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Ethical Issues with Newborn Screening in the Genomics Era

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Abstract

Continued technological advances have made the prospect of routine whole-genome sequencing (WGS) imminent. To date, much of the discussion about WGS has focused on its application and use in clinical medicine. Relatively little attention has been paid to the potential integration of WGS into newborn screening programs. Given the structure and scope of these programs, it is possible that the early applications of WGS will occur in state-run newborn screening programs. Assessment of the pressing ethical issues currently facing the newborn screening community will provide insight into the challenges that lie ahead in the genomics era.

INTRODUCTION

The coming year marks the 50th anniversary of Guthrie's (25) publication describing the use of dried blood spots to screen children for phenylketonuria (PKU). The scope of this test's implementation is remarkable; it is the only screening test that nearly every individual born in the United States undergoes. Yet despite the fact that newborn screening has saved the lives of thousands of children and spared many more from lasting disability (46), it stands in danger of becoming a victim of its own success as we enter the genomics era. To date, newborn screening programs have sought to identify and treat children with inherited conditions for which early intervention and treatment can decrease morbidity and mortality (2, 3). This mission has depended heavily on technological innovation to spur the development of screening tests and treatments (45). The downside is that in some instances, technology creates a "therapeutic gap" by making it possible to screen for a disorder before effective treatments are available. The imminence of financially feasible whole-genome sequencing (WGS) is likely to transform this gap into a chasm and, in the process, raise numerous ethical challenges for newborn screening programs (22). In this review, we highlight the major ethical challenges currently facing each facet of newborn screening (Figure 1) and discuss how these challenges are likely to be exacerbated by the availability of routine WGS.

ONE NATION, 51 PROGRAMS

Any attempt to assess the ethical challenges facing newborn screening programs must begin with a review of their organization. Newborn screening is performed by state-run public

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health programs, which means that each state has the responsibility and authority to decide how to structure and operationalize the program for its citizens. Not surprisingly, this has resulted in variation across states with regard to many aspects of the program (61, 66), including the specific disorders screened (64), financing (29), consent and notification processes (42), genetic counseling practices (14), educational information provided to parents (31), and long-term follow-up procedures (27).

The most publicly visible manifestation of this state-level variation is the differences in the disorders screened. As a result, some children are not screened for certain disorders simply by dint of being born on a particular side of a state line (1). Although state variation in newborn screening panels has been an issue throughout the history of newborn screening programs (61, 62), the degree of variation was exacerbated in recent years owing to the implementation of tandem mass spectrometry (MS/MS) testing technology. Between 1995 and 2005, the average number of disorders screened across states jumped from 5 to 24 (34), constituting the most rapid expansion in US newborn screening history.

MS/MS measures the size and quantity of molecules and molecular fragments in a liquid or gas. Its advantage for newborn screening is that it can screen for multiple disorders using only a small amount of blood. Owing to the difficulty of acquiring support within a program, funding limitations, and the need for an advisory board recommendation (20), MS/MS was implemented in a patchwork fashion across states. This created marked variability in the numbers of disorders screened across the United States; in 2005, some states were screening for as few as 4 disorders while others were screening for as many as 46 (64).

This pronounced variation across state newborn screening panels prompted concern and action at the federal level. The Maternal and Child Health Bureau—a federal health bureau within the US Department of Health and Human Services that is responsible for providing financial, educational, and organizational support for newborn screening services—commissioned the American College of Medical Genetics (ACMG) to review the available evidence on screening for various disorders and to recommend a uniform screening panel for states (3). In its report, the ACMG recommended that each state screen for 29 core conditions and 25 secondary target conditions (3). The report drew sharp criticism for relying too heavily on expert opinion and giving greater weight to conditions with tests that already existed or that could be screened for using a multiplex assay (e.g., testing for multiple analyses simultaneously) (9, 45). Nonetheless, this recommended uniform screening panel (RUSP) was eventually endorsed by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC), a federal newborn screening advisory committee. It is important to realize, however, that this RUSP provides a floor and not a ceiling for the number of disorders screened. Although every state has mandatory screening for the 29 core conditions (43), other states screen for conditions not included in the RUSP. For example, New York screens for Krabbe disease and Illinois screens for lysosomal storage disorders (47). So, in spite of the RUSP, variation still exists across state newborn screening panels.

