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Parental Views on Expanded Newborn Screening Using Whole-Genome Sequencing

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abstract

BACKGROUND AND OBJECTIVE: The potential application of whole-genome sequencing (WGS) to state-mandated standard newborn screening (NBS) challenges the traditional public health approach to NBS and raises ethical, policy, and clinical practice issues. This article examines the perspectives and values of diverse healthy pregnant women and parents of children diagnosed with a primary immunodeficiency disorder about traditional NBS and expanded NBS with the use of WGS.

METHODS: We conducted 4 focus groups (3 in English and 1 in Spanish) with socioeconomically and ethnically diverse pregnant women ($n = 26$), and a comparison group with parents of children diagnosed with a primary immunodeficiency disorder ($n = 5$).

RESULTS: Pediatric policy-relevant themes that emerged from our analysis of the focus group data are presented within 4 categories: (1) perspectives on traditional NBS, (2) informed consent, (3) return of results, and (4) storage and retrieval of results. Analyses indicate that study participants desired greater inclusion in the NBS process. Despite an optimistic orientation to the potential benefits and limited harms likely to result from genomic applications of NBS, parents voiced concerns about privacy and control over test results. Limited trust in the medical system and the state-run NBS program informed these concerns.

CONCLUSIONS: Expanded NBS with WGS for pediatricians may require management of more genetic conditions, including mutations that convey risk to both the child and parents for adult-onset disorders, and an informed-consent process to manage the genomic data and storage of blood spots. Attention to how these technologies are understood in diverse populations is needed for effective implementation.



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The potential application of whole-genome sequencing (WGS) to standard newborn screening (NBS) challenges the traditional public health NBS paradigm, premised on the early identification of newborns at risk of a narrowly defined set of clinically actionable disorders. NBS with WGS has the potential to increase the number of disorders identified without significantly increasing the cost of screening.¹ Such screening would generate massive amounts of detailed genetic information about the child and potentially reveal genetic information about both the child and parents unrelated to childhood-onset diseases. Furthermore, because of the public health approach of traditional NBS, it has been practiced with an opt-out option but without requiring parental consent. The potential of NBS screening with WGS challenges this public health approach and raises many ethical, policy, and clinical practice issues.

This is not the first time that NBS has been challenged by technological advances.² Disagreement over the recommendation to expand the screening panel from 9 to 29 disorders with the advent of tandem mass spectrometry in the late 1990s³ revealed divergent views on the benefits of NBS, while also highlighting the influence of advocacy groups and commercial interests in promoting the inclusion of additional disorders.⁴ Although potentially reducing costs while improving and expanding NBS,^{1,5-7} WGS would pose similar challenges, such as how to manage unintended findings unrelated to treatable disorders that manifest in childhood, how to establish criteria for the evaluation and incorporation of new disorders, and how to provide access to appropriate follow-up care.⁸ The implications for pediatricians include the likelihood of being responsible for a greater number of conditions that would be identified, as well as

implementing an informed-consent process and management of the genomic data produced by the test. Public health NBS programs will have to consider social concerns about privacy raised by genomic information, such as the prospect of NBS as a means of genetic profiling and potential genetic discrimination, demands for a formal informed-consent process and control over the data produced, and the role of the states in administering the NBS programs.^{1,6,8-11} Technical issues such as how to mitigate false-positive results, the considerable uncertainty of genomic data as variants of uncertain significance are identified, and the scope of WGS results to return add to the many practical, ethical, and policy issues that need to be addressed.¹²⁻¹⁴

In recent years, concern about the use of residual NBS blood spots for biomedical research has come under intense public scrutiny.¹⁵ Privacy advocates' concerns have prompted lawsuits in Minnesota and Texas, which resulted in court-mandated destruction of >5 million banked blood spots.^{16,17} A growing body of literature suggests the need for stakeholder engagement and education to establish and maintain public trust, and yet parents are often not well informed about the NBS program.^{6,11,18} Recent federal legislation (Newborn Screening Saves Lives Reauthorization Act of 2014) categorizes the use of banked NBS blood spots for federally funded projects, such as human subjects research, and mandates consent; thus, the legal, practical, and ethical landscape for research use of residual blood spots has substantially changed.¹⁹

Given the wide range of social, ethical, and policy issues raised by the potential expansion of NBS with WGS, it is critical to understand the perspectives of key stakeholders, particularly parents. Although several studies have examined

parental and public preferences about the expansion of NBS panels and attitudes toward genetic testing of newborns,^{6,10,20-25} there is little information on parental views about using WGS to expand public health NBS programs or about the sharing of information from expanded NBS.^{6,22,26} With the goal of informing policy debates, we examined the views, perspectives, and value preferences of healthy pregnant women and parents of children with primary immunodeficiency disorders (PIDs) about both traditional NBS and expanded screening with the use of WGS.

