

Prenatal **Whole Genome** *Sequencing*

JUST BECAUSE WE CAN,
SHOULD WE?

BY GREER DONLEY, SARA CHANDROS HULL, AND BENJAMIN E. BERKMAN

With whole genome sequencing set to become the preferred method of prenatal screening, we need to pay more attention to the massive amount of information it will deliver to parents—and the fact that we don't yet understand what most of it means.

Whole genome sequencing is quickly becoming more affordable and accessible, with the prospect of personal genome sequencing for under \$1,000 now widely said to be in sight.¹ The ethical issues raised by the use of this technology in the research context have received some significant attention, but little has been written on its use in the clinical context, and most of this analysis has been futuristic forecasting.² This is problematic, given the speed with which whole genome sequencing technology is likely to be incorporated into clinical care. This paper explores one particular subset of these issues: the implications

of adopting this technology in the prenatal context without a good understanding of when and how it is useful. This way of adopting whole genome sequencing would be what Benjamin Wilfond and Kathleen Nolan call *extemporaneous*, where the independent market, professional practice, and legal and consumer forces determine utilization. Conversely, in the *evidentiary* model, new technologies are adopted after an examination of the underlying normative considerations that arise from their use. An extemporaneous adoption of new technologies, Wilfond and Nolan argue, can lead to harmful consequences that could be circumvented if reasonable deliberation occurs at the onset of the technology's incorporation into clinical care.³

Prenatal whole genome sequencing differs from current prenatal genetic testing practice in a number of ethically relevant ways. Most notably, whole

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genome sequencing would radically increase the volume and scope of available prenatal genetic data. The wealth of new data could enhance reproductive decision-making, promoting parents' freedom to make well-informed reproductive decisions. We argue, however, that there is potential for prenatal whole genome sequencing to alter clinical practice in undesirable ways, especially in the short term. We are concerned that the technology could (1) change the norms and expectations of pregnancy in ways that complicate parental autonomy and informed decision-making, (2) exacerbate the deleterious role that genetic determinism plays in child rearing, and (3) undermine children's future autonomy by removing the option of not knowing their genetic information without appropriate justification.

In light of these concerns, and given that existing genetic testing guidance does not adequately anticipate the ethical issues that prenatal whole genome sequencing will raise,⁴ exploring the impact of this new technology is vital.⁵ Its potential negative effects must be balanced against the possible benefits it might offer for reproductive decision-making. Responsible adoption of prenatal whole genome sequencing in clinical practice requires a concerted public effort to assess these risks and potential benefits.

The Transition to Prenatal Whole Genome Sequencing

Current prenatal genetic testing practice typically consists of relatively small, targeted groups of tests. The tests are selected based on the offspring's risk of inheriting certain serious genetic conditions. This risk is calculated based on factors such as the parents' race, ethnicity, age, family history, a prior positive screen, and existing parental or familial genetic test results.⁶ The genetic information generated from the most common prenatal tests is *diagnostic*, and the medical conditions tested for are

severe. For instance, many parents of Jewish descent are offered a select group of targeted tests that look for, among other things, whether a child has Tay-Sachs disease, a debilitating condition that typically results in the child's death by age five.⁷ Genetic information about Tay-Sachs disease can help parents prepare themselves either financially or psychologically for raising a child with special needs, and it also allows them to consider terminating the pregnancy. These benefits for reproductive decision-making might be tempered by concerns that the information puts unfair pressure on parents, particularly mothers, to

replaced with prenatal whole genome sequencing, the amount of information generated will increase exponentially and will expand into categories of information beyond those currently available.¹¹ What is now a general practice of testing for no more than a few dozen genes could transition into testing for thousands of possible known phenotype-influencing variants. Sequencing a complete genome will reveal much more than just diagnoses of severe conditions; it will also produce variants of unknown significance, nonmedical genetic markers, carrier status, susceptibility genes, and genes expressing condi-

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make full use of the information.⁸ Although there may be positive and negative aspects of current prenatal genetic testing, and the perceptions of these benefits may vary across cultures or ethnicities, we will assume for this article that current prenatal genetic testing confers enough parental benefit to justify its use.

The positive and negative implications of whole genome sequencing in the prenatal context have yet to be robustly analyzed, however, despite how quickly genomic science is advancing toward clinical adoption.⁹ While not yet available in the clinic, recent drops in the cost of sequencing, plus the advent of noninvasive technology that can isolate the entire fetal genome from a mother's blood sample, suggest that commercial adoption is imminent.¹⁰

Whole genome sequencing will generate an unprecedented amount of genetic information and represents much more than an incremental step beyond traditional genetic testing. If targeted, risk-based prenatal tests are

tions with late onset (see Table 1). Although whole genome sequencing may more efficiently produce information relating to diagnostic tests for serious medical conditions—the kind of information currently tested for—information from the five other categories will comprise the majority of data produced and will likely be found in every genome sequenced. Each of these categories will be further discussed below.