THE GOLDEN TICKET: MAKING IT TO THE RECOMMENDED UNIFORM SCREENING PANEL

There is a long history of disorders being added to state newborn screening panels due, in part, to intense lobbying by patient advocacy groups (53). In fact, one advocacy group, the National Association for Retarded Children, was largely responsible for garnering the political and emotional will to initiate newborn screening for PKU in the 1960s (28). In recent times, the power of advocacy groups has been strengthened through partnerships with industry (53). Although the fundamental mission of advocacy groups—to bring attention to

causes and issues that might otherwise be overlooked by the general public—is a laudable one, the groups are often motivated by the “rule of rescue,” the impetus to save lives with less attention focused on the attendant costs (11, 44).

Given the increasing availability of new screening tests and dwindling state public health budgets, there has been an attempt to objectify the evaluation of disorders prior to widespread adoption. Chartered in 2003, SACHDNC provides the secretary of the Department of Health and Human Services with recommendations on newborn screening policies. SACHDNC recently instituted a much more rigorous evidence review process than was used in the 2005 ACMG report to decide whether disorders should be added to the RUSP (55).

Although numerous candidate disorders have been considered for universal screening since 2005, only two—severe combined immunodeficiency and critical congenital heart disease (CCHD)—have been added to the RUSP. The latter is an interesting addition because it represents a continued shift in the screening paradigm, which has relied almost exclusively on testing that can be conducted in laboratories on dried blood spots. Prior to the addition of CCHD screening, the only non-laboratory-based point-of-care screening test was for hearing; CCHD is the first disorder to involve point-of-care testing, in this case pulse oximetry screening, as a routine part of clinical care. As such, the CCHD test has moved newborn screening into the clinical care arena and in effect mandated a common clinical practice. The upcoming evaluation of neonatal hyperbilirubinemia screening—a standard and recommended clinical practice—for addition to the RUSP will determine how far newborn screening programs are willing to insert themselves into routine standards of clinical care.

It is important to note that although states are not legally obligated to follow federal recommendations (35), the political pressure to do so can be significant. Once disorders are added to state newborn screening panels, their screening becomes mandatory. In the case of CCHD screening and other point-of-care screening tests that may follow, public health programs will require more resources for surveillance and tracking than actual testing—a departure from the rest of newborn screening, which is heavily laboratory based.

MANDATORY: WHAT’S IN A WORD?

The mandatory nature of newborn screening has been justified based on the individualized child welfare/child benefit model, which supports the addition of tests to mandatory screening panels under the argument that information gathered from newborns is used to directly benefit children. States support mandatory screening on the basis of *parens patriae* power, which gives them inherent authority to act to promote the welfare of children (23). If a state is concerned that forgoing screening could result in harm to a child, *parens patriae* permits the state to override the parents’ autonomy.

Yet the use of the term mandatory to describe newborn screening is slightly misleading. Although formal parental permission is generally not required for testing, the mandatory nature of testing does not mean that parents are prohibited from refusing or opting out of screening. In fact, many states allow parents to refuse newborn screening for religious or other reasons (42), and such refusal does not usually engender civil or criminal penalty. One exception is Nebraska, where a case in which parents refused newborn screening for their child was considered neglect and led the state to temporarily remove the child from the home (48).

Recent expansion of newborn screening panels with MS/MS has raised important questions about the original welfare-oriented goals of newborn screening programs that justify

mandatory testing. In addition, there has been a growing clamor for expansion of the notion of “benefit” in newborn screening, from one focused on individual medical benefit to one that includes psychosocial and research benefits to other recipients, such as family members and society as a whole (1). In the end, such a mission shift remains a societal value judgment; newborn screening programs can choose to shift their mission to include screening for conditions to promote a notion of benefit that is broader than just direct benefit to the infant’s health. However, this reconceptualization of benefit does not justify mandatory screening that can override parental authority. Thus, transforming the mission of newborn screening through a broader definition of benefit becomes ethically and socially problematic within this existing child welfare/child benefit framework that justifies mandatory screening (57).

