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Whole Genome Sequencing and Newborn Screening

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Abstract Clinical applications of next-generation sequencing are growing at a tremendous pace. Currently, the largest application of genetic testing in medicine occurs with newborn screening through state-mandated public health programs, and there are suggestions that sequencing could become a standard component of newborn care within the next decade. As such, newborn screening may appear to be a logical starting point to explore whole genome and whole exome sequencing on a population level. Yet, there are a number of ethical, social, and legal implications about the use of a mandatory public health screening program that create challenges for the use of sequencing technologies in this context. Additionally, at this time we still have limited understanding and strategies for managing genomic data, supporting our conclusion that genome sequencing is not justified within population-based public health programs for newborn screening.

Keywords Newborn screening · Whole genome sequencing · Next-generation sequencing · Public health · Ethics · Population screening

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Introduction

The development of next-generation sequencing (NGS) technologies may provide a new mechanism for the conduct of public health and medicine. It is predicted that this technology will improve diagnosis and management of some genetic disorders. Already, during pregnancy cell-free DNA is used for noninvasive prenatal testing for aneuploidy using NGS [1•]. With children, genome-scale sequencing (whole genome or whole exome sequencing) is already used to identify causes of rare genetic diseases [2]. NGS could become a component of clinical and public health programs that currently use extensive genetic testing methods such as newborn screening. The prospect of using genome-scale sequencing (GSS) in the context of newborn screening (NBS) has been widely discussed in recent years. The National Human Genome Research Institute, the Eunice Kennedy Shriver National Institute of Child Health and Development, and the NIH Office of Rare Diseases sponsored a workshop in December 2010 titled "Newborn Screening in the Genomic Era: Setting a Research Agenda." [3]. In September 2013, the NIH provided $25 million in funding for four projects to conduct GSS in the context of newborn screening [4].

GSS could be used in a variety of ways in the NBS context. We have a limited understanding of the genetics of many conditions for which we currently conduct NBS. Further, most NBS test modalities are not DNA-based tests because targeting the accumulation or deficit of other biomarkers in affected individuals is currently more sensitive and specific. So one potential application of sequencing in NBS would be to better characterize these conditions from a genomic perspective, enabling a transition to DNA-based testing and/or enhancing understanding about phenotypic variants and prognosis based on genomic

variants. However, once these disease genes are better characterized, presumably targeted testing of these genes in the clinical context would be sufficient, and sequencing of the whole genome/exome would not be necessary.

A second application in the NBS context would be to better understand sequence variations at other sites in the genome that may impact disease severity or response to different treatment modalities. GSS is an excellent *research* tool to identify these modifying genetic factors. Again, once a better understanding of these factors is obtained, targeted testing for clinically meaningful variants would be in order, and GSS would not be necessary.

Genome-Scale Sequencing (GSS)

GSS is a powerful new technology with evolving potential in a variety of clinical domains. The reduction in cost for the DNA analysis in recent years gives confidence that a goal of the $1000 genome will be achieved in the foreseeable future. Although this cost goal does not account for the substantial additional costs of sequence interpretation and follow-up, the analytic cost brings the technology into the range of cost acceptable for regular clinical use.

GSS is being utilized widely in research to identify sequence variants that are associated with polygenic or multifactorial conditions. This work has proven difficult due to the fact that many of these conditions are far more complex from a genomic perspective than had been hoped. Nevertheless, realistic expectations remain that GSS will provide important insights into many such conditions. Accordingly, the NIH is devoting substantial resources to improvements in the technology and sequence analysis and to clinical research seeking genotype–phenotype correlations.

In the clinical context to date, GSS has shown the most promise in elucidating genomic etiologies for patients with a previously undiagnosed condition [5]. For patients who have congenital or apparently heritable conditions that cannot be diagnosed with traditional tests or syndrome identifications, sequencing can establish a genomic cause in a modest but significant number of cases. Identifying a genomic etiology often may not provide direct clinical benefit to the individual, but many families experience significant psychological benefits from simply knowing the cause of a serious condition, and a genetic etiology may provide useful information for future reproductive planning. Another work has shown that it is feasible to perform GSS on a fetus from DNA circulating in the maternal bloodstream and through cross-referencing with the mother's and father's sequences [6]. The clinical application of fetal genome sequencing remains uncertain.

