Neonatologists' Attitudes About Diagnostic Whole-Genome Sequencing in the NICU

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abstract

Using focus group methodology, we studied the attitudes of neonatologists regarding diagnostic rapid genome sequencing for newborns who were critically ill in a NICU. One focus group took place within the first year after whole-genome sequencing testing became available, and another focus group took place 3 years later. Focus groups were audiotaped, transcribed, and analyzed by using standard techniques of grounded theory. Different analysts coded them for themes. The analysts then discussed differences and agreed on major themes. Twelve doctors participated in the first focus group, and 9 doctors participated in the second; 62% were attending physicians, and the rest were fellows. There were 14 women and 7 men. We did not collect any other demographic information on participants. Surprisingly, we found few differences between the earlier focus group and the later one. Comments were categorized as falling into 4 domains: (1) uncertainty about the interpretation of results, (2) issues about parental consent and limits on their right to know genomic information, (3) different opinions about whether and how genomic results could be clinically useful, and (4) potential harms of genomic testing.

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Genomic sequencing (GS) is a powerful tool that is in need of a useful application. One area in which it is thought to have promise is in the diagnosis of rare diseases among infants in NICUs who are critically ill. After all, many infants have congenital anomalies and/or genomic syndromes that are rare and difficult to diagnose. Approximately 7% of stillborn infants and 0.5% of live-born infants have a chromosomal abnormality.[1] Approximately 3.5% of all infants have a congenital malformation.[2] Infants with genetic disorders are at a high risk for mortality. Between 20% and 30% of all infant deaths are due to genetic disorders.[3] Congenital malformations, many with a genetic etiology, account for 30% to 50% of postneonatal deaths.[4] Diagnosing these diseases earlier could lead to effective treatment in some. Alternatively, it might end a diagnostic odyssey and lead to earlier redirection of care toward palliation rather than life prolongation.

GS may be more efficient than other forms of diagnostic testing. GS allows doctors to test for not just 1 or a dozen genetic variants but every variation in the entire genome. GS testing should be more accurate and cost-effective and should generate results quicker than testing 1 gene at a time. The primary disadvantage of GS is that it inevitably generates a lot of ambiguous information that is difficult to interpret.

We wanted to understand how neonatologists thought about the trade-offs between the potential advantages and disadvantages of this new technology. We were fortunate to be at a center that was at the cutting edge of diagnostic GS. Thus, we were able to study neonatologists near the time when GS first became available as a clinical test. We then studied them again 3 years later to see if their views had changed.

METHODS

The study was conducted at Children's Mercy Hospital (CMH) in Kansas City, Missouri. CMH is a freestanding, 354-bed medical center. CMH provides comprehensive primary and tertiary specialty care to children from an ~189-county region in Missouri and Kansas. The NICU admits ~1000 infants per year. There are 23 attending physicians in neonatology and a fellowship program that has 9 fellows at a time (3 per year).

We invited all of the neonatologists and fellows to participate in two 90-minute focus groups about their attitudes and beliefs regarding whole-genome sequencing (WGS) in newborns. They were offered $100 to participate in the focus groups. One focus group took place within the first year after WGS testing became available. The other took place 3 years later. The focus groups were conducted by trained qualitative researchers. The discussions were audiotaped, transcribed, and analyzed by using standard techniques of grounded theory. Different analysts coded them for themes. The analysts then discussed differences and agreed on major themes.

RESULTS

Twelve doctors participated in the first focus group, and 9 doctors participated in the second; 62% were attending physicians, and the rest were fellows. There were 14 women and 7 men. We did not collect any other demographic information on participants. Surprisingly, we found few differences between the earlier focus group and the later one.

Comments were categorized as falling into 4 domains: (1) uncertainty about the interpretation of results, (2) issues about parental consent and limits on their right to know genomic information, (3) different opinions about whether and how genomic results could be clinically useful, and (4) potential harms of genomic testing.

Uncertainty About Interpretation

Clinicians were excited to have access to the additional information provided by WGS. They believed that this information could help them diagnose diseases and then treat their patients. However, there were several concerns about whether they themselves truly understood the genomic results and thus, whether they could effectively communicate the findings to patients. Two representation comments were as follows: "We're going to find things out that we're not sure what it means and we're going to suggest that it could mean something that it doesn't, at least until we know more." "How to interpret the stuff that nobody knows about including geneticists? We're finding deletions and changes that have never been reported before. So what do you do with that?"

The clinicians were worried that neither they nor the geneticists would be able to interpret many findings and that parents would be even more confused: "If I know what that information means, I can share it. But if I don't know what it means, I cannot just share it, throwing names and numbers at them, because it's going to confuse them and confuse me."

Clinicians felt overwhelmed by the sheer volume of information presented to them. One said, "It's almost like we have the capability to get more information than we know what to do with, than we know how to interpret, than we know what it means."