METHODS

We conducted 4 focus groups (3 in English and 1 in Spanish) with socioeconomically and ethnically diverse pregnant women ($n = 26$) and a comparison focus group with parents of children diagnosed with a PID ($n = 5$), who had either screened positive by NBS or whose disorder was identified subsequently through clinical presentation early in infancy. We received institutional review board approval of all study procedures.

Sample and Recruitment

Pregnant women were eligible if they were between 18 and 30 weeks' gestation at the time of the focus group, spoke English or Spanish, and were receiving prenatal care at either of 2 urban California medical sites, an academic medical center (AMC) and a public hospital (PH). Eligible pregnant women were identified through medical chart review and were approached by a research assistant before a routine clinic visit or after a centering group class. Three of the pregnant women's groups were conducted in English (2 at the AMC and 1 at the PH) and 1 was conducted in Spanish (at the PH). PID participants were identified through a clinic that serves as a

referral center for patients receiving positive NBS results. English-speaking parents of child patients in the clinic were eligible to participate if their child was diagnosed with a PID or had died of a form of PID, whether or not it was found via NBS. Clinic staff sent invitations by mail to potential participants.

Procedures

Written informed consent was obtained immediately before each focus group and participants filled out anonymous demographic surveys. The 2.5-hour sessions were audio-recorded, and participants received \$60 as an incentive. To address anticipated differences in scientific/genetic literacy among participants, we provided basic information about current NBS and NBS with WGS. We showed the “Baby’s First Test” video²⁷ and reviewed sections of the California Department of Public Health’s NBS pamphlet.²⁸ Our review included discussion of California’s NBS policies and procedures whereby all infants are screened unless the parents explicitly opt-out for religious reasons or personal/philosophical beliefs.²⁹ In California, parents are required to opt-out in writing and may do so only for religious reasons. Because many newborn nurseries have routinized the heel-stick and sample collection procedures, in practice NBS is mandatory. After discussing the participants’ impressions and concerns about the current NBS program, including the state’s opt-out policy, we then introduced the topic of expanded NBS with WGS. Discussion topics included the following: 2 case examples of NBS expanded by WGS (testing for pharmacogenomic variants) and for adult-onset disorders (such as breast cancer or Alzheimer disease), parental consent for NBS with WGS, and storage and research use of NBS blood spots (data regarding research use are not included in this analysis).

Finally, participants were prompted to discuss what role, if any, the public should have in program expansion. The focus group guide is available on request.

Data Analysis

Focus group recordings were fully transcribed and checked for accuracy. In the case of the Spanish-language focus group, the recording was simultaneously translated and transcribed. We analyzed focus group transcripts by using thematic analysis and the constant comparative method.^{30,31} Each of the 5 members of the research team coded the first 2 transcripts; met to review codes, clarify definitions, and reconcile differences; and agreed upon a codebook that 2 researchers (CY and FC) then used to code the remaining transcripts. Atlas.ti, which enables qualitative analysis, supported coding; coded text was analyzed to identify themes, make planned comparisons, and account for outlying responses.

RESULTS

Focus group participant demographic characteristics are detailed in Table 1. We present pediatric policy-relevant themes that emerged from our analysis of the focus group data within the following categories: (1) Perspectives on Traditional NBS, (2) Informed Consent, (3) Return of Results, and (4) Storage and Retrieval of Results. Within each category we discuss subthemes that convey the range of views that emerged in the focus groups. Quotes presented below are identified by first name (all names are pseudonyms), by site where the participant was recruited (AMC or PH), by PID if recruited from the PID clinic at the AMC, and by “Spanish” if the participant participated in the Spanish focus group at the PH.

Perspectives on Traditional NBS

Timing of NBS Education

Among our participants none remembered having had a discussion about NBS with a provider during their current pregnancy or during previous pregnancies. Yet, among our pregnant women participants, there was a clear consensus in favor of receiving information about NBS during the prenatal period rather than immediately after birth. They were concerned that genuine participation in NBS education and decision-making after birth is precluded by circumstance. Some participants expressed dismay when they realized that during their previous pregnancies, NBS screening had been performed without informing the mother ahead of time.