Seeking parental permission for screening may address the implications raised by this type of expanded screening by giving parents more choice about testing. However, doing so could be logistically challenging for programs and have an unintended negative effect on the effectiveness of the newborn screening system. Parental permission for participation in a state’s newborn screening program is a contentious issue because some are concerned that asking parents to give permission to test newborns would decrease the effectiveness of newborn screening (19). One solution is to preserve mandatory screening for disorders, which meets the standard of direct benefit to infants, but require parental consent for screening where the direct-benefit standard is not met (56, 57). However, this tiered approach raises concerns that parents may misunderstand the difference between mandatory and voluntary screening, and then may choose to forgo screening for mandatory conditions.

PARENTAL EDUCATION

Concerns about the potential for parents to misunderstand newborn screening are well founded. It is widely accepted that parents are woefully undereducated about newborn screening. Numerous studies have shown that few parents remember that the newborn screening was performed and even fewer adequately comprehend the reason for the testing (12, 26). The causes of poor parental understanding are multifactorial. First, testing is mandatory, but education is not. A recent study found that 50 out of the 51 US newborn screening programs utilize pamphlets or brochures to inform and educate parents about screening, yet overall, only 25 states currently have specific regulations requiring that parents be given educational materials (31). To complicate matters, past systematic evaluation of the content and readability of programs’ parental educational brochures has found that they did not meet standards set by the American Academy of Pediatrics (31). Additionally, 12 programs have specific requirements that newborn screening information be provided by a birth attendant or other hospital staff, whereas 9 have requirements for the distribution of educational materials but no regulations on how that should be done (e.g., in person or through pamphlets) (31). Yet even when the content of and dissemination process for educational materials are clearly laid out in statutes, the responsibility for the act of educating parents is at risk of being diffused because newborn screening programs are run by state public health agencies but administered by health care providers in hospitals (10).

Second, parents are emotionally and physically exhausted after the birth of their child, making it difficult for them to learn and retain information about newborn screening. Parents have reported a preference for receiving information about newborn screening prenatally (12, 26). Historically, the obstetrics community has resisted the responsibility to educate parents about newborn screening, contending that they are already tasked with discussing numerous prenatal tests with parents (13, 18). This perspective seems to be changing, however; the American College of Obstetricians and Gynecologists recently recommended

that prenatal providers give information about newborn screening to their patients through informational brochures, electronic sources, or discussion during prenatal visits (4).

Galvanizing will and commitment is an important first step in improving the education of parents about newborn screening. The important and challenging next step is to transform this will into effective action and meaningful outcomes—especially as newborn screening confronts the prospect of WGS within the context of a public that struggles with basic genetic concepts (38).

CONFIRMATORY TESTING AND SHORT-TERM FOLLOW-UP

Communication of Newborn Screening Results

Communication is a matter not just of providing enough information but also of ensuring that individuals understand it. In the case of newborn screening, the communication of results is a complicated process that involves a number of stakeholders, including the state newborn screening program, the parents, the primary care physician, and sometimes a specialty physician or genetic counselor. Currently, the responsibility for informing parents about newborn screening results rests with the primary care physician (33). Anecdotally, normal newborn screening results are often treated as “no news is good news.” Yet this assumption can lead to disastrous consequences if an abnormal result is routed to the wrong physician. The state serves as a safety net to ensure that follow-up happens in a timely manner.

The communication of positive newborn screening results presents another challenge. Many of the disorders screened are rare, and primary care physicians have expressed a lack of comfort with explaining them to parents (32). Scenario-based studies about physician-patient newborn screening communication have supported these concerns, showing that resident physicians’ conversations did not contain a significant amount of content judged necessary for parental understanding and sometimes contained misleading content (16, 39). In a study that asked parents to rate how well their primary care physicians explained the results, fewer than half indicated that this was done “well” or “very well,” and parents with low health literacy were more likely to rate their primary care physicians unfavorably (17).

The success of a newborn screening system must be measured not only by its capacity to identify potential disorders but also by its ability to communicate results in an effective and sensitive manner. There is a clear need to improve the ways in which parents are educated and counseled about screening results, which will only become more challenging as programs face the prospect of WGS.

