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# Whole-Genome Sequencing and Disability in the NICU: Exploring Practical and Ethical Challenges

Michael J. Deem, PhD

abstract

Clinical whole-genome sequencing (WGS) promises to deliver faster diagnoses and lead to better management of care in the NICU. However, several disability rights advocates have expressed concern that clinical use of genetic technologies may reinforce and perpetuate stigmatization of and discrimination against disabled persons in medical and social contexts. There is growing need, then, for clinicians and bioethicists to consider how the clinical use of WGS in the newborn period might exacerbate such harms to persons with disabilities. This article explores ways to extend these concerns to clinical WGS in neonatal care. By considering these perspectives during the early phases of expanded use of WGS in the NICU, this article encourages clinicians and bioethicists to continue to reflect on ways to attend to the concerns of disability rights advocates, foster trust and cooperation between the medical and disability communities, and forestall some of the social harms clinical WGS might cause to persons with disabilities and their families.



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Whole-genome sequencing (WGS) has emerged as a powerful diagnostic tool for uncovering previously unknown gene-disease associations and establishing the genetic etiology of undiagnosed conditions in individual patients.<sup>1-5</sup> The time and monetary costs required to sequence an entire human genome continue to decrease, making the implementation of WGS in clinical practice increasingly feasible. Many researchers and clinicians believe that clinical WGS will lead to faster diagnoses and better management of care.

WGS also gives rise to challenging practical and ethical questions. This is especially the case with respect to the increasing use of WGS for therapeutic guidance in the NICU.<sup>6-8</sup> Families and health care professionals frequently face difficult decisions about the appropriate clinical management of neonates who have profound disabilities, especially when clinicians encounter difficulties in diagnosing these conditions. Sometimes WGS can provide a genetic diagnosis for these neonates and lead to a more precise prognosis for survival and outcomes of available treatment options. However, several disability rights advocates have expressed concern that the clinical use of genetic technologies may reinforce and perpetuate stigmatization of and discrimination against disabled persons in medical and social contexts.<sup>9-11</sup> There is growing need, then, for clinicians and bioethicists to consider how the clinical use of WGS in the newborn period might exacerbate these potential harms to persons with disabilities.

This article explores ways to extend some of the concerns of disability rights advocates to clinical WGS in neonatal care. By considering these concerns during the early phases of expanded use of WGS in the NICU, I hope to encourage clinicians and bioethicists to continue reflecting on

ways to foster trust and cooperation between the medical and disability communities, and to forestall some of the social harms clinical WGS may cause to persons with disabilities and their families.

### DISABILITY CRITIQUES OF PRENATAL GENETIC TESTING

The offer of prenatal genetic testing (PGT) during pregnancy is becoming a standard aspect of perinatal care. With the advent of noninvasive modes of testing, such as MaterniT21,<sup>12</sup> NIFTY,<sup>13</sup> and direct-to-consumer tests that can also provide information about fetal gender in the early stages of pregnancy, we can expect even greater uptake of PGT in the near term. PGT's primary function is the identification of genetic and chromosomal abnormalities in developing fetuses, and it is widely held that this information can augment patient autonomy and reproductive choice. Although many laud the apparent benefits of PGT, this testing is also an area of deep contention between providers of genetic services and many disability rights advocates.<sup>14,15</sup>

Some disability rights advocates maintain that the routine use of PGT has had negative effects on the disability community. It has, they contend, led to further stigmatization of and discrimination against persons with certain kinds of disabilities. Although the details of disability rights critiques of PGT vary, 2 common themes emerge. One theme is that the offer of PGT to pregnant women is a tacit recommendation that pregnancies should be terminated if the fetus is diagnosed with certain genetic disorders.<sup>16-18</sup>

On this view, the targeting of specific disabilities has the consequence of separating and labeling some fetuses and pregnancies as "abnormal," thereby increasing the likelihood of social stigmatization and marginalization of persons who

are born with these disabilities. A second theme is that decisions to terminate pregnancy after detection of fetal abnormality express a negative and hurtful message about disability and the value of persons living with prenatally diagnosable conditions.<sup>19,20</sup> Selective termination for disability, it is argued, sends a twofold message to disabled persons. First, it expresses a view of persons with genetic disorders as reducible to a single undesirable trait. Second, it suggests that it would have been better had their birth been prevented.

