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Concerns About Justification for Fetal Genome Sequencing

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Concerns About Justification for Fetal Genome Sequencing

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The proposal by Chen and Wasserman (2017) contributes to a long-standing debate about the scope of prenatal screening services. With realistic prospects of fetal genome-scale sequencing from noninvasive maternal blood sampling (NIPW), their framework is timely. However, we outline a number of concerns regarding this approach, ranging from the philosophical to the social and clinical.

A key concern in this literature is that the framework lacks a clear philosophical foundation. Despite the long history of prenatal diagnosis (PND), a central question remains regarding the core justification for these services.

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Prenatal screening, testing, and pregnancy termination represent a complex, value-laden, and expensive enterprise, preferably delivered by professionals. If society believes that these services should be routinely offered to pregnant couples, as recommended by the American College of Obstetricians and Gynecologists (Rose and Mercer 2016), then justification is necessary. Any proposal to dramatically increase the scope of these services requires further explanation for why an expansion is consistent with the core justification. There are three traditional justifications for PND (Bot- kin 1995). A child-centered justification argues that prenatal screening is intended to serve the interests of the future children. While the prenatal detection of certain conditions can benefit the child and family through advance planning, this is not the primary justification. The objective of prenatal genetic testing is to detect health problems that could affect the woman, fetus, or newborn and provide the patient and her care providers with enough information to allow an informed decision about pregnancy management, including termination. So the question is whether termination of a fetus can be construed as a benefit to the future child. Wrongful life lawsuits implicitly or explicitly sup- port this notion. But for the most part, wrongful life suits have not been successful in the courts, and this line of argument in the literature has dwindled because the premise makes little sense. There are few, if any, conditions for which we might make a cogent argument that termination is preferable to life with that condition.

A social justification suggests that prenatal diagnosis benefits society by reducing the number of children born with expensive health conditions. There is a history of studies that claim to show the economic value of PND, but these studies are often of poor quality due to questionable assumptions and the value-laden nature of the analyses. Further, the notion that society should support PND for the purported social benefits obtained through the prevention of undesirable members is plainly eugenic. A justification of PND solely for such social benefit is no longer accepted.

The justification for PND as a service that promotes the interests of prospective parents remains viable. Here the argument is that prospective parents benefit from these services by being able to make informed choices about the birth of a child with a condition that may have important impacts on their family or by providing time to plan for the birth of an affected child. This line of argument is strongest when the conditions targeted have significant implications for parents and the family, such as conditions that are lethal for the child or severely debilitating. This rationale has much less force when talking about screening for milder conditions or non-health-related conditions. If Chen and Wasserman support this general line of argument, they need a more explicit justification for why parents have a positive right to genome-scale information on the fetus and why enormous new resources should be invested in this enterprise. Our second broad concern relates to their assumptions regarding the association between genotype and phenotype.

Their arguments presuppose that the identification of a DNA variant in a fetus will be directly related to a health outcome. Unlike molecular testing in the pediatric population, in which an individual with clinical fi dings has molecular analysis as an attempt to identify or confirm a diagnosis, prenatal testing strategies with NIPW are much more complex. Routine prenatal screening is performed in the context of evaluating a normal-appearing fetus; a fetus with obvious birth defects is currently referred for diagnostic testing with chorionic villus sampling (CVS) or amniocentesis (Rose et al. 2016). It is known that healthy individuals can harbor many deleterious genes without clinical findings (Cooper et al. 2013). Therefore, the clinical validity of genome-scale screening results in unselected populations is likely to be very poor. Further, there are no population-based studies that will capture data on phenotype– genotype correlations in the context of fetal genome sequencing. In the future, collecting such data would be resource intensive and only likely to be justified for conditions considered serious for the child and family.