Some of the data produced by whole genome sequencing will be helpful for reproductive decision-making, but the implications of many genetic markers have yet to be fully understood by the scientific community.¹² The field of genetics is rapidly evolving, and it will likely take decades to gain a more comprehensive understanding of the genome. Today, the function of more than 90 percent of annotated genes in the human genome is unknown, as is the function of 98 percent of the noncoding regions.¹³ In other words, only a small number of the

Table 1.
Potential Prenatal Testing Categories

<i>Type of information</i>	<i>Does it inform reproductive decision-making for current pregnancy?</i>	<i>Might the future child have an interest in not knowing the information?</i>	<i>Could it provide immediate benefit to the future child?</i>
<i>Variants of unknown significance</i> (genetic variations whose association with disease risk is unknown)	<i>No</i>	<i>Yes</i>	<i>No</i>
<i>Nonmedical genetic markers</i> (genetic variations that have no health-related significance)	<i>No</i>	<i>Yes</i>	<i>No</i>
<i>Carrier status</i> (possession of genetic variations that do not cause illness in the carrier but might contribute to illness in the carrier's offspring)	<i>No</i>	<i>Yes</i>	<i>No</i>
<i>Susceptibility genes</i> (genes with variants that indicate increased likelihood for developing a condition)	<i>Sometimes</i>	<i>Yes</i>	<i>No</i>
<i>Late onset genetic conditions</i> (highly penetrant genetic conditions that display no symptoms until late in life)	<i>Sometimes</i>	<i>Yes</i>	<i>No</i>
<i>Medical conditions found by current prenatal genetic tests</i> (conditions with 100 percent penetrance that seriously affect health and quality of life throughout the life cycle)	<i>Yes</i>	<i>NA</i>	<i>Sometimes</i>

genetic markers that whole genome sequencing will produce have been studied enough to substantiate their connection to disease. Although the scientific community is in the budding stages of research on many new markers, preliminary results are often subject to change, as is illustrated by a number of published genomic discoveries that have subsequently been retracted after additional evidence has come to light.¹⁴ As the nascent field

of genomics continues to develop, much of the data generated from prenatal whole genome sequencing over the next few years (or even decades) will be of questionable utility at the time they are generated, and even findings that seem clinically relevant could be subject to later retraction or revision. Reflecting this scientific uncertainty, some commentators and scientific leaders have articulated restrained optimism about the speed

with which genomic medicine will be clinically useful.¹⁵

Nevertheless, the popular promise of “personalized medicine” suggests that there will likely be a desire to use testing as soon as technically feasible. If so, there may well also be a tendency to overinterpret and oversell the results, especially when the technology is first introduced, to make it more appealing for consumers.¹⁶ Additionally, despite uncertainty about

the technology's real benefit, as it becomes increasingly reliable and affordable in clinical care as well as the research setting, several factors will push for its utilization in the prenatal setting.

First, it is likely that significant economic benefits will motivate the use of whole genome sequencing. Once the genome can be sequenced at a reasonably affordable cost¹⁷—as is likely to happen in the near future—there will be no targeted, risk-based tests that can produce a comparable amount of information for anywhere near the cost.¹⁸ Commercial whole genome sequencing cost estimates from the past few years have ranged from \$4,000 to \$9,500 and are dropping rapidly; given the informational advantage of whole genome sequencing, the difference in price between it and some standard groups of tests is already modest, even though currently there is no way to accurately project the actual cost of whole genome sequencing in the prenatal context.¹⁹

Second, some parents may feel pressure to employ whole genome sequencing if it becomes widely available or is offered directly to them, just as many now feel obligated to use prenatal or direct-to-consumer genetic testing.²⁰ Americans generally value “cutting-edge” technologies, regardless of the technology's demonstrated benefit. Given the widespread discourse about personalized medicine and the potential benefits of genomic research, it is easy to project that there will be a market for it.²¹ Of course, data on the attitudes of potential parents are needed to explore the scope of this potential market.

Parental expectations aside, prenatal whole genome sequencing may not prove very helpful in informing their reproductive decisions. Much of the information the technology produces will be ambiguous and likely confusing, at least while the technology is first being introduced and refined, and possibly beyond. Moreover, even information that has a more robust scientific evidence base may not be relevant to parents as they

think through their reproductive options. Without careful consideration, making the technology available in clinical practice will likely move the culture away from the current risk-based threshold for recommending genetic testing, which might have serious implications for the norms surrounding the obligation parents feel to consider and act upon prenatal genetic information. Research is needed to determine both the extent to which parents will demand this technology and whether the informa-

variation in a functionally relevant region of the genome that codes for a protein associated with heart disease, but without further research, it is unclear whether or how that variant will alter the function of the protein in a way that affects disease expression. Because the health-related impact of VUS cannot be stated with any degree of certainty, the variants do not yet reveal any medically important information. This inherent uncertainty is the main difference between VUS and the diagnostic information

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The Expansion of Prenatal Genetic Information

To consider whether the information generated by whole genome sequencing will be useful for informed reproductive decision-making, a good place to begin is by questioning whether that information is different in ethically relevant ways from the information generated by targeted, risk-based tests. To do so, we will first explore the categories of novel information that the new technology produces.²²

Variants of unknown significance. As research on the genome continues to advance, whole genome sequencing will uncover many variants of unknown significance, known as VUS. Although often found in regions associated with important health functions, VUS are variations in a genetic sequence whose association with disease risk is, by definition, unknown. For instance, a test may reveal a novel

revealed through current prenatal genetic tests.