Several philosophers and bioethicists have engaged in important debates over the philosophical merits of disability critiques of PGT.<sup>21-24</sup> Rather than rehearse those arguments here, it is worth considering the extent to which the historically close association between PGT and selective termination for disability has affected persons living with disabilities and their families. Many families of children with prenatally diagnosable conditions report feeling subject to negative social attitudes on account of their decisions not to terminate pregnancy. The remarks of Patricia Bauer, a mother of a child with Down syndrome, are representative of these families' concerns:

More and more these days, we parents of people with genetic anomalies are being called to account by the well-tested public for our reproductive choices and our lives. . . . "Didn't you have *the test* [emphasis added]?" someone asks, eyeing our child's face with a raised eyebrow that seems to betray surprise, curiosity, disapproval. . . . Wouldn't it have been better, we hear the questioners asking, if this person didn't exist?<sup>25</sup>

The influence of social expectations of selective termination after PGT can affect the perspectives of health care professionals and bioethicists as well. Dena Davis, for example, attests to the impact of these social expectations on her intuitive

response to children with prenatally diagnosable disabilities:

In my own mind I can discern a subtle shift in the way in which I view people with certain anomalies. Twenty years ago, seeing a woman in the supermarket with a child who has Down syndrome, my immediate reactions were sympathy and a sense that that woman could be me. Now that testing for Down syndrome is virtually universal in the United States, when I see such a mother and child I am more likely to wonder why she didn't get tested.<sup>26</sup>

## DISCONNECTING DIAGNOSIS AND DECISION

What explains the pervasiveness of the social perception that a decision for selective termination should follow a positive PGT result? The circumstances surrounding the initial introduction of PGT into perinatal care may provide a partial answer. When PGT was originally presented to the medical community, some clinicians touted it as both a diagnostic test and as a determinant of a specific medical outcome in the event of a positive test result. Strong emphasis was placed on PGT's value as an aid for decisions about whether to terminate pregnancies in which genetic or chromosomal abnormalities are detected.<sup>27</sup>

The early association of PGT with selective termination reverberates in genetic counseling today.<sup>28-30</sup> Genetic counselors have recognized the negative social consequences of the historical association of PGT and selective termination, and many have initiated important efforts to recover lost trust between clinical genetics practice and the disability community.<sup>31,32</sup>

Now, the traditional connection between PGT and selective termination does not imply that medical genetics is solely responsible for social harms to the disability community brought in the wake of PGT. An argument could be made that social biases and discriminatory attitudes toward disability existed

before the routine use of PGT, and that the early medical association between PGT and selective termination simply reflected those prevailing public attitudes toward disability. Whatever the case may be, it is important to consider what clinicians and bioethicists who advocate for the expansion of clinical WGS can learn from PGT and selective termination. But before we can answer this question, we need to ask what, if any, analog there is between WGS of newborns, on the one hand, and PGT followed by selective termination, on the other. A good candidate is the initiation of palliative care in newborns after a molecular diagnosis via WGS. Like the various modes of PGT, WGS is a powerful diagnostic tool, and the data it generates will likely have a significant effect on the management of patient care in the NICU. Just as the early association of PGT with selective termination played a significant role in shaping public attitudes toward prenatally diagnosable disability, the social impact that routine use of WGS in the NICU will have on the disability community will turn, in part, on the way in which health care professionals portray and promote its clinical function.

In contrast to the initial implementation of PGT, the current expansion of WGS has not yet been closely linked to a redirection toward palliative care after molecular diagnosis. In the medical literature, however, there are discussions of palliative care being one possible option after a molecular diagnosis by WGS. There also is discussion of particular cases in which WGS may have factored in decisions to redirect management of care toward palliation.<sup>6,33</sup> Although these early discussions do not tightly link WGS with palliative care, we should nonetheless consider carefully how the portrayal of diagnostic WGS as a tool for determining whether

to withdraw aggressive medical interventions and initiate palliative care in newborns might reinforce negative social attitudes toward disability.