...they should always tell you, ‘So this is what’s going to happen...’ just so you know.... At least I’d know what’s going on. ‘This is why we do it.’ So I’m glad I came today [to the focus group discussion] ‘cause I had no idea and so that makes me overwhelmed, not knowing.... (Jasmin, AMC)

Desire for Participation and Control

For some participants, the desire to be fully informed in advance was linked to the hope or expectation that knowledge would provide a greater sense of control during labor and the uncertainty that follows.

...I want to be the one who’s making the decisions and if I’m not in a mental state where I can make the decisions...I want that to be a joint decision with my husband and me. So having these choices and anything else being laid out to me beforehand and being able to have a good conversation with my doctor about it I think is a very critical part. I think everyone would want something like that. (Rajam, AMC)

Trust/Mistrust of NBS as Part of the Medical System

Although we did not explicitly ask, in both the English and Spanish PH groups the discussion of education about NBS turned into a question of, “Would you do the testing or not?” Some participants in the English

TABLE 1 Participant Demographic Characteristics

	Pregnant Women			
	Parents of Children With PID (<i>n</i> = 5)	AMC (<i>n</i> = 13)	PH (<i>n</i> = 13)	Total (<i>N</i> = 31)
Age range (mean), y	32–46 (40)	35–42 (31.2)	18–37 (29.2)	18–46 (31.8)
Born in United States, <i>n</i> (%)	3 (60)	10 (77)	6 (46)	19 (59)
Self-identified race/ethnicity, <i>n</i>				
Black/African American	—	2	4	6
Asian	—	2	2	4
White	4	4	4	12
Other ^a	1	3	2	6
Mixed	—	1	—	1
Missing	—	1	1	2
Education, <i>n</i>				
Less than high school	—	—	2	2
High school graduate	—	2	5	7
Associates/vocational degree	—	1	1	2
Some college	1	4	3	8
College graduate	2	1	2	5
Graduate degree	2	5	—	7
Annual household income, <i>n</i>				
<\$20 000	—	3	10	13
\$20 000–\$40 000	1	2	2	5
\$60 000–\$80 000	—	1	—	1
\$80 000–\$100 000	—	1	—	1
>\$100 000	4	6	—	10
Missing	—	—	1	1

—, not applicable.

^a In addition to the 5 Office of Management and Budget-required racial categories, participants self-identified with greater specificity including white/Native Mayan (*n* = 1), Creole (*n* = 1), Middle Eastern/Arab (*n* = 1), white/Armenian (*n* = 1), black/African American/Portuguese (*n* = 1), black/African American/Nigerian (*n* = 1), and mixed (*n* = 1).

group initially said they would not allow their infant to undergo NBS due to their lack of understanding of the test, fear that the infant would be injected with a harmful substance, or that the infant would be hurt by the “heel prick.” Several participants expressed distrust in physicians and the medical system. For example, Lola viewed the NBS process as “secretive”; she wanted the screening but wanted to be informed of the benefits of testing beforehand, whereas Denise told us that her NBS experience was okay because she was invited to see what was happening to her infant.

...if it helps the baby and can save their life, of course I think any mother would be like, ‘Okay, yeah.’ ...But still, we know that there’s always other things that go on and we just want to know and have knowledge of that and have a choice, basically. (Lola, PH-English)

In contrast, one of the Spanish speakers explicitly expressed trust in the medical system, especially when compared with experiences she had

seeking medical care in her home country. Nevertheless, the women in the Spanish group uniformly expressed the desire to be informed about NBS before the birth.

...I really trust the doctors here. And I know that the things that they do and recommend are for my own good and my baby’s. (Ida, PH-Spanish)

It’s very good to know because, because sometimes you—they’re not going to tell you what they’re doing...because we don’t know what they’re doing. It’s better to know before, before the baby is born. (Isabel, PH-Spanish)

“Ignorance Is Bliss” Versus “Knowledge Is Power”

A few PID parents suggested that “ignorance is bliss,” and thinking back to a more innocent time before having an ill child suggested that “not knowing” about NBS might prevent unnecessary worry.

...it’s traumatic enough giving birth to your first kid. So it’s going to be another worry that you’re going to have. It’s like the amniocentesis and everybody worries. Then if you don’t know about

this [NBS], but it’s done, it’s not going to do you any harm. You know, it’s not going to cause you undue stress.... (Anna, PID)

One parent in the PID group wasn’t sure that being informed would have made a difference, because as a first-time parent the information might not have been meaningful.