Nonmedical indicators. Nonmedical genetic markers will also be revealed through prenatal whole genome sequencing. In addition to basic characteristics like eye color, parents might also have access to information about genes that can help predict various nonmedical characteristics, such as athletic ability, loyalty, criminality, and intelligence.²³ This information stands in stark contrast to the diagnostic health information about serious disorders currently given to parents who engage in prenatal genetic testing. Although many parents might be interested in learning about nonmedical indicators if the indicators were offered to them, parents in one study did not express a desire to pursue prenatal tests for nonmedical genetic information.²⁴ Possibly, however, their lack of interest stemmed from the fact that relatively little was known about the genetic contributions to nonmedical characteristics available at that time.

Carrier status. Another category of information that can be generated from prenatal whole genome sequencing is a child's carrier status for genetic conditions. If a child is a carrier of a genetic condition, then once she reaches reproductive age and decides to have children, her offspring would generally be at risk of having that condition only if her partner is also a carrier for the same condition. This is true even if the child will not express any characteristics of the condition herself. If her partner is not a carrier for that condition, however, then their offspring might become carriers for the condition without being affected by any characteristics of the disease. Some examples of genetic diseases for which one can be a carrier include hemophilia, cystic fibrosis, and color blindness. Unlike the current information revealed through targeted, risk-based tests, carrier status does not usually reveal any health information relevant to the child's immediate health. Because there are no personal medical consequences to being a carrier for a genetic condition, being aware of one's carrier status for genetic conditions is generally useful only in adulthood, when one is likely to start a family. For this reason, testing for carrier status in children is discouraged by nearly every professional organization (see Table 2).

Conditions of late onset. Highly or moderately penetrant late-onset conditions can also be discovered by prenatal whole genome sequencing. Although these conditions often cause severe medical diseases, they generally do not affect a person's health until later in life. Paradigm examples of late-onset conditions are Huntington disease or Alzheimer disease, although there are many other late-onset conditions that occur later in life with less devastating symptoms. The main difference between this category of information and the information currently found in targeted, risk-based tests is that late-onset conditions will not affect the person during childhood. As many of these late-onset conditions have

limited treatment options, the information often merely provides a window into the end of one's life. This makes the information very powerful, and the reaction to it emotionally intense. Many adults decide not to be informed about this kind of finding.²⁵ Predictive testing for late-onset conditions is uniformly discouraged in the pediatric setting for these reasons.²⁶

Susceptibility genes. Prenatal whole genome sequencing will also reveal many disease susceptibility genes; these are genetic markers of low or variable penetrance that suggest a genetic predisposition, or increased statistical likelihood, for developing a disease. This is importantly different from the *diagnostic* information currently offered, which allows parents to make decisions based on information about the definitive presence of disease. Many chronic conditions belong in this category; for instance, genes indicating susceptibility for diabetes, mental health disorders, heart conditions, and some cancers have already been discovered. The presence of susceptibility genes, however, does not mean that developing the disease is inevitable, or perhaps even likely. Instead, the information will only give parents complex probabilities that their child could develop a medical condition. This probabilistic information is further complicated by the fact that environmental and behavioral factors play a large role in disease development.

Of our five new categories of information that prenatal whole genome sequencing will produce, the implications of variants within the susceptibility genes category are the broadest, with variants relating to lower and higher probabilities of developing a condition, as well as a range regarding the severity and age of onset of conditions. Some genes, for instance, probably increase the risk of developing a condition by only a small percentage. Scientists have also discovered genes for less important medical conditions, like stuttering, that can have a variable impact on a child's quality of

life.²⁷ The category of susceptibility genes is very large and diverse, and it will continue to grow.²⁸

The Challenge of Too Much Information

The five new categories of information we outlined above are different from the information currently available through targeted, risk-based tests in a key way: much of the new information is arguably less useful for reproductive decision-making, at least at this time (see Table 1). Although one important goal of offering prenatal whole genome sequencing would be to improve reproductive decision-making for parents,²⁹ most of the information that the technology generates would probably not be as helpful for parents making such choices as information uncovered by the current categories of prenatal genetic tests.

In light of the uncertain usefulness of the information available through whole genome sequencing, there are a number of ways in which using it in a prenatal context could be problematic. First, we are concerned that its availability will cause a shift in norms and expectations, such that parents will be expected to both use and act on the information it provides. Given the uncertain meaning of much of this information, these shifts could create unnecessary anxiety and confusion in parents who are unsure of how to process or act upon the vast array of information they are faced with. This anxiety and confusion could result in an increase in pregnancy termination, as well as conflicts between parents and providers over whether the information should be distributed and how it should be acted on. Second, we are concerned that broad knowledge about a child's genetic information could exacerbate an inappropriate belief in genetic determinism, which could affect how parents raise their children in potentially harmful ways. Finally, in light of concerns about the uncertain utility of this technology, we worry that

children's future autonomy and the "right not to know" will be undermined without sufficient justification. We will explore each of these potential concerns below.