A related issue was whether the results were useful for either diagnosis or prognosis: "We don't want to be sounding like we're predicting the future. Because we don't know. I don't think there's

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a way for us to know. We might be predicting, we might give them the numbers, but there's no way for us to know."

Some results seemed more definitive than others: "If the results are positive, I think it is okay to make a decision based on that."

Physicians clearly struggle with interpreting results from WGS. They worry that their own lack of knowledge may reflect widespread lack of knowledge about the meaning of genomic results. They worry that the lack of knowledge may lead to difficulty in explaining results to parents and to parental frustration.

Parental Consent

The doctors in these focus groups were offering GS as part of a prospective randomized trial of the efficacy of such testing compared with standard genomic testing. Thus, the consent process for GS was part of the consent process for a research study. It may have been more detailed and rigorous than a typical consent for diagnostic testing in the NICU. The doctors nevertheless had concerns about whether consent was necessary and whether parents could be adequately informed. Clinicians noted that parents had to consent for genetic testing to be in the research study but did not have to consent for routine genetic testing, such as a microarray or a karyotype. Clinicians were unsure whether detailed consent ought to be required. One said that consent was essential and that parents alone should decide whether testing was appropriate or not: "We allow parents to make these decisions. Our job is to make sure parents are best informed, and then they make the decision."

Others thought that the decision belonged to the doctors: "Do you order genetic testing without talking to the parents? I think the answer is yes. We should inform the parents but we don't need to get their permission."

One made an analogy to mandated newborn metabolic screening: "Look at the newborn screen. You send the newborn screen without consent. And sometimes it comes with information that could change their life."

Usefulness of the Results

Physicians had different views about whether GS results were clinically useful in the sense of making a positive difference in the clinical care of a particular infant. Skeptics noted the following: "I have not personally made any big decisions based on the test results because the results came back and the patient was already improving. It took three or four days to come back." "I said okay, we'll do [GS] but it's not going to change my management."

Despite this skepticism about the value of diagnostic testing, many physicians thought that GS results could be useful in other ways. The most frequent response was that the test led to a diagnosis that was more definitive, which helped both doctors and parents make choices: "It has been really useful in a couple of kids. We actually made a diagnosis that kind of led to a decision that we felt was right for the patient."

Clinicians used the test results not only to make a diagnosis but also to formulate a treatment plan and as a tool to talk to parents. One said, "If we can give the family some definitive information about some of those situations then it helps us and helps them charge a course of what they think is best for their baby, and their baby's life."

All thought that the faster the results were returned, the more useful the test could be. One said, "Two times I have done it when the babies were very, very sick so the tests that I needed to know about were six to eight weeks to come back and I wanted to know something quickly."

Potential Harms

Although the potential benefits of WGS are immense, there also exists the potential for harms. One of the biggest concerns, voiced by several clinicians, was the potential for the information to be misused by outside parties. One said, "It has the potential of really being abused by third parties like insurance companies when these kids turn twenty and try to get insurance."

One clinician was concerned that if testing led to decisions to withdraw life-sustaining treatment, then it could be abused to advance a eugenic agenda: "It gets very concerning, if this test can be used to decide who deserves to live and who doesn't. If that becomes ending their life, then that becomes eugenics. You can get to very weird things, very scary things."

Another potential harm was the risk of receiving undesired information: "You might learn something that really may never create disease but creates a risk for disease, breast cancer, that sort of thing, and has a lot of implications forty years later. For a newborn, you kind of wonder… some families may not want to know that." "There are implications of finding things that you may not want to know. And how do you handle that?"

One doctor cited a case in which test results led to marital disharmony because 1 parent blamed the other for the child's illness: "A few families felt like genetic testing would contribute to assigning blame to one parent or the other. Not that we do that but that the family would or the extended family would."

CONCLUSIONS

Physician responses to the introduction of rapid GS as a clinical

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test clustered around 4 main themes: interpretation of results, parental consent, usefulness of the test, and potential harms. Many of these responses sound similar to concerns that have been raised about previous genetic testing modalities.[5,6] Concern about the meaning of test results dogged some of the earliest attempts to screen children for sickle cell disease.[7] They continue to be a concern regarding many tests that are on the newborn metabolic screening panel.[8]

WGS with rapid return of results raises the stakes regarding all of these issues. The key questions raised by these focus groups are the following: What sort of parental consent is appropriate before allowing a child to undergo GS? How can physicians be better educated to understand and communicate results? And how can we minimize the psychosocial harms that may result from testing? The clinical use of GS means that clinicians outside of the field of genomics will have to grapple with these issues more than ever.

ABBREVIATIONS

CMH: Children's Mercy Hospital
GS: genomic sequencing
WGS: whole-genome sequencing

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