Yeah, I don’t know that it would’ve made a difference if I knew because it wouldn’t have meant anything to me, especially I think as a new mom or your first child, and you just think everything’s going to be fine. At least you hope. (Linda, PID)

Despite such doubts about being informed in advance about NBS, overall our participants preferred to be educated about NBS during the prenatal period, so that they could be genuinely included in the NBS process, even if they did not provide formal consent.

Informed Consent for Traditional and Expanded NBS

After explaining California’s opt-out policy to participants, we asked for their opinions about it and whether

TABLE 2 Consent for Current NBS Screening

	Participant Responses
Desire for consent due to distrust of the medical system	"...they tell you [you can] say no, but technically it's a test they would like for you to have for your baby. So 9 times out of 10 that's something that if you don't do it, they might contact CPS [Child Protective Services]. So it's like you pretty much have to do it. ... Like you can say no but then you put yourself at risk for not necessarily having your child taken away but having the red flag on you as somebody who goes against medical advice." (Nicole, AMC)
Desire for consent to ensure parents are adequately informed before NBS	"I think having this [discussion group] as a session or having all the consent as a requirement before the baby is born would really help because I really would want to know everything that's going on." (Rajam, AMC)
Desire to be informed, but formal consent not necessary	"...ask them because it's their child, right? To show that respect. But I think that it should be done with all of the babies. ... it's for the good of the baby and its health." (Francisca, PH-Spanish)
Formal consent as a potential deterrent to NBS	"I think personally, as a newborn parent, I had no idea of a lot of things and I think it's great that it's mandatory because you're not aware of diseases and things that babies are diagnosed with. ... we all have kids with medical issues, but I think that before I had my children [if] they had asked me, 'Do you want [newborn screening]?' No, I wouldn't want them to be tested. Now I would answer, absolutely 'Yeah, test'." (Anna, PID)

they believed permission should be requested of all parents for current NBS and for NBS with the use of WGS ("Should parents have to say yes?" or "give their permission?"). No consensus emerged, revealing a trade-off, articulated as such by the participants, between ensuring a transparent process (having a choice or being notified) and safeguarding access to the benefits of NBS to all who are eligible. It is noteworthy that although the moderator began using the language of "permission," many participants answered in the language of "consent."

Consent for Traditional NBS Screening

Although many participants believed that the current procedures of mandatory testing were acceptable, several participants (at both the PH and AMC) expressed a desire for written informed consent, whether for state-mandated NBS or NBS with WGS due to mistrust in the medical system (see Table 2). Various comments indicated distrust in the medical system, including statements about potential or actual abuses, such as infecting infants with AIDS, rather than treating or screening. One participant said, "They kill babies at [the AMC]." Others reported personal experiences of poor or disrespectful treatment by medical providers, mentioning in particular medical students or other providers "being

rough" with newborn infants. One woman worried that even if she were offered a choice, she would be "red-flagged" for refusing NBS and risk being turned over to child protective services for making the "wrong" choice.

Other participants offered different reasons to require consent, such as to ensure that parents were informed about all procedures performed on their infant. Spanish- and some English-speaking participants wanted to be informed, "out of respect" but did not consider a formal informed-consent process necessary. Others worried that formal consent would deter them and others from having NBS, which they believed was important. Similarly, PID parents acknowledged that before having a child with a serious medical issue, they might not have agreed to NBS if consent had been required. With the knowledge they gained raising an ill child, they believed that NBS should be mandatory to ensure that naive parents would not opt-out to the detriment of their infant.

Consent for Expanded NBS With WGS

Participants offered a range of opinions regarding the need for informed consent if NBS were performed with WGS (see Table 3). Although some participants did not think consent was necessary, many in the AMC groups thought it was

warranted to warn families of privacy risks and to explain the uncertainty of genetic test results. One parent of a child with PID whose first child had died of a serious immunodeficiency disorder believed that her son might have survived if the WGS test had existed when he was born, and as a result viewed consent as a potential barrier to utilization of NBS with WGS. Other PID parents preferred that only disorders affecting infants in childhood be included in NBS. The idea of allowing parents to opt into or out of various components of the test and associated disorders came up in the groups of pregnant women as well as in the PID group.

