 2015) seem less likely. Nonetheless, the uptake of these technologies, and their impact on human genetic variation, remain to be determined in this era of genomic medicine.

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