One must, of course, delineate cases in which introducing palliative care as an option to families after receiving a molecular diagnosis via WGS is appropriate. For example, there may be cases in which a newborn is suffering unremitting pain, and additional cure-oriented interventions exacerbate that suffering or have a very low probability of improving the outcome for that child. WGS may provide a definitive or likely diagnosis where conventional clinical diagnostic methods failed, providing families with the knowledge and closure they need to accept their child's terminal prognosis. The ability to explain to families the genetic etiology of a terminal condition may aid health care professionals in providing compassionate counseling and additional support to families, where uncertainty would have otherwise placed obstacles.

How, then, can we portray WGS in the NICU in a way that is conscious of the concerns of the disability community? We should be careful to portray clinical WGS for what it really is: a diagnostic tool that has the potential to play an important informative role in determining proper clinical management of acutely ill newborns. Again, a useful comparison can be made with PGT. Despite the fact that PGT is frequently used today for several other ends, for example, to plan perinatal interventions, to initiate perinatal palliative care, and to help prepare families emotionally and psychologically for caring for a child with diagnosable disabilities, selective termination has largely crowded these benefits out from public perception. WGS may impact individual patient care in a number of possible ways, including, but

hardly limited to, the initiating of palliative care where appropriate. When our general discussions of WGS expressly link it to palliative care, we risk similarly obscuring several potential benefits WGS delivers to individualized care. Moreover, by stressing that WGS might be a cost-effective way of moving more quickly to comfort care, health care professionals might reinforce the idea that disability is a costly drain on medical and societal resources.

The medical portrayal and social reception of PGT, then, provides us with important lessons for presenting to the public the rapid advance of diagnostic WGS in the NICU. We should not only be cautious with respect to how we characterize the benefits of WGS, but also consider how associating WGS in the NICU with redirection to palliative care might implicitly communicate a harmful message to disabled persons and their families, potentially fueling distrust toward the use of genetic technologies in clinical care.

## MISINFORMATION AND INFORMATIONAL OPACITY

The preceding discussion of disability critiques of PGT connects to another major concern that disability rights advocates express regarding prenatal screening. Some have argued that the routine use of screening in perinatal care largely depends on misinformation about the lives and experiences of children with disabilities and their families.<sup>34–36</sup> This misinformation is thought to be rooted in the widely held assumption that life with profound disability is inherently tragic, laden with relentless suffering and frustration for both the disabled child and the family. Routine testing of fetuses for genetic and chromosomal anomalies takes place, it is argued, because of the persistent belief that a life with the associated diseases and disabilities either is not worth living

or places an extraordinary burden on caretakers.

This concern is not without grounds. Empirical studies of parents' perspectives of prenatal screening suggest that information provision to families about the capacity and accuracy of detection of fetal abnormalities remains inadequate, and some families of children with prenatally diagnosed disabilities report that genetic counseling provided little or no information about the quality of life for children with disabilities and their families.<sup>28,37–40</sup> Concern that misinformation about disability erodes responsible medical decision-making arises not only from routine prenatal screening. Indeed, disability rights advocates point to cases in neonatology, pediatrics, and end-of-life care in which assumptions about the quality of life of persons with profound disabilities may be responsible, at least in part, for families' and clinicians' decisions to discontinue life-sustaining interventions.<sup>41</sup>

The expansion of WGS in the NICU almost certainly will compound the difficulties involved with ensuring that decisions about the clinical management of newborns with profound disabilities are informed and responsible. WGS yields an immense amount of data that must be analyzed and interpreted to provide potential benefits to clinical care. The sheer volume of raw genomic data presents tremendous challenges to the effective communication of their potential clinical significance to clinicians and to the clinical counseling of families of ill neonates. Here I will focus on 3 such challenges, all of which involve informational opacity in the interpretation and transmission of genomic information.