Carriers

The controversy over the reporting of genetic carrier status revealed by newborn screening dates back to the 1980s, when states first began mandatory screening for sickle cell disease (7). The sickle cell screening history is littered with examples of racism and misinformation that resulted in employment and health insurance discrimination (59). Although the field has moved beyond this discrimination, there are data to suggest that nearly 30 years later parents still confuse sickle cell trait with sickle cell disease and do not understand the inheritance pattern of sickle cell disease (37).

Providers are not immune from problems either. Evaluations of resident physicians using standardized patients suggest that conversations are at risk of being too complex and jargon-rich to be understood by patients (15). Perhaps more troubling is the fact that physicians in a recent national survey were less likely to think that a sickle cell carrier required formal genetic counseling compared with a cystic fibrosis carrier (32). Finally, the majority of

newborn screening programs offer genetic counseling services to sickle cell and cystic fibrosis carriers, but do not assess the quality of the counseling (14).

In summary, despite the years of experience with carrier screening, physician communication and management as well as patient education need to improve. This does not bode well for newborn screening programs' ability to communicate with patients about future results from genetic testing for complex common conditions or genetic risk variants.

False-Positive Results

Concerns about false-positive results date back to the early days of PKU screening, when the term "PKU anxiety syndrome" was coined (58). Subsequent studies revealed that some parents of children who received false-positive newborn screening results for congenital hypothyroidism had persistent psychological distress and lingering anxiety (21). The potential for false-positive results to provoke anxiety continues to raise concern in newborn screening circles. In a recent study that took place after the introduction of expanded MS/MS screening in Massachusetts, parents were found to have an increased level of stress up to a year after receipt of a false-positive result (24). Exactly how such anxiety affects parents and children is unclear. Although an initial smaller study revealed an increase in health care utilization unrelated to the newborn screening result (68), larger, population-based studies have failed to find an association (41, 65).

What are we to make of this? It may be, as Fyro & Bodegard (21) have noted, that this psychosocial stress represents a complex interaction between individual and experience that is mitigated by successful coping strategies. That being said, different factors, none of which are mutually exclusive, may be relevant. For example, it may be that certain subgroups of parents, such as those with underlying anxiety or a history of difficult conception, might be at risk for this "false-positive anxiety syndrome." This kind of subgroup effect may not be readily apparent in a population-based analysis. It is also possible that, as noted in a recent large-scale qualitative study of the communication of newborn screening carrier results, modes and methods of communication moderate levels of distress (30). In short, work remains to be done to sort out exactly who is at risk for significant psychosocial distress after a false-positive newborn screening result, what the magnitude of the harm is, and how that harm can be mitigated. This need only becomes more urgent when one considers the potential for false-positive results due to sequencing errors that could result during WGS.

Indeterminate Results

To complicate matters, some children with positive newborn screening results have confirmatory test results that are neither normal nor classically abnormal. These children are often categorized as "diagnostic dilemmas" (50) or "patients in waiting" (36). The problem is that in some cases, like Krabbe disease, the treatment might be as harmful as the diagnosis. Krabbe disease is a lysosomal storage disorder caused by inadequate galactocerebrosidase (GALC) activity, which leads to progressive and irreversible neurologic decline ending in death during childhood. The treatment is an allogeneic hematopoietic stem cell transplant, and earlier treatment seems correlated with more successful outcomes (54).

Unfortunately, it is not easy to sort out which infants with positive Krabbe screening results will actually develop clinical symptoms. In New York, the only state with mandated newborn screening for Krabbe disease, children with positive results (i.e., low GALC activity and one or more *GALC* gene mutations) are triaged into one of three risk categories—high, moderate, or low risk. All children with positive results are followed over time, and the hematopoietic stem cell transplant treatment is usually offered only to those with

particularly severe biochemical and genetic phenotypes and/or those who have clinical findings of Krabbe. Even children categorized as high risk are followed clinically for signs of Krabbe in lieu of undergoing an immediate bone marrow transplant. Of the high-risk children for whom follow-up data are available, more than half have remained asymptomatic (54).

Currently, there are no published studies on how parents cope with the looming uncertainty of a Krabbe diagnosis during this follow-up period. However, Krabbe is not a unique case in this regard. Similar challenges with indeterminate results have surfaced with cystic fibrosis screening, leading to the adoption of a new diagnostic term, “CFTR-related metabolic syndrome” (8). Given the real possibility of uncovering mutations of unknown clinical significance with WGS (34), the dilemma of indeterminate results is likely to become more common.