Return of Results

We provided participants with information about WGS and its potential to identify more genetic information about their child than is currently revealed with standard NBS. We asked participants to consider 2 different types of genetic information that might be revealed: (1) pharmacogenomic information and (2) genetic variants revealing risk of serious adult-onset disorders, such as breast cancer or Alzheimer disease. Overall, there was no clear consensus as to what extent the results from WGS should be returned to parents and families. In considering what results they would want to receive, participants

TABLE 3 Consent for Expanded NBS With WGS

	Participant Response
Consent not necessary	"They're already there, the baby's already in the nursery getting the prick done, already having that sample going on a piece of paper. Why not run the rest of it that's going to tell me more about my child?" (Larisa, AMC)
Consent necessary to protect privacy	"I think it would have to be stricter regulations with it because it's way more invasive to privacy than the newborn screening that's current." (Anna, PID)
Consent necessary due to uncertainty of results	"...so I would definitely be concerned if it falls under the category of newborn screening program and it's not something that you have to consent to... maybe this would be very helpful information, but it's still very speculative." (Adelle, AMC)
Consent necessary if returning results relevant only in adulthood	"I think once you go beyond the kind of childhood things, I think then those should be more optional or not mandatory but keep the childhood type things mandatory." (David, PID)
Allowing parents to opt-in or opt-out of WGS test components	"I think it would be nice if they could keep the part that's mandatory, mandatory and then this [other stuff] is like an option, you know, like, 'do you want to have this information for the future or not?' type of thing." (Marsha, PID)

TABLE 4 Return of Pharmacogenomic Results

	Participant Response
As much information as possible	"As a mother you're going to worry about that and want to make sure they're getting the medication that works for them. But there's nothing that I don't want to know." (Ida, PH-Spanish)
The scope of the test	"I guess my question would be, what's the scope of it? ...If they had the ability to give you a rundown of, 'Your baby is sensitive to X, Y, Z and you should avoid trying this—it does not cover these hundred most common things.' ...but without a delivery mechanism, I don't think I have a good enough memory to actually remember if an issue comes up." (Bella, AMC)
Potential of pharmacogenomic results to prevent trial and error with drugs	"I think I would be okay with it. I know for like any parents, we have the kids in the hospital and there's a lot of testing with the medication. ...it seemed like while we were trying, it just kind of kept getting worse and worse until they finally found something that had worked for her or [she] didn't have a severe reaction so, yeah, I think in some cases it will benefit the child." (Monica, PID)
Potential of pharmacogenomic results to save a child's life	"And you could also have a totally healthy child who slips and falls and needs surgery and if you had that information then it could save their life. I don't think it would hurt to know their reaction to medications. It could only help." (Marsha, PID)

weighed several factors, including the following: who would receive the results (parent, child, pediatrician, and "medical system"), the timing of the dissemination (immediately after testing, only if symptoms arose, adulthood), and the balance between benefit (treatment and prevention) and harm (discrimination and unnecessary worry). Although all participants agreed that they would want to receive any results relevant to immediate treatment (such as those conditions currently included on NBS panels), there was no consensus as to where to draw the line in terms of returning secondary findings or variants for adult-onset disorders. Most individuals wanted pharmacogenomic results returned in childhood, even if they did not wish to receive results for adult-onset conditions.

Pharmacogenomic Results

The general consensus across all groups was a desire to receive pharmacogenomic information during childhood. Some participants initially had questions about how the new testing would be performed, but after hearing that the pharmacogenomic results would come from the same blood spot test that is currently being used for NBS, opinions were uniformly positive. Participants wanted to receive as much information as possible that would be relevant to their child during childhood (see Table 4). Yet, some were aware of the limits of the technology and raised substantial concerns about how these results would be communicated, stored, and used. For example, several participants indicated that it would be important to know the scope of the test, and to have an easy way

to keep track of what was included and excluded, for the results to be useful. A few respondents recounted personal experiences of extended periods of trial-and-error in finding an effective medication, which they believed might have been preempted by knowing their child's relevant genotype. The parents also tended to focus on the potential for the results to save a child's life. They were able to easily imagine a scenario in which an accident resulted in a trip to the emergency department, and knowing their child's pharmacogenomic information could prevent her/him from receiving a drug that could induce a potentially lethal reaction.

Adult-Onset Disorders

As in the discussion of informed consent, the PID parents' group in particular struggled with whether "ignorance is bliss" or "knowledge is power" in the context of their