No More Perfect Babies

When prenatal whole genome sequencing is adopted into clinical care, the norms and expectations around the use of large-scale prenatal genetic testing will almost certainly change in important ways. First, the threshold used by clinicians to recommend prenatal genetic testing is likely to evolve. Current prenatal genetic tests are recommended selectively, based on risk factors; if parents do not have sufficient risk, testing is not recommended. Prenatal whole genome sequencing, however, might be more universally offered to all parents because all prenatal genomes have the potential to reveal relevant information, independent of known risk factors.

This could lead to a shift in how expectant parents understand the concept of a normal, healthy baby. Because few conditions are currently tested for in targeted, risk-based tests, it is relatively rare for parents to learn about any medical problems facing their future child. If a targeted, risk-based test reveals health information, it is generally of a very serious nature. With prenatal whole genome sequencing, however, information about a large and growing number of health conditions will be available to parents prenatally. Early experience with the new technology suggests that any individual's genomic data will likely contain a nontrivial number of clinically significant (or possibly clinically significant) findings. For example, one study sequenced the genomes of twins and found 430 genetic variants, fifty-six of which were associated with human disease.³⁰ Although this is only one study, it illustrates the reality that whole genome sequencing will generate a wide variety of findings, only some of which will be sufficiently severe or be

well enough understood scientifically to clearly be medically relevant. Depending on the threshold one chooses to determine the kinds of findings that should be routinely returned to parents, prenatal whole genome sequencing could result in a deluge of information about a future child.

Unless an extremely restrictive threshold is established, every parent who chooses to undergo prenatal whole genome sequencing will receive some medically relevant information about their future child, even though much of that information will reveal less serious, or less well understood, genetic markers. As a result, the new

how it will affect parents' perceptions before birth.

Regardless of whether the idea of a "perfect child" evolves, it is reasonable to project that the qualities and quantities of new information generated by whole genome sequencing will augment the anxiety that parents feel about their child during pregnancy.³¹ Without adequate education and genetic counseling, parents may be inclined to overestimate or overvalue the genetic information they learn about their child prenatally. Unfiltered prenatal genetic information runs the risk of confusing parents and creating intense concern;

Sequencing a complete genome will reveal much more than diagnoses of severe conditions. To the extent that parents now think of their child as a "clean slate" during pregnancy, the prenatal image of a normal, healthy baby will be dramatically altered by this technology.

technology will prompt parents to face the future illnesses of their children before they are even born. Since current prenatal genetic testing practice is targeted only toward parents with identified risk of serious genetic diseases (and even these parents receive information only from a modest number of tests), most parents do not yet have to digest troubling genetic information about their future child. To the extent that parents now think of their child as a "clean slate" during pregnancy, the prenatal image of a normal, healthy baby will be dramatically altered by this technology. We expect perceptions to change naturally as the technology is incorporated into clinical care and parents are educated about the scope of findings it makes possible, but we cannot be sure of the scope or magnitude of this shift without data. Substantial research is needed to understand the psychosocial impact of this information and

data are needed to determine the extent to which parents would have such inclinations.

Much of this anxiety will be unnecessary, and each category of information will likely affect parents in different ways. For example, in the case of late-onset conditions, the information will likely cause many parents to be anxious about their child, knowing what conditions will affect him or her later in life without any ability to help. In the case of VUS, susceptibility genes, and carrier status, the anxiety that parents experience will be based on nondiagnostic and sometimes ambiguous information. If the child remains healthy (or has healthy children), as many will, then the anxiety experienced by the parents would have been unwarranted. Nonmedical genetic markers might also run the risk of causing unnecessary anxiety and even changes in parenting style—for example, if a child were found to have markers

Table 2.
Comparison of Genetic Testing Guidelines from Relevant Professional Organizations

Organization	<i>Genetic Testing Recommendations for Children</i>	<i>Genetic Testing Recommendations for Fetuses</i>
American Medical Association ¹	When preventive or therapeutic options are available, genetic testing should be offered and in some cases required. When no preventive or therapeutic options are available and onset is in childhood, testing is up to parental discretion. For conditions with adult-onset or carrier status, testing should not be performed unless the information is needed to prevent substantial harm in a family member, or the child will never reach mental capacity.	If prenatal diagnosis is performed, the principle of patient autonomy requires that all medically relevant information generated from a fetal test be passed along to the parents.
National Society of Genetic Counselors ²	Testing during pregnancy or childhood allows the parent, rather than the individual (fetus or child) being tested, to provide informed consent to proceed. Given that many at-risk adults may elect not to be tested, testing in pregnancy or during childhood should be undertaken cautiously. Parents should consider whether the decision to test should be reserved for the child to make upon reaching adulthood.	Testing during pregnancy or childhood allows the parent, rather than the fetus or child being tested, to provide informed consent to proceed. Given that many at-risk adults may elect not to be tested, testing in pregnancy or during childhood should be undertaken cautiously. Parents should consider whether the decision to test should be reserved for the child to make upon reaching adulthood.
American Academy of Pediatrics ³	Testing should not be offered in children unless there are immediate medical benefits (such as the availability of measures that can prevent the disease, delay its onset, limit its severity, or prevent secondary disabilities), or there is a benefit to another family member and no anticipated harm to the minor. Carrier status should not be offered to children and adolescents, with a possible exception for well-informed adolescents planning a pregnancy.	No relevant recommendations.
Institute of Medicine ⁴	Children should generally be tested only for genetic disorders for which an effective curative or preventive treatment exists that must be undertaken early in life to provide maximum benefit. Childhood testing is not appropriate for carrier status, untreatable childhood diseases, and late-onset diseases that cannot be prevented or forestalled by early treatment.	No relevant recommendations.