At the present time, GSS constitutes a non-specific search for associations between phenotype and genotype when the sequencer does not know what he or she is looking for. If a clinician has a suspicion about a specific genetic condition amenable to targeted genetic testing, genome sequencing will not replace targeted testing (including targeted sequencing). Even if the analytic cost of GSS per se is low, the cost of interpretation and costs of follow-up for incidental findings should always make more specific testing better than a less specific testing [7•].

Newborn Screening

A central concept in newborn screening is that services are provided within a system. Newborn screening programs are public health programs in the United States that are conducted by state or territorial health departments. Blood from the newborn's heel is spotted and dried on Guthrie cards at the birthing facility (or home) and sent to the state laboratory or a commercial partner. Results are returned to the physician of record for the child and the health department for follow-up. Screen-positive infants will undergo diagnostic confirmation and affected infants will, for most conditions, be referred to a subspecialist for ongoing care. Therefore, the system involves birthing facilities, the health department, a laboratory, primary care providers, parents, and subspecialty clinicians. These systems are remarkably efficient with coverage of greater than 98 % of the newborn population. If the incidence of conditions targeted by current newborn screening programs is approximately 1 in 500 newborns [8], roughly 8000 infants per year are diagnosed through the state systems within the 4 million infants born per year in the U.S. In recent years, the number of conditions on the screening panels has increased dramatically, now with every state screening for more than 32 conditions [9].

A hallmark of the state programs since their inception is that screening is mandatory in all states except Wyoming and the District of Columbia. The rationale has been that screening confers such benefit to children that parental permission is not required. This aspect of NBS has been somewhat controversial over the years, although it is widely recognized that a meaningful consent process for parents in the post-partum period would be an enormous logistical challenge. In the research context, for example, an informed consent process involving a signed form can be associated with a significant decrease in participation due primarily to logistical challenges rather than parental refusals [10]. Unfortunately, the information processes for parents within our mandatory state NBS systems are only marginally effective. [11, 12] There is no serious discussion within the state programs of moving to a consent model for NBS.

Most states fund NBS programs through a "kit fee" to the birthing facility for each Guthrie card [9]. Birthing

facilities, in turn, charge patients for the service. Currently, most kit fees are roughly $100 per newborn to screen for over 30 conditions and this fee covers screening, diagnostic testing, and short-term follow-up in most states. Although the cost of the NBS systems is borne by consumers, state legislatures and/or health departments typically are cautious about approving kit fee increases. In general, efforts are made to keep the incremental cost of screening for new conditions below about $5 per infant.

The single largest technical and system challenge for NBS is false positive results. A relatively low positive predictive value is characteristic of almost all population screening programs where screening tests have less than 100 % sensitivity and the targeted conditions are uncommon in the population. Substantial improvements in positive predictive values have been made in recent years for a number of the NBS tests; nevertheless, the notification of parents, confirmatory testing, and managing results disclosure constitute a significant burden and cost to parents, clinicians, and NBS programs. Further, because some of the conditions on the newborn screening panels can cause a rapid deterioration and death within the first 2 weeks of life, rapid turnaround for results is a high priority. Therefore, the NBS systems are designed to conduct high-throughput screening for large numbers of infants with a prompt, intensive focus on screen-positive infants, all at a modest cost per family.

An inherent ethical challenge for all population screening programs is the need to balance the potential benefits to those individuals who are accurately identified through screening with the costs and burdens to those who obtain false positive results. "False positives" are those newborns who are healthy but receive an out-of-range result, those with subclinical forms of the condition who were not destined to become ill, and those with results of uncertain clinical significance. A big part of the problem in balancing these considerations is the lack of quality data on outcomes. Wilcken notes in recent publication that we still have very limited outcome data on many of the conditions currently on NBS panels [13].

Problems with GSS as a Primary Screening Tool

We can identify a number of serious or prohibitive challenges with potentially integrating genome sequencing into NBS programs as a primary screening tool. These concerns range from the practical to the philosophical.

Feasibility

As noted, the NBS system is designed to be high-throughput with a rapid response times. Large states such as California have more than 500,000 births per year, meaning more than approximately 1370 specimens per day must be managed by the NBS program. Medium-sized states like Virginia have about 100,000 births per year, meaning the NBS program must manage roughly 274 specimens per day, each and every day. While conducting GSS on dried bloodspots is feasible, it is not easy using current technology. Moreover, sequencing typically takes several days to complete. Added to this sequencing workload is the task of interpretation. The interpretation of sequence data is constantly evolving, and the identification of uncommon variants requires knowledgeable analysis that is currently not amenable to automation. The prospect of conducting GSS on hundreds of specimens per day, day in and day out, in a state-based program is far beyond foreseeable capabilities without a massive investment in infrastructure.