Overdiagnosis

In an overdiagnosis—a phenomenon already well recognized in cancer screening—confirmatory testing of a child with a positive newborn screening result reveals a biochemical phenotype (or genotype) identical to that of a child with disease; however, the child who has been overdiagnosed never develops clinically significant disease symptoms, if any at all. To complicate matters, because screening occurs in an asymptomatic population, clinical characteristics cannot be used to distinguish between a true case of disease and a case of overdiagnosis. When faced with an asymptomatic child who has a biochemical phenotype (or genotype) consistent with disease, it is understandable that a practitioner may feel compelled to recommend treatment—especially if the disease has been known to be potentially life threatening. Ironically, though, the phenomenon of overdiagnosis is usually “discovered” during screening programs.

The issue of overdiagnosis has already emerged in MS/MS screening. Two disorders on the ACMG’s RUSP—short-chain acyl-coenzyme A (CoA) dehydrogenase deficiency (67) and 3-methylcrotonyl-CoA carboxylase deficiency (60)—present with symptoms ranging from no symptoms to death. Treatment for children diagnosed with these disorders requires avoidance of fasting, specific dietary restrictions, and sometimes use of dietary supplements. The challenge of overdiagnosis will certainly become more complicated with the use of WGS.

TREATMENT AND LONG-TERM FOLLOW-UP

It is crucial to remember that newborn screening is a system, not a test. Some have cautioned that the addition of new tests to screening panels is taking place without the funding or infrastructure needed to provide adequate follow-up care and clinical services to newborns and their families (9). Any expansion of newborn screening does not absolve a program of its duties to provide access to necessary testing and treatment resources.

Concerns about access to treatment and long-term follow-up are not new in newborn screening. A lack of comprehensive insurance coverage for PKU formula during the early years of mandatory screening meant that some children were left with a diagnosis but no means to treat it (52). Section 2713 of the Patient Protection and Affordable Care Act of 2010 (51) provides coverage for screening of disorders in the RUSP but not for treatment. Children may be able to receive insurance coverage through Title V funding in their state, often provided through Children with Special Health Care Needs Programs. However, studies have shown that the coverage of medical formulas (e.g., formulas created to meet a disorder’s specific metabolic requirements) and foods for disorders that require dietary

treatment is a patchwork across states (70). In any mandatory screening program, failure to provide affordable treatment raises ethical concerns.

Even for disorders in which affordable treatment is provided, follow-up of long-term medical outcomes is critical. For many disorders, there is limited long-term disease history information available because they are rare—which is precisely why a coordinated effort with adequate infrastructure and funding is needed for research. We can learn from the past here. Without attention to long-term outcomes, we would not have discovered that without continued treatment during adulthood, children born to women with PKU are at risk of suffering significant neurological damage (40, 69).

BLOOD SPOT STORAGE AND USE

Although this review focuses on the clinical aspects of newborn screening, it is important to acknowledge the current controversies related to blood spot storage and use because they will undoubtedly become more prominent in the genomics era. The potential value of the blood spot from a newborn screening extends beyond the initial testing for inherited diseases conducted shortly after birth. Because blood spot collections contain the DNA of all state residents born each year and often span many years, they represent an important source of population-representative genetic samples that could be used for population-based genomic studies. Moreover, given the recent calls for better translational research both within and outside of newborn screening, there has been a heightened interest in utilizing these residual newborn screening blood spots for research purposes.

As programs begin to consider expanding to include complex genomic technologies such as whole-exome and whole-genome sequencing, there may be an increased call for genomic studies utilizing these residual samples for testing new methodologies. However, like expanded screening, the use of these specimens for research purposes raises a number of ethical, legal, and social challenges that involve public trust, privacy, and consent as well as broader questions about the public health ethic that justifies and sustains the practice of mandatory newborn screening.