TABLE 5 Return of Adult-Onset Results

	Participant Response
"Ignorance is bliss" but "knowledge is power"	"It's a different world when you have a child with illness, so you want to know, you need to know" (Monica, PID)
Belief that information in childhood is useful for prevention of adult-onset disorders	"Cause a lot of times [even if the condition is] something that might affect you years later, there's things you can do...to kind of help better the scenario, so I'd rather know." (Nicole, AMC)
Information can lead to worry	"You're just going to freak me out my whole life and then I won't get it anyway. I mean, what's the point? And you're just living your life out of fear. So I don't know. There are things that I would want to find out and there are maybe some things that I would rather not." (Betty, PH-English)
	"So the pediatrician said that...if I wanted them to do a test to see...what disease [my baby] would develop in the future. So my husband was there and she left and I said it's fine, it was fine with me, right? Better to be aware than to not know. But he said, 'Why do you want to know? Then you're not going to, you're not going to be able to sleep. You're going to be thinking that this or that is going to happen to your son.'" (Marianela, PH-Spanish)
Concern for child's autonomy	"I just want to know the stuff, like that he might get while I'm taking care of the baby or like while he's growing up, so I can prevent stuff like for the kid. And then the stuff that they say, that he's going to have this at the age of whatever, 40, 30, that's his problem. I don't like think about, okay? So it's his option if he wants to check it. If he wants to know, then I'll tell him, 'Oh, you have records here that you can go find out.'" (Betty, PH-English)

child's health (see Table 5). Their experience was that knowledge about their child's illness is powerful and had been hard to come by, but they were dealing with a serious medical condition and did not necessarily want more information than they needed. However, they also knew the value of having advance warning about medical issues that could come up in the future.

In the 4 groups of healthy pregnant women, some individuals did not believe that the information could directly affect their ability to prevent disease and therefore did not want to receive results for adult-onset disorders. However, several of the pregnant participants felt that having adult-onset information in childhood could be potentially useful for prevention of the illness. These women felt that even if the disease had a genetic component, it was not genetically determined, and other factors such as diet and exercise could play a role in prevention.

Several pregnant women had concerns that genetic risk information could be inaccurate and cause unnecessary worry. One indicated that she and her husband were not in agreement about getting genetic information about their infant's future. She wanted the information, but her husband was

afraid that it would make her worry rather than help her or the child.

A further concern for both PID parents and pregnant women was the parental obligation to preserve a child's autonomy to learn genetic risk information about adult-onset disorders if she/he wanted, and then only at a time of his/her choosing. If the parents received the information, they would eliminate their child's ability to make the decision for him-/herself about if and when to learn specific genomic information as they got older.

Storage and Retrieval of Results

Some participants' comments reflected their faith in progress and technology. Many PID parents and some pregnant women expressed a desire to keep WGS results (whether limited to a certain subset of conditions or to the entire genome) in the child's medical record, with the hope that the information could be retrieved at a future time when it would be useful. Many believed that a doctor would be able to go into the medical record or be notified when a particular aspect of the patient's genomic information became relevant (see Table 6.)

Other parents were less hopeful about the power of the medical record to hold this information

and be available as the information became relevant (although they agreed it might be useful in limited ways). Instead, they articulated concerns about the health care system's ability to keep track of their child's medical issues and preferred to have control over genomic results, rather than having them only in the child's medical record. Several parents also expressed concerns about how the genomic data might be used if it were kept in the medical record, suggesting it would make their child vulnerable to loss of insurance, privacy violations, and other potential misuses. As 1 participant put it, laws and regulations regarding the use of genetic information can change over an individual's lifetime, and there are no guarantees.

DISCUSSION

Technological advances such as the potential expansion of NBS with WGS can facilitate the addition of disorders to NBS programs and reduce the associated incremental costs, as occurred in the 1990s with the advent of tandem mass spectrometry. Yet such technological advances raise ethical, social, and practical questions about which tests should be included and what

TABLE 6 Storage and Retrieval of Results

	Participant Response
Trust in the medical system for storage of genomic data	<p>"That can be flagged then when something's found out about it, you know. And it's like, 'Oh, hey, when we had your baby tested 5 years ago we weren't really sure but now we have this new research and it's saying X, Y, Z. We'd like to get you back in or we're looking into this' or something." (Nicole, AMC)</p> <p>"You know, in case anything comes up. Say—I mean, 'cause all kinds of things can happen. Like say your child is epileptic and seizes, and goes into some kind of coma and they don't know why, okay? Well, let's go to the genetic records and go see if that child is at risk for epilepsy...." (Aliza, PH-English)</p>
Concerns about medical system storage of genomic data	<p>"I think we're transitioning in the medical records, where the doctors actually talk to each other. I think we're getting there but we're not there yet, so I wouldn't trust that if it went to the pediatrician, that that would get passed on to their next doctor if we moved or something." (David, PID)</p> <p>"I think especially in the beginning it would be really hard for me to trust any sort of storage or security system, and it's not my information. You know what I mean? Like that's my baby's information.... It would just be hard for me to put that out there and not know—I mean, especially like for me, I think about just like my own health history and things that I don't qualify for because there's a chance of this or that. And I don't want to put that information out there and take a risk that that could happen to my baby." (Milly, AMC)</p> <p>"So having the results...available to view by both me and the doctor, I think that would be good. If it is raw genome data, then I definitely don't want it posted anywhere." (Rajam, AMC)</p> <p>"It's like the information, once it's out there, it's out there. But policies, legislation, you know, leadership changes over time and I feel like that's where it becomes really kind of—there's like this gray area where it's like, you know, you really can't get these guarantees about it." (Adelle, AMC)</p>