In one of the first explorations of the implications of routine use of WGS in the NICU, Stephen Kingsmore and Carol Saunders lamented the lack of a clinical-grade general

database of identified variant-disease associations, which analysts and clinicians could refer to after performing WGS on ill newborns.<sup>42</sup> A half-decade later, no such a database is available, although there is reason for optimism. ClinVar, for example, is a publicly accessible database that aggregates reported data on variant-disease associations.<sup>43</sup> This aggregation of data, however, depends on the initiative of clinical laboratories to report novel findings and interpretations, and the accuracy of these data may vary widely. Until there is a clinical-grade general database available to analysts and clinicians, as well as broadly accepted methods for standardizing interpretations of sequence variants, it will remain a challenge to ensure that clinicians are sufficiently familiar with and have ready access to the most recent emerging data about variant-disease associations and their clinical significance.

The absence of a general database and accepted standards of interpretation leads to a second complication in providing appropriate post-WGS counseling to families. Before it can provide guidance to decision-making about the clinical management of ill newborns, the diagnostic information that WGS yields first passes through multiple levels of interpretation. Genomic data are initially analyzed and interpreted by genetic analysts and clinical laboratories, with one possible outcome being the identification of variants that are clinically actionable. Discrepant interpretations of the clinical significance of identified sequence variants, however, are common, even when it comes to well-studied genes and genome regions.<sup>44,45</sup> Interpretive discrepancies at this level can undermine high-fidelity transmission of information about the clinical utility of sequence variants from analysts to clinicians, as well as lead

to differential return of results in clinical practice.

Varying degrees of genetic literacy among clinicians can also affect the handling of diagnostic information from WGS. Clinicians are not merely passive recipients of genomic information returned by analysts but must interpret how this information will guide clinical management. They also must determine ways to translate and effectively communicate this information to families making decisions about care. Although some clinicians have training in genetics or genomic medicine, many physicians feel they are unfamiliar with clinical applications of genetic technologies in medical care.<sup>46-48</sup> The general level of genetic literacy among clinicians in the NICU specifically is difficult to ascertain. What is clear is that the rapid advance of genomic technologies in clinical care will increasingly demand of neonatologists a firm grasp of the risks and benefits of WGS, and an ability to communicate and tailor complex, personalized genomic information to individual families.

It is important for clinicians to consider how these forms of informational opacity complicate their counseling of families in the NICU. Collective steps can be taken to correct misinformation that may impact decision-making about the care of newborns with disabilities. To reduce and resolve discrepant interpretations of sequence variants between clinical laboratories, health care professionals and associations can promote greater adherence to, and greater cohesion between, professional guidelines for standardized reporting of sequence variants and their interpretation.<sup>49</sup> Increased data sharing and cooperation among laboratories should also be encouraged. To further augment genetic literacy within the NICU, hospitals and clinics might continue expanding opportunities

to provide genetics and genomic education through professional webinars and continuing education opportunities for staff.<sup>50,51</sup>

If disability rights advocates who point to the troubling role uncritical assumptions about disability play in the clinic are correct, then it appears that clinical counseling before and after WGS can suffer from an additional source of misinformation. Whereas informational opacity will likely dissipate as data sharing expands across analysts and clinical laboratories, clinicians can more directly control the flow of misinformation from assumptions about disability and quality of life. Implicit biases against disability can impact the manner in which health care professionals counsel families of neonates with profound disabilities, especially in cases in which novel genetic variants are identified and no reliable data set on which to base predictions of phenotypic expression exists. An important step toward mitigating the negative effects of possible bias, even in these cases, is to consider the extent to which counseling is informed by the actual perspectives and reported experiences of members of the disability community and their families. Another worthwhile measure is to increase direct interactions between the medical and disability communities through the inclusion of disabled persons or disability rights advocates on research review boards and hospital ethics committees.<sup>52</sup>

It should be noted that there may be cases in which WGS provides a definitive, terminal diagnosis for neonates with profound disability, and the recommendation of palliative care to families is appropriate. Even in these cases, when clinicians strive to inform the counseling with the perspectives of disabled persons and their families, they show respect not only for the interests and concerns of

the disability community but also for their patients and their families.

## DOWNSTREAM EFFECTS ON PERSONS WITH DISABILITIES

Because WGS provides rapid, simultaneous testing of nearly all of a patient's genes, clinical WGS will routinely uncover multiple sequence variants whose relation to diagnostic indication is uncertain. In some cases, clinicians may have sufficient data for assessing risks for the development of other diseases or disabilities. In other cases, findings might be broadly classified as variants of unknown significance or as likely benign, and clinicians accordingly would not consider them to be clinically actionable at the time of sequencing.