associated with aggression or violence. Even though genetic indicators of behavioral traits cannot predict the child's nature with any certainty, parents are likely to have serious concerns about raising a child predisposed to certain behaviors or diseases.

We are also concerned that parents may let this anxiety and confusion affect their reproductive choices in a way they would later regret. U.S. law upholds the legitimacy of pregnancy termination based on the parents' values and discretion; however,

having an abortion can be a painful experience and ought to be based on a reasoned decision that is consistent with the parents' values.³² Currently, given the relatively small number of targeted, risk-based genetic tests that are recommended, most parents are

Organization	Genetic Testing Recommendations for Children	Genetic Testing Recommendations for Fetuses
American Congress of Obstetricians and Gynecologists ⁵	Timely medical benefit to the child is the primary justification for genetic testing in children and adolescents. If the medical benefits are uncertain or will be deferred, the argument for testing is less compelling. If the medical or psychosocial benefits of the test will not accrue until adulthood (as in tests for carrier status or adult-onset disease), genetic testing generally should be deferred.	If pregnancies will be carried to term, consideration should be given to whether, as in the case of testing children, the decision to test should be reserved for the child to make upon reaching adulthood. Considerations should also be given to personal preference, that is, the interests individuals may have in terminating a pregnancy that may result in a life that they feel morally obliged or prefer not to bring in to the world.
American Society of Human Genetics and American College of Medical Genetics ⁶	Same as above.	No relevant recommendations.
National Human Genome Research Institute's Task Force on Genetic Testing ⁷	Genetic testing of children for adult-onset diseases should not be undertaken unless direct medical benefit will accrue to the child, and this benefit would be lost by waiting until the child has reached adulthood.	No relevant recommendations.

1. American Medical Association, "Opinion 2.138—Genetic Testing of Children," June 1996, at <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion2138.page>; American Medical Association, "Opinion 2.12—Genetic Counseling," June 1994, at <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion212.page>; American Medical Association, "CEJA Report D-I-92—Prenatal Genetic Screening," 1994, at <http://www.ama-assn.org/resources/doc/code-medical-ethics/211a.pdf>.

2. National Society of Genetic Counselors, "Position Statement: Prenatal and Childhood Testing for Adult-Onset Disorders," 1995, at <http://www.nsgc.org/Advocacy/PositionStatements/tabid/107/Default.aspx>.

3. Committee on Bioethics, "Ethical Issues with Genetic Testing in Pediatrics," *Pediatrics* 107, no. 6 (2001): 1451-55.

4. L.B. Andrews et al., *Assessing Genetic Risks: Implications for Health and Social Policy* (Washington, D.C.: National Academy Press, 1994).

5. American College of Obstetricians and Gynecologists, "ACOG Committee Opinion 410: Ethical Issues in Genetic Testing," June 2008, at <http://www.acog.org/-/media/Committee%20Opinions/Committee%20on%20Ethics/co410.pdf?dmc=1&ts=20120529T1309427522>.

6. American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors, "Points to Consider: Ethical, Legal and Psychosocial Implications of Genetic Testing in Children and Adolescents," *American Journal of Human Genetics* 57, no. 5 (1995): 1233-41.

7. National Institutes of Health, National Human Genome Research Institute, "Final Report of the Task Force of Genetic Testing," September 1997, at <http://www.genome.gov/10001733>.

not confronted with a decision about abortion based on prenatal medical information, and those who choose to terminate a pregnancy based on a positive test result generally do so because of the devastating nature of their child's disease. Every parent who engages in prenatal whole genome

sequencing, on the other hand, will suddenly be faced with medical information about their future child, prompting and perhaps altering decisions about the threshold for considering termination. The anxiety and pressure that parents might feel as a

result of these decisions could be immense and extremely distressing.³³

Reproductive decisions are complex and very personal. Potential parents have different views about the kinds of medical conditions that they would be willing or able to watch their child experience, and how much

disease risk they believe a child can or should tolerate. If whole genome sequencing helps parents make these difficult choices by giving them access to more information, then it is a useful new reproductive technology. On the other hand, to the extent that some decisions to terminate pregnancies based on this kind of information represent confusion or a lack of complete understanding, the dissemination of this information would be problematic.