Currently, a number of states are involved in debates over the storage and use of their leftover newborn screening blood spots, which have led to lawsuits in Minnesota and Texas that have resulted in the destruction of stored blood spots in both states (5, 6). These debates have focused on the balance between the use of public health data for research and the rights of citizens from whom the data have been collected. Unfortunately, there is a lack of policy guidance available to programs on how to address the ethical, legal, and social issues raised by expanding the framework of newborn screening to include use of residual blood spots for research. In addition, because of the mandatory nature of screening, parents currently have few opportunities to learn about the potential uses of leftover samples beyond their clinical purpose. If newborn screening remains mandatory and parents are not given clearer options to opt out of having their child's sample used for research, some may feel that their privacy is being violated and become skeptical of the screening program (63). This may, in turn, harm both the newborn screening program and the potential to utilize residual samples for research.

NEWBORN SCREENING IN THE GENOMICS ERA: NEWBORN SCREENING OR SCREENING OF NEWBORNS?

The ability to know a child's entire genome sequence at birth will soon be within reach. The unanswered question is what it will mean for newborn screening programs, which collect

dried blood specimens from nearly every child born in the United States. We can look to past and present experiences in newborn screening for preliminary answers.

First, the relationship between technological innovation and newborn screening expansion has revealed a pattern of adoption that favors multiplex testing, as WGS would involve. Therefore, to the extent that genome sequence data can be used for screening and confirmation of numerous conditions, adoption of multiplex genetic testing (e.g., conducting multiple genetic tests simultaneously) may be viewed as financially and technically advantageous. The story line is likely to unfold similarly to that of MS/MS, where the technology garnered support among the newborn screening laboratory stakeholders and the opportunity to screen for previously unscreenable disorders galvanized disease-specific advocacy groups. The increasingly common pattern of industry-advocacy partnerships is likely to augment the power and influence of these groups. It should be recognized that genetic analysis already plays a key role in the newborn screening algorithm for cystic fibrosis. In most states, screening for cystic fibrosis involves an enzyme-level analysis for immunoreactive trypsinogen followed by a reflexive mutational analysis of the *CFTR* gene using the dried blood spot. In some states, infants who have elevated immunoreactive trypsinogen levels but no *CFTR* mutations are considered to have screened negative for cystic fibrosis and require no further testing. As use of these types of reflexive genetic analyses grows, it is conceivable that the incremental cost of sequencing the genome may become lower than the cost of conducting separate mutational analyses for different disorders. However, WGS is unlikely to replace all of the current newborn screening tests. There are still instances in which biochemical tests perform better than genetic analyses in screening and diagnosing disorders. For example, direct measurement of phenylalanine level is a simpler and more accurate method to detect infants with PKU than DNA-based testing. That being said, genomic analyses are still likely to become an increasingly useful adjunct to newborn screening.

Nonetheless, the potential integration of WGS into newborn screening is likely to exacerbate the existing newborn screening challenges discussed above. First, the states hold the ultimate authority in deciding which disorders to screen for and how. Historically, SACHDNC has not provided recommendations on what laboratory standards states should use in screening for disorders that it recommends in the RUSP. As was clearly demonstrated by the MS/MS expansion, SACHDNC focuses its recommendations on disorders and not technology—even though the two may be closely linked (3).

Even if states choose to adopt WGS simply because it makes technical and financial sense, they will grapple with how to handle the excess information that is generated. To not filter results from WGS may leave clinicians and families drowning in genomic data but with little useful information. This will only exacerbate the challenges related to indeterminate results, education, and communication that already exist for parents and providers. Yet filtering WGS data so that only information on disorders in the RUSP is included may also raise public concern, not only because these are genomic data but also because the data were obtained within the context of a mandatory public health program. The public will undoubtedly want to know what happens to the filtered data. It seems that prior to the integration of WGS, it will be critical to educate and engage the public in the broader decision-making process. The challenge lies in finding ways to successfully and productively engage the public in a meaningful discussion.

In summary, it is likely that newborn screening will imminently confront the prospect of integrating WGS. Whether WGS will transform the current child welfare ethical framework underpinning newborn screening or be adopted as a technological enhancement for screening and diagnosis of disorders within that framework remains to be seen. Regardless,

the existing ethical challenges facing newborn screening are likely to be exacerbated by the use of WGS. As newborn screening programs enter the genomics era, they must focus on addressing issues of equity, access, and education that have persisted since the system's inception 50 years ago.

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Figure 1.
The birth and life of a newborn screening blood spot.