Our third concern goes directly to the core assumption about the negative impact that “line drawing” in PND has for people with the conditions that are explicitly targeted. A central rationale for the proposed framework is that a full disclosure model avoids the identification of specific conditions in public policy for which PND and pregnancy termination are considered justified. But there is a set of assumptions here that have not been validated. Does the offer of PND for Condition A lead to increased stigma or discrimination against those with Condition A? This question can only be answered by analyzing broad social trends, which are influenced by multiple factors beyond any experimental control. With this large caveat, our observation is that social stigma and discrimination have substantially decreased in recent decades for individuals with conditions like Down syndrome (DS), spina bifida, sickle cell disease, cystic fibrosis, and the like that have been the primary focus for PND.

There are several trends in contemporary medicine that illustrate and perhaps influence

relevant social attitudes. First, there has been a remarkable investment in treatments for all of the conditions traditionally targeted by PND. The life span for people with cystic fibrosis has progressively improved and there are established and exciting new possibilities for cure for many people with sickle cell disease (Tasan, Jain, and Zhao 2016). Children with Down syndrome and their families now have a broad range of interventions and supportive services that can address associated medical conditions, developmental challenges, and speech and language issues. Clearly these types of improvements in health care would not have occurred if society and families with affected children did not highly value affected individuals. This is not to claim that discrimination against those with disabilities is not an ongoing problem, only that the medical landscape is dominated by energetic treatment and support efforts despite advances in PND.

A second observation is that the prevalences of many conditions traditionally targeted by PND have not decreased dramatically as a result. In the United States, the prevalence at birth of Down syndrome has increased in recent years (Mai et al. 2013). This increase is likely due to competing influences of a trend toward older age at birth for mothers versus the role of PND in decreasing birth prevalence, although neither of these trends is dramatic. de Graaf and colleagues (de Graaf, Buck- ley, and Skotko 2015) estimate that the proportion of DS fetuses terminated is about 30% and this fi has remained stable over the past 20 years. Rising prevalence and stable termination rates occur in the face of changes in PND approaches that involve offers of screening to progressively larger proportions of the pregnant population and progressively less invasive screening tools. These data points suggest that developments in PND have not led to expanding demand for these services. To our knowledge, there is no lay advocacy movement calling for more and better prenatal diagnosis. The use of PND remains in the realm of personal choice and, for a variety of reasons, the majority of pregnant couples are not effectively using existing PND technologies to prevent the birth of children with DS. We think it unlikely that NIPW will lead to a significant new demand for actionable information on traits with considerably less impact on families.

Finally, public policy in recent decades in the United States has been enacted to attempt to counter stigma and dis- crimination against those with disabilities. The Rehabilitation Act, the Americans with Disabilities Act (ADA), the ADA Amendments Act, and the Individuals with Disabilities Education Act all reflect commitments at the federal level to inclusion of people with disabilities. Many other federal and state laws also address disability discrimination. Nonetheless, problems of inclusion clearly remain. To offer just two examples, people with disabilities continue to be significantly under or unemployed, and Medicaid coverage for home- and community-based services remains inadequate in many states. Given such circumstances, it is unclear whether Chen and Wasserman's proposal promises any impact on discrimination where it plainly exists. A preferable alternative in our judgment is to continue to press for the social conditions that can support parents in making informed choices in accord with their values in a limited set of conditions for which there is clear justification. Chen and Wasserman have not yet made a convincing argument that "line drawing" in the context of PND has led or will lead to stigma or discrimination for those with targeted conditions, or that sweeping a wider net with NIPW will impact the remaining problems of stigma and dis- crimination experienced by those with disabilities.

CONFLICTS OF INTEREST
In 2016, Nancy C. Rose received an honorarium for writing the American College of OB GYN

Practice Bulletin on Aneuploidy Screening. She has received travel reimbursement from ACOG to act as their representative to the American Institute of Ultrasound in Medicine. She has received travel reimbursement and an honorarium from the Hastings Center for Bioethics. She is receiving travel reimbursement from the Utah Center for ELSI research for a recent CEER meeting. In 2015 she received laboratory services from Progenity, Inc for a research project that is being submitted for publication.

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