types of evidence are needed before adoption. For pediatricians, the advent of NBS with WGS could present significant challenges and practice changes. Private companies have already begun to offer expanded screening tests for purchase. As a result, pediatricians may face parents who have obtained these direct-to-consumer genomic tests and need help to interpret and manage the results. If public health NBS programs begin to use WGS to perform NBS, pediatricians may be called upon to obtain informed consent from parents. Given the 2014 federal law requiring informed consent for the research use of NBS blood spots and proposed changes to the Common Rule governing human subjects research^{19,32} as well as research showing that the individuals want to be asked,^{33–36} pressure to incorporate a consent process for NBS as a public health screening is mounting. Consent is already required in 2 states (Maryland and Wyoming).²⁹ Furthermore, given the range of disorders that would be identified by WGS technology, pediatricians' role in managing concerns about disease risk, including adult-onset disorders, may expand, and they will need

appropriate referral resources (eg, to genetic counselors and specialized treatment centers) that may not exist in adequate numbers.

Major concerns on the part of policy makers, NBS practitioners, clinicians, and parents about the potential expansion of NBS with WGS fall into 2 interdependent categories: first, the flood of information that will be available due to technological advances, and second, the related social concerns about privacy, trust, and desire for control over one's own and one's child's genomic information.²⁸ An understanding of stakeholder perspectives on these 2 interdependent sets of concerns is an important step in policy deliberations.^{20,37,38} Our data inform these policy debates by providing insight into the views and concerns of socioeconomically diverse, healthy pregnant women and parents of children with immunodeficiency disorders. Given that the conditions found in NBS are rare, it is especially important to hear the voices of those who have experienced receipt of life-saving NBS results, because their views on the benefits and risks of screening may differ substantially from those of parents who have never received NBS results.³⁹

Among our key findings is that parents want a meaningful role in the NBS process, including being asked or consulted about screening. According to our participants, this conversation about NBS should happen before labor and childbirth, whether or not NBS is conducted with or without WGS. Of central importance is having time to process the information, the opportunity to ask questions, and to learn about the procedure at a moment when prospective parents can genuinely engage. This finding is consistent with previous studies that have queried parents' opinions regarding the timing of NBS.^{6,11,18,22} However, we found no consensus among our participants about whether NBS education should involve a formal permission or consent process for the screening. Rather, we found that the desire for a formal consent process was contingent upon a number of factors, such as a desire to ensure education about NBS before the procedure, to create a respectful process for parents, and to combat potential abuses and coercion. On the other hand, some of our participants noted a more urgent need for consent if NBS were performed with WGS, given the increase in quantity and

complexity of genetic information such a test would produce, and the related issues of privacy, data management, and clinical utility.

Like some of our participants, state public health NBS programs may be reluctant to implement consent procedures for fear that they will be too onerous, leading parents to opt out, and thus reducing the likelihood of identifying and saving critically ill infants.^{13,40} Not surprisingly, the parents of children with PID expressed a more nuanced understanding of what would be lost if parents chose not to allow their newborn to undergo NBS. A few PID parents spoke passionately about the importance of NBS; they feared that new parents would forego NBS if consent were required and thus risk missing a severe disorder until it was too late. Notably, some PID parents admitted that before having an ill child, if they had been asked to consent to NBS they might have said no. This admission speaks to a central issue in the debate over consent for NBS. If a consent process is instituted, it will be essential to ensure that pregnant women and their partners understand the benefits and risks of screening at a time when it may be hard to imagine having a seriously ill child. The question of who would be responsible for administering consent is an open one. If the task falls to pediatricians and their staff, how will it be managed and coordinated with prenatal practitioners?