This latter concern would be exacerbated by an extemporaneous adoption of prenatal whole genome sequencing. Without carefully obtained data about its use and effects, the training of clinicians, and thoughtful deliberation about the amount and types of prenatal information that should be provided to parents, adopting this type of genetic testing risks influencing reproductive decision-making in inappropriate ways. One worry would be that inexperienced providers would give information to parents haphazardly, leading them to make choices based on confusion and anxiety rather than on their values and goals. It would be concerning if a disconnect between the expectation of carrying a perfect baby and the imperfections any child's genome will reveal has an undue influence on parents' reproductive decisions. For example, parents might choose to abort a child because it has been discovered to have an array of genetic variants—for example, fifteen VUS, eight susceptibility genes, and a condition of late onset—similar to the results that most healthy people would have if their genomes were sequenced.

We do not think that this concern necessarily justifies an absolute restriction on the use of whole genome sequencing; rather, our goal is to demonstrate the need for protections to ensure that the technology is incorporated appropriately and thoughtfully into clinical care.³⁴ Under an evidentiary adoption model, where proper education and genetic counseling are routine, most controversial

termination decisions should be kept to a minimum, mitigating the potential backlash and reducing the likelihood of undermining the useful benefits of the technology by political or moral disagreement.

The more the medical community deliberates about the kinds of decisions the technology might force parents to face, as well as the impact and meaning of genomic variants, the more prepared medical professionals can be to educate and support parents who are struggling with these complex choices. Concerns about the effect of prenatal whole genome sequencing on reproductive decision-making can be tempered, at least in part, by ensuring that any reproductive choice—to terminate a pregnancy or carry a child to term—is guided by clearly communicated information delivered by a trained genetic counselor. Data are needed to determine the extent to which the genetic counseling field could accommodate a high demand for such interpretation.

Mediating prenatal whole genome sequencing information through the medical community (although a necessary part of any acceptable use of the technology) is not without its own potential issues. Given the strong views people hold regarding abortion, this type of genetic testing could cause conflict and debate at the provider level as well. Especially early on in its adoption, medical professionals will likely have strong opinions about how helpful or harmful it is, as well as about what kinds of information ought to be disclosed or acted upon. For instance, some professionals today will not test a fetus for Huntington disease unless the family agrees to terminate the pregnancy if the child is found to be afflicted.³⁵ On the other hand, some professionals who are morally opposed to abortion may have concerns about giving parents the full range of information that the technology will produce for fear that the information will lead parents to make termination decisions. Disagreements about what

kinds of information parents ought to have access to will also occur; for instance, some parents might want to learn if their child will have genes associated with athleticism, while some physicians will likely feel uncomfortable providing such information to parents. This conflict is not new. Providers and patients have clashed over the issue of sex-selective abortion, for example. But with prenatal whole genome sequencing, the disputes could become much more common,³⁶ and the conflict could lead to heated arguments, a breakdown of doctor-patient trust, and in some cases, legal action.

Genetic Determinism

In addition to influencing reproductive decisions, whole genome sequencing could also have an impact on child rearing. Because current prenatal genetic tests only offer diagnostic information for serious medical conditions, parents' knowledge of the genetic information should not have any effect on whether the disease manifests in the child. Giving parents access to the wider categories of information generated via the new technology, on the other hand, has the potential to harm a future child in the form of parental expectations and self-fulfilling prophecies. For instance, in the case of nonmedical genetic markers, learning a child's predicted IQ before birth may affect familial expectations, which in turn could influence how the child is raised. If intellectual expectations are low, the parent might become more tolerant of poor academic outcomes. The resulting lack of parental encouragement and support could cause the child to fall below what his or her performance might have been without knowledge of the genetic associations.³⁷ Because children and parents today are largely unaware of the child's genetic aptitude for many concealed traits, some potential deficiencies may never recognizably manifest. Knowledge of this information

could lead to an erroneous acceptance of genetic determinism.

A similar concern relates to the theoretical risk of the “self-fulfilling prophecy” often discussed in the context of susceptibility genes. There is a worry that the anxiety caused by awareness of one’s susceptibility to a condition, as well as parental expectation for the disease to develop, might actually increase the likelihood of the condition manifesting in the child. Giving parents access to this information, however, also has the potential to benefit the child. As many susceptibility genes are influenced by the environment, parental awareness could also play a role in suppressing gene manifestation. For instance, if a child is known to be susceptible to lung cancer, parents can ensure that they do not smoke around the child and can make a special point of educating the child about the risks of smoking. Because the information prenatal whole genome sequencing generates might produce both harms and benefits in the context of child rearing, adequate justification is needed for providing parents with certain types of information.

The Conflict between Autonomy and Knowledge

Finally, the implications of utilizing whole genome sequencing prenatally can reach into that child’s adulthood. Although parents have a strong interest in obtaining information that informs their reproductive choices, there are questions, as we have argued, about the extent to which much of the data this technology produces will be of value to them. Meanwhile, the children, who might one day become autonomous adults, have a competing interest in not knowing certain kinds of genetic information about themselves.