Much of the current debate over the management and reporting of these incidental findings centers on questions about the timing and appropriateness of returning this information to patients and research subjects after genomic sequencing.<sup>53-56</sup> With respect to addressing specific ethical challenges that incidental findings pose to acquiring informed consent from patients or their families, the focus of clinicians and bioethicists tends to converge on a common set of issues. These include the patient's or family's preferences about which results will be returned, their understanding of the risks posed by routine data sharing and storage to their confidentiality and privacy, and their attitudes toward future use of genomic data and recontacting.<sup>57-60</sup> But another important consideration, which has attracted comparatively less attention in the literature, is how diagnostic results from WGS could affect a patient's access to certain medical interventions in the future. These results include definitive or likely diagnoses, as well as incidental findings.

What effects could diagnostic results from clinical WGS have on future medical care for persons with disabilities? Given the novelty of clinical WGS and the relatively small sample of cases in which its implications for future care have played out, it is difficult to predict precisely what the downstream effects will be. But perhaps a representative example of how disability presently results in differential access to medical interventions can provide some ground for speculation. Persons with disabilities are sometimes viewed as poor candidates for particular medical interventions. A familiar example is the denial of organ transplantation for persons with certain genetic disorders, such as trisomy 21 and cystic fibrosis. Some medical centers view these persons as poorly suited for transplantation. Although continual advances in the medical and social care of persons with trisomy 21 and cystic fibrosis have led to longer life expectancies and, in many cases, greater independence for persons living with these conditions, the question of whether a scarce medical resource such as a heart or lung should be provided to persons with these disabilities remains open among clinicians and bioethicists.<sup>61,62</sup> Clinicians often base decisions about transplantations for persons with these disabilities on objective considerations, such as the probability of a good outcome or increased risk of malignancy associated with certain genetic conditions. But members of the disability community may object to the continuing role that clinicians' assessments of quality of life or degree of functional independence play in determining who will receive precious medical resources, particularly if such assessments do not draw from the perspectives and experiences of persons and families living with these conditions.

We might also consider a recent case report from the Medical College of Wisconsin that documents how clinicians together with a family arrived at a decision against providing a potentially life-extending liver transplant to an acutely ill infant with a diagnosed genetic disorder.<sup>63</sup> The report describes the detection of *TWINKLE* gene mutations through next-generation sequencing. The infant presented with fulminant acute liver failure, and clinical evaluation suggested mitochondrial DNA (mtDNA) depletion and possible seizure activity. Next-generation sequencing revealed recessive *TWINKLE* mutation. Clinicians determined that long-term prognosis was poor, given the infant's mtDNA depletion and a previously established association between *TWINKLE* mutations and development of intractable epilepsy in older children and young adults. In consultation with the infant's parents, a decision against liver transplantation was reached, and she died of multiorgan failure and sepsis at 6 months of age. What remains unclear is how much weight the clinicians gave to the probable development of neurologic deterioration in reaching this decision. The report states: "Given the abnormal neurologic examination and sequence-based confirmation of a primary mtDNA depletion disorder and previous published experience, a decision was made that [the infant] would not be an appropriate candidate for liver transplantation." Some may worry that the decision against transplantation was reached largely on account of the possibility of development of a particular neurologic disability, namely intractable epilepsy, without consideration of the reported perspectives of persons living with that disorder.<sup>64</sup> In fairness to the clinicians, we cannot reasonably conclude that these perspectives did not inform the clinicians' views.

Nor do we have grounds to deny that the decision resulted from data about poor outcomes after liver transplantation in patients who had other forms of mtDNA depletion accompanied by neurologic disorder.<sup>65</sup> But the report's omission of such considerations taking place might lead some to worry that the prospect of profound neurologic disability primarily drove the decision against transplantation.