Our finding that parents agreed they would want pharmacogenomic results returned to them is consistent with findings that individuals generally want results from WGS in research studies⁴¹ and with 1 previous NBS study that addressed this matter.²⁴ Our participants expressed no consensus on the return of variants revealing adult-onset disorders, a finding that is also aligned with previous research.^{42–44} Responses in our study indicated a

clear desire for clinically useful or actionable information, whether that information is needed immediately, in case of emergency, or due to an illness later in childhood. Beyond childhood, however, clinical usefulness was less apparent to the pregnant women and parents of ill children in our study, and therefore results regarding adult-onset disorders were less desirable. Although knowledge of a *BRCA* mutation, for example, could make preventive treatments feasible, many participants did not want to anticipate their infant's possible illness in adulthood or had concerns about disrupting the child's autonomy to choose to know, or not know, about potential health issues for him- or herself. However, others believed such information would be useful in childhood, by allowing them to potentially prevent adulthood illness through interventions such as diet and exercise during childhood. Of course, information about an infant's *BRCA* mutation would also have implications for the parents, at least one of whom would be a carrier. Such a scenario would present a particular challenge for pediatricians, who might wish to offer findings to parents and make appropriate referrals for the parents of their patients. Similarly, information about carrier status could be included in WGS reports and may have reproductive implications for parents that pediatricians would have to address. Thus, for pediatricians, limiting the results returned from WGS in NBS to those with clinical utility or those that only affect the child in childhood might help to minimize the impact of a transition to NBS with the use of WGS. Although pediatricians typically take a life-course and family view of the patient, the potential impact of results of adult-onset disorders and carrier status of parents could create difficult challenges and new areas of practice for pediatricians.

Except for a few participants who were exceptionally knowledgeable about genomics, our participants in general did not grasp the uncertainty of genomic data that would likely result from the use of WGS in NBS. Participants' hope for clear, useful information, and faith in technological progress, seemed to override the focus group moderator's repeated explanation of the potential for variants of uncertain significance and the fact that often only risk is predicted, not a certainty of disease. At the same time, participants expressed concerns about the state-run NBS program and the medical system's trustworthiness to hold and make available and usable the information obtained via WGS.

The diversity of our participants revealed some potentially important issues to consider in analyses of social, ethical, and policy concerns related to NBS. For example, it was striking that in discussions of permission or consent for NBS with WGS or traditional NBS, several African-American participants expressed distrust in the medical system (although they did not tie their perspectives explicitly to racial discrimination). Also, in discussions of the storage and management of WGS results, participants with the most knowledge of genomic science expressed distrust in state-run NBS programs, and the government generally, to guard their child's privacy. This diversity of views as it relates to historical memory and social positions should be considered in policy deliberations and in pediatric practice regarding implementation of NBS with WGS.

This study has important limitations. Although participants were socioeconomically diverse, they were all drawn from 1 geographic region within California. We reviewed educational materials as a basis for discussion but did not assess participants' understanding of the issues before our discussion.

We did not discuss point-of-care newborn screening (eg, screening for congenital hearing loss or congenital heart defects). Historical events that were widely covered in the media may have influenced our results. At the time of our focus groups, concerns about the role of parental control over the administration of childhood vaccinations were widely publicized in the California news media, and were raised by focus group participants when informed consent was discussed. In addition, the controversy over the use of NBS blood spots in Texas and Minnesota, as well as the concerns about privacy due to the Edward Snowden National Security Administration revelations and hacking incidents that resulted in privacy breaches, may have influenced concerns about WGS and privacy. Finally, our discussions were based on a hypothetical implementation of WGS. Results might differ in the context of actual NBS performed with WGS.

CONCLUSIONS

Our focus group participants desired greater inclusion, not necessarily complete control, in the NBS process, suggesting the need for revision of existing policy as NBS with the use of WGS becomes more feasible. Despite an overall optimistic and enthusiastic orientation to the potential benefits and limited harms likely to result from genomic advances in NBS, we identified concerns about privacy and control over test results, and limited trust in the medical system and the state-run NBS program informed parental views of expanding NBS with WGS. Pediatricians will need to be prepared to address these issues with their professional colleagues and their patients' parents. If they are tasked with administering consent, they will need to understand concerns and enable robust consent and reflection. Thus, pediatricians will benefit from participation in

the policy process, and participation in discussion of these issues in coordination with obstetricians/gynecologists across the perinatal continuum of care given the need to educate parents before delivery, and the potential of prenatal genetic testing to interact with NBS as each becomes more comprehensive due to technological change. Finally, and importantly, our data suggest concerns about how these technologies will be understood in diverse populations and point to important trust issues that will need to be addressed if expanded NBS is to be implemented effectively.

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ABBREVIATIONS

AMC: academic medical center
NBS: standard newborn screening
PH: public hospital
WGS: whole-genome sequencing

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