The tension between these two interests is exacerbated by an existing asymmetry between the guidelines for genetic testing in children, which recommend safeguarding certain kinds of information until adulthood, and

prenatal genetic testing guidelines, which are more diffuse. Though parents usually have far-reaching authority to make choices on behalf of their children, the consequences that stem from removing children’s choices to remain uninformed about their genetic information have been deemed important enough to limit parental access.³⁸ Because of the risk of harms and loss of autonomy that can result from this knowledge, allowing parents to pursue genetic testing for their child is taken very seriously and is generally discouraged unless doing so would provide immediate benefit to the child or prevent later medical

complications.³⁹ In these cases, the benefit is thought to outweigh the risks.

Although this practice has limitations,⁴⁰ it remains the current paradigm for determining what genetic tests are appropriate to offer children. Relevant professional societies have created guidelines that generally recommend that clinicians safeguard children’s genetic information by discouraging any genetic test that would not provide benefit to children during their childhood. This has created a default whereby the standard of care is to delay nonbeneficial and nonactionable genetic testing until a child has had the opportunity to consent as an informed, autonomous adult.⁴¹ The guidelines for genetic testing in children are not completely parallel across organizations, but deferred testing represents a common trend (see Table 2).

In contrast to the testing guidelines for children, many prenatal genetic testing guidelines have not

consistently or thoughtfully considered the future autonomy of children. (The guidelines promulgated by ACOG and NSGC are notable exceptions to this trend.) Given the existing prenatal practice of targeted, risk-based testing, this is not surprising. Because the medical conditions revealed by these diagnostic tests are severe, recognizable, and often require treatment in childhood, children are unlikely to become autonomous adults without already having learned that they are affected by the conditions. As a result, decisions about whether they want to know their status for the specific

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genetic conditions tested for prenatally when they reach adulthood are irrelevant; granting parents prenatal access to this information, therefore, does not remove from children any options not to know their genetic information. Because targeted, risk-based tests do not raise this worry, parents are not forced to face trade-offs between acquiring information that may aid their reproductive decision-making and protecting the child’s future autonomy. Even if the child’s future autonomy were explicitly considered under this paradigm, however, the beneficial nature of the medical information and relevance for reproductive decision-making would justify the current testing.

As one moves away from the clear case of diagnostic tests for severe conditions, a tension arises between granting parents access to information that they feel will help in their decision-making (which might lead to the termination of the pregnancy) and safeguarding that same

information to protect their child's ability to control whether to learn about her genetic information (if the child is carried to term). Because these two interests are in conflict, it is very important to ensure that the information given to parents will actually be helpful in making reasonable reproductive decisions, so as not to violate the child's future autonomy without proper justification (see Table 1).⁴² Without careful deliberation about how best to implement prenatal whole genome sequencing, the current guidelines for prenatal genetic testing will likely be used to determine its appropriate use. As many guidelines for prenatal genetic testing have yet to address the future autonomy of the child, they are unlikely to serve as adequate gatekeepers to restrict the dissemination of prenatal information to parents. As such, specific guidelines should be developed to address the kinds of information that should be given to parents and how parents should be informed about the tradeoffs they are making.

Recommendations

Many considerations should be taken into account in making decisions about how to incorporate prenatal whole genome sequencing into clinical practice. The ability to make informed reproductive choices is of paramount importance, but given the potential harms we identified above, care should be taken to ensure that there is enough evidence of benefit to justify using this technology. We offer four preliminary conclusions.

First, different kinds of genetic information have different levels of relevance for reproductive decision-making. Only some of the information prenatal whole genome sequencing generates will be relevant to the vast majority of parents, and it will be important for the medical community to clearly articulate the default, or recommended, categories of information that should be offered to parents. Public dialog may help identify the defaults. Clearly, though,

diagnostic information for serious medical conditions is one of the most important kinds of information that a prospective parent might want to know, but some other information the technology produces has a more obscure relationship to health and quality of life. Moreover, even though some parents might view that information as initially relevant, receiving the information all at once (especially when the technology is first being introduced) might produce anxiety and confusion that could complicate, rather than support, parental reproductive decision-making. Parents should not be precluded from requesting any category of information, but a choice to deviate from standard practice should be accompanied by careful counseling to mitigate the potential harms discussed above.

Second, to the extent that the medical profession and society are committed to safeguarding the born child's option "not to know" on the basis of her potential to become a fully autonomous adult who could be harmed by having this option removed, they should similarly be committed to protecting this option for children prenatally (see Table 1). In our view, the future autonomy of a child may be prenatally breached only if the information is clearly useful for the parents or can improve health outcomes in the child. It remains to be seen under what circumstances prenatal whole genome sequencing will meet these criteria. We recommend that relevant professional societies revise their prenatal testing guidelines to ensure that their recommendations are sufficient and appropriate for next generation sequencing technologies.

Third, as we have indicated throughout this paper, more data are needed to guide the deliberation of professional societies and the public. Research on three topics in particular would enhance the discussions:

1) *The kinds of information that parents find relevant to reproductive decision-making.* Given the new kinds of genetic information that will be made

available by prenatal whole genome sequencing, what are the categories of information that parents find relevant for reproductive decision-making? How do the amount and type of information affect their preferences and choices? Will having access to this information complicate or help them make reproductive decisions? Such data would be very helpful in shaping general recommendations about how best to use the technology, particularly in formulating the default set of findings that should routinely be offered as the standard of care.