Generalizing from these examples, we can anticipate how diagnostic information from clinical WGS could impact future clinical management for persons with genetic disorders. It is well known that definitive or likely diagnosis of genetic disease can impact present and future clinical management of acutely ill newborns, including the potential restriction of access to scarce medical resources. But how might incidental findings that are not related to diagnostic indications or that are not considered to be clinically actionable impact that management? In cases in which WGS uncovers sequence variants that are currently associated with later development of certain disabilities, similar restriction may be possible. But this situation may also be true of cases in which WGS uncovers variants of unknown clinical significance. As clinical application of WGS increases, we can expect a significant expansion of clinical genomic databases such as ClinVar and data sharing between clinical laboratories. Analysts and clinicians will likely have wide accessibility to up-to-date analyses of identified sequence variants, including analyses that will potentially result in future emendations to current interpretations of the clinical significance of detected variants. Some incidental findings presently classified as variants of unknown significance might later be associated with particular disorders or be considered clinically actionable. That possibility generates considerable

uncertainty over how the outcomes of genomic analyses will play out in the long term for newborns receiving WGS.

The potential impact that WGS will have on a newborn's future medical management complicates the clinician's task of ensuring that parental consent for testing is properly informed. Parental understanding of how diagnostic results might impact medical management is crucial to informed, responsible decisions about whether a child should receive WGS. Clinicians cannot rule out the possibility that incidental findings will have negative downstream effects on patients' future medical care. Insofar as understanding the potential risks associated with WGS is a requirement for consent to be truly informed, clinicians who recommend WGS for ill newborns should counsel families not only about how the genomic information will be managed but also about the possibility that this information will have downstream effects on their child's future options for clinical management. Part of appropriate clinical counseling, then, will involve informing parents that the clinical utility of uncovered variants may change over time, and that one implication of this change could be restriction of their child's access to scarce medical resources.

A more robust consent process, however, will likely have the effect of slowing the rate of WGS uptake. But these challenges to acquiring or approximating informed parental consent for WGS present an opportunity for advocates of clinical WGS to align their interests with those of disability rights advocates. Assuming that the uncertainty surrounding the downstream effects of WGS will affect WGS uptake, clinicians who wish to see greater uptake of WGS in the NICU might consider advocating for the inclusion of disability perspectives into decisions about appropriate medical

interventions and the allocation of scarce medical resources for persons with genetic disorders. Before routine clinical WGS was even on the horizon, Adrienne Asch suggested that such advocacy could have wide-ranging practical implications:

If the disability community correctly perceives the dominant [social] view to be one that questions whether a life with disability can be rich enough to warrant access to scarce medical resources, then physicians and bioethicists who become sensitized to the disability perspective may do a lot to educate the rest of society on these issues.<sup>34</sup>

The voices of clinicians have a powerful influence on the shaping of attitudes in the hospital and among the wider public. Not only might such advocacy signal to the disability community that their interests are being taken seriously by the medical community, but it also might signal to parents of acutely ill newborns that members of the medical community are working to remove some obstacles that persons with disabilities face in gaining access to certain medical resources.

### CONCLUDING REMARKS

Clinical WGS promises to enable swifter diagnosis and improved care for acutely ill newborns in the NICU. But, as I suggest in this article, these are not the only marks according to which the success of clinical WGS should be measured. The extent to which clinicians and bioethicists attend to the concerns that the disability community expresses over the impact of medical genetics on persons with disabilities will determine, in part, the success of WGS programs from practical and social standpoints.

Attending to these concerns need not be a limiting factor on the use and expansion of clinical WGS. By actively soliciting and compassionately listening to the real experiences and perspectives of disabled persons and their families, clinicians and

bioethicists might rebuild bonds of trust between the medical and disability communities. But, perhaps just as importantly, sensitivity to these concerns could improve care in the NICU. Many of the patients who receive clinical WGS in the NICU have or will develop profound disabilities. Awareness of and sensitivity to the experiences of persons living with disabilities may help clinicians provide better individualized care and more effective counseling to families of acutely ill newborns who receive WGS. This, in turn, might have the effect of furthering the goals of both advocates of clinical WGS and disability rights advocates.

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### ABBREVIATIONS

mtDNA, mitochondrial DNA; PGT, prenatal genetic testing; WGS: whole-genome sequencing

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