INVITED COMMENT

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Non-Invasive Fetal Genome Sequencing: Opportunities and Challenges

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We recently predicted the whole genome sequence of a human fetus using samples obtained non-invasively from the pregnant mother and the father [Kitzman et al., 2012]. This advance raises the possibility that it may soon be possible to perform genome-wide prenatal genetic testing without an invasive procedure early in pregnancy. Such a test would substantially broaden the scope of fetal genetic results that could be available prenatally.

Non-invasive fetal genome sequencing (NIFGS) does not inherently raise new ethical issues, or those that cannot be addressed within the existing framework of medical bioethics. Indeed, many of the same issues have been raised by the introduction of other prenatal testing/screening technologies, now in wide use, and again more recently by the introduction of whole genome sequencing for clinical diagnosis [Benn and Chapman, 2009; Ravitsky, 2009; Schmitz et al., 2009; Berg et al., 2011; Sayres and Cho, 2011; Tabor et al., 2011]. However, the ethical issues are somewhat magnified by the possibility of NIFGS and compounded by controversies surrounding elective pregnancy termination, rights of individuals with disabilities, and eugenics. Accordingly, the prospect of successful NIFGS, even on a research basis, is likely to generate considerable controversy and debate about the acceptability of developing such technologies, much less if and how they should be used. We view this response as very positive because it provides all stakeholders and the broader public in general with the opportunity to carefully consider and deliberate these issues in what we would hope is a thoughtful and balanced way.

As NIFGS becomes technically tractable and increasingly cost-effective, and as an acceptable false positive/false negative profile is achieved, one population for which it might be of great benefit may be pregnant women who are currently offered invasive prenatal diagnostic testing. Such women are typically at risk for genetic conditions based on screening results or family history, and NIFGS would likely reduce if not eliminate adverse outcomes from invasive testing for most of these women.

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The expanded use of NIFGS would present several advantages and challenges. Broader use of NIFGS might lead to the greater detection of Mendelian disorders in families who would not otherwise have been offered prenatal testing, as well as families who might have refused invasive testing because of risks to the pregnancy and fetus.

NIFGS could augment or even replace current approaches to neonatal screening as most such disorders are autosomal or X-linked recessive (e.g., hypothyroidism and congenital hearing loss are only sometimes Mendelian). Prenatal identification of disorders now found in neonatal screening would afford for earlier parental education, diminished false positives and the accompanying costs of retesting and parental anxiety and earlier therapeutic interventions. Earlier detection of such disorders would also foster improved prenatal care, pregnancy and delivery management and/or postnatal intervention. For example, 90% of genetic variants in *SCNA1* that cause seizure disorders are de novo, and identification by NIFGS could allow for diagnosis before the onset of seizures and consideration of appropriate precautions and/or pharmacological treatment [Marini et al., 2011]. Similarly, 50% of mutations causing multiple endocrine neoplasia 2B are spontaneous, and earlier identification of these mutations could prompt prophylactic thyroidectomy and improve outcomes [Carlson et al., 1994].

The availability of NIFGS could increase the utilization of prenatal testing, and in turn increase rates of elective termination, both for disorders for which testing is currently available and for the wide arrange of disorders and traits for which testing would be newly available [Tischler et al., 2011]. On the other hand, NIFGS might also make pregnancy termination safer, less costly, and less traumatic as it could be performed early in gestation. Broad use of NIFGS might result in increased societal pressure for pregnant women to undergo screening and terminate any fetus suspected to have a Mendelian condition. This could reverse important and continuing social progress towards civil rights and social support for people and families with disabilities. In addition, this societal pressure might threaten parental autonomy over reproductive decision-making.

Broader use of NIFGS might also create or magnify social stigmas or inequities. NIFGS would likely remain expensive and may not be reimbursable by insurance in the short-term. This might exaggerate disparities between people who can easily afford access and those who cannot. If access is limited to those who can afford it, it is possible that a disproportionate number of lower income families could suffer from the higher rates of morbidity and mortality of invasive testing. In the extreme scenario, children with Mendelian conditions would be disproportionately born to lower income families that could not afford NIFGS. Such a disparity would likely further stigmatize many of these conditions and exaggerate existing disparities in access to healthcare and benefits for these populations.

Another key issue raised by NIFGS is that it represents a substantially more comprehensive test for Mendelian disorders with a known cause, and will identify variants that are beyond the scope of conventional prenatal screening and diagnosis. Specifically, variants will be identified that indicate increased risk for developing adult onset conditions. This is not unique to NIFGS: in fact this is an ongoing challenge in pediatric clinical genetic testing [Wilfond and Ross, 2009]. Such information may be irrelevant or inappropriate to return for the benefit of the fetus/future child, but may have direct implications for the health of the parent, and therefore provide indirect benefit to any current or future children. However, if NIFGS is more broadly implemented, the scope of the results identified and the number of individuals affected may increase substantially. This will further overwhelm the existing infrastructure for providing genetic counseling.

As with other applications of whole-genome sequencing, NIFGS will identify variants of ambiguous clinical utility in genes known to be associated with both pediatric and adult complex disease. For example, Kitzman et al. found a de novo novel missense variant in *ACMSD*, a gene in which common variants have been associated with Parkinson disease by genome-wide association [Kitzman et al., 2012; International Parkinson Disease Genomics Consortium et al., 2011]. This variant causes substitution of a highly conserved amino acid residue, but in the absence of compelling evidence of its role in Parkinson disease or other conditions, its detection is of limited clinical value. While this is no different than the challenge of interpreting WGS information in general, pregnancy might be a particularly vulnerable time in which to receive this information and parents might feel compelled to give more credence to the information than it warrants.

There are several other important issues that require consideration. Will the non-invasive nature of this test, combined with the enhanced detection of Mendelian disorders, lead to a substantial increase in the number of women who consider prenatal diagnosis? How will the medical community meet the challenge of providing genetic counseling to address the complex nature of the information that may be identified? These concerns raise the possibility that some women may not be able to provide adequate informed consent, or may proceed with actions such as terminations without complete understanding of the test results or the prognosis for various rare Mendelian disorders. If NIFGS allows for the creation of a record of a child's whole genome prior to its birth, what should happen to that data? Should it be stored as part of the child's medical record, with the possibility for future updating, analysis and mining for medically relevant information? Or should it be destroyed? Who should make this decision and have control over the data?

As with many new technologies, NIFGS will be accompanied by many ethical and social challenges. We think that it is imperative that these questions and issues be discussed and addressed by a diverse group of stakeholders, as well as through collection of empirical data on stakeholder perspectives and concerns. Much can be learned from the history of the implementation of other prenatal testing approaches, such as amniocentesis and CVS, as well as the ongoing debates about pediatric genetic testing and return of results from whole genome sequencing [Rapp, 2000].

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