2) *The likelihood that prenatal disclosure of genetic information will harm or benefit children, and the potential magnitude of such harms or benefits.* The intensity and prevalence of the harms incurred by learning genetic information before adulthood—where there are such harms—ought to play a large role in determining how to recommend safeguarding the information, particularly if the information is of marginal usefulness to parents.

3) *How health care systems should accommodate the adoption of prenatal whole genome sequencing.* What should the prenatal clinical interaction look like as we incorporate whole genome sequencing, and specifically, how should this large amount of varied genetic information be conveyed to parents? Who will be responsible for relaying the information? How will parents be educated? What kinds of institutions or clinicians will offer this technology? Can the field of genetic counseling accommodate a potentially high demand for it? To evaluate the ethics of its use, it will be important to understand the context in which it would be used.

As these data emerge, our final recommendation is that professional societies play an active role in educating clinicians on how whole genome sequencing differs from traditional prenatal genetic tests, and on how to educate parents about the tradeoffs involved in choosing to engage in it. Parents should be informed of the risks to themselves and their children

before they undergo prenatal whole genome sequencing. It will be important for professional societies to generate recommendations about how clinicians can communicate these concepts to parents in a thoughtful way that helps them make the best decision for their families.

Disclaimer

The opinions expressed here are our own and do not reflect the policies or positions of the National Institutes of Health, the U.S. Public Health Service, or the U.S. Department of Health and Human Services.

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2. Common problems that have been enumerated range from the complexities of informed consent to the availability of genetic counseling resources and the difficulties in maintaining privacy. See T. Caulfield et al., "Research Ethics Recommendations for Whole-Genome Research: Consensus Statement," *PLoS Biology* 6, no. 3 (2008): e73; J.A. Robertson, "The \$1,000 Genome: Ethical and Legal Issues in Whole Genome Sequencing of Individuals," *American Journal of Bioethics* 3, no. 3 (2003): 35-42; A.L. McGuire, T. Caulfield, and M.K. Cho, "Research Ethics and the Challenge of Whole-Genome Sequencing," *Nature Reviews Genetics* 9, no. 2 (2008): 152-56; K. Ormond et al., "Challenges in the Clinical Application of Whole-Genome Sequencing," *Lancet* 375 (2010): 1749-51.
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14. See P. Sebastiani et al., "Retraction of Sebastiani et al.," *Science* 333 (2011): 404.
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sequencing. However, without a clear commitment discouraging such disclosures, we cannot assume that this information will be withheld from all or most parents. This might be of a particular concern in this category given that this information might be disseminated to parents whether or not the parents were initially interested in receiving it. See E.A. Ostrander, H.J. Huson, and G.K. Ostrander, "Genetics of Athletic Performance," *Annual Review of Genomics and Human Genetics* 10 (2009): 407-429; J.R. Garcia et al., "Associations between Dopamine D4 Receptor Gene Variation with Both Infidelity and Sexual Promiscuity," *PLoS One* 5, no. 11 (2010): e14162, DOI: 10.1371/journal.pone.0014162; K.E. Burdick et al., "Genetic Variation in DTNBP1 Influences General Cognitive Ability," *Human Molecular Genetics* 15, no. 10 (2006): 1563-68.

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28. Future work might further subdivide this category, but that level of analysis is beyond the scope of this paper.

29. Other important goals might be to eliminate certain health conditions, prepare for a child with special needs, or improve health outcomes for the child.

30. Only a portion of these fifty-six disease-associated variants rose to a level of clinical significance that justifies returning the results to the subjects. B.D. Solomon et al., "Incidental Medical Information in Whole-Exome Sequencing" *Pediatrics* (in press).

31. One cause of parental anxiety is that some genetic information discovered in the child may have implications for the health status of the parents. This will likely not be expected and could add additional stress. Though this already happens with current prenatal genetic testing, the amount of information will make these kinds of discoveries more common. Rothman, *The Tentative Pregnancy*.

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40. Some have argued that requiring children to wait until adulthood to receive certain genetic tests creates a bias toward children who prefer not to know their genetic information in the future, as opposed to children who reach adulthood wishing that they had learned their genetic information in childhood. The preferences of the latter group, it is argued, are not upheld in this paradigm. Though we agree that this is a valid concern, we endorse the current standard of care because we think the potential for harm is greater for people whose decision is removed compared to people whose decision is delayed.

41. We acknowledge that guidelines are not binding, and that they are not always followed precisely. Nevertheless, they represent an important articulation of widely accepted norms and serve as a touchstone that shapes the standard of care.

42. Though termination is theoretically the largest infringement on the autonomy of a fetus, we are concerned in this article with the autonomy of already born children. Hence, we are setting aside the complicated question whether fetuses have interests and simply address whether giving parents access to certain prenatal information could harm the interests of the child after it is born.

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