Another element of feasibility is cost. The goal of a $1000 genome does not include the costs of interpretation, diagnostic confirmation, or information management. Nevertheless, if we assume that $1000 will cover this whole package at some point, the cost of GSS for the U.S. NBS programs would be $4 billion per year (4 million infants born per year X $1000 per sequence). An investment of this magnitude would require the demonstration of substantial benefits from such screening and a demonstration that $4 billion per year would not be much better spent for other child health or welfare programs.

Criteria for Conditions Targeted

An on-going challenge for NBS programs is how to determine what conditions should be targeted. Criteria for population screening were developed by Wilson and Jungner in 1968 [14] and were refined and updated by Andermann in 2008 [15]. Central to these criteria is the realization that population screening is quite difficult to conduct successfully. The Secretary's Advisory Committee on Heritable Diseases in Newborns and Children was established in 2006 to conduct evidence-based reviews to make recommendations on what conditions should be added to the Recommended Uniform Screening Panel (RUSP). A particular controversy arose over the adoption by SACHDNC of a panel of 29 conditions (and 25 secondary conditions) following a recommendation by the American College of Medical Genetics (ACMG) in 2006. The central guiding principle for inclusion of a condition on the panel was a demonstrated benefit to affected children. However, another significant factor in the adoption of this panel was that most of the conditions could be identified on a multiplex platform—tandem mass spectroscopy.

GSS is the epitome of all multiplex platforms. Results would include variants with strong disease associations,

weak disease associations, and carrier states. In addition, there would be findings on a whole host of variants of unknown clinical significance. Genome sequencing entails a deep analysis of a child's genome that will yield information that may not only provide immediate and significant benefit to the child for some conditions, but will also provide information about smaller health risks, carrier states, variants of unknown significance, and conditions that may not impact the child for decades or during his/her lifetime.

Further, newborns would be identified who are at high risk for adult-onset conditions, including cancers and neurodegenerative conditions. Identification of an infant who has a BRCA1 mutation may not have immediate clinical relevance to that child, but the information would have clear relevance to one of the parents who would be an obligate carrier.

The issue here is not simply one of information management. The literature clearly shows that a substantial number of parents of children who receive false positive results from NBS experience prolonged uncertainty and anxiety about the health of the child [16].

If we decide that there is no obligation to return any of these GSS results unless they meet traditional criteria for newborn screening programs, then there is little need to conduct screening through GSS in the first place. If we decide that there is an ethical obligation to return some or all of these kinds of results, then the task becomes twofold: (1) decide what information should be revealed, and (2) manage the enormous volume of information generated. The ACMG recently offered a set of recommendations on what variants should be routinely targeted in all cases when WGS/WES is conducted in a clinical context [17•]. They provide a report of 56 genes that are associated with 26 conditions and that report includes patients of all ages. A number of these conditions are adult-onset, so this means that newborns undergoing GSS would receive results on adult-onset conditions. The justification is that this information is relevant to the healthcare of a parent who is an obligate carrier and may be useful for the child in future years. The ACMG recommendations are controversial, in part because of the traditional professional standards that discourage genetic testing of children for adult-onset conditions unless there are clinical measures to be taken during childhood.

For arguments sake, if we were to adopt the ACMG list as a starting point for disclosure of results following GSS in the newborn screening context, we could anticipate a true positive finding in approximately 1 % of sequenced individuals. Newborn screening is conducted on 4 million newborns per year, meaning that 40,000 newborns per year would have a positive screen for a condition on the ACMG panel. This would be above and beyond the roughly 8000 true positive infants identified per year on the current NBS panel. From this simple calculation, it would appear that newborns with ancillary conditions identified by virtue of sequencing would be fivefold greater in number than the newborns with conditions currently targeted by NBS programs. The predominant set of activities in NBS programs would constitute management of ACMG targeted conditions rather than conditions on the current RUSP. Obviously, this would be a fundamental change in NBS systems because of the basic differences between the ACMG panel and the RUSP. The RUSP is focused on benefits of screening to the newborn with secondary benefits to parents, while the ACMG panel, in this context, would be focused to a significant degree on benefits to the parents with secondary or potential future benefits to the child. This would represent an entirely different philosophical basis for the programs.

We know that the current NBS system is a challenge for many primary care providers who must disclose and manage the information because they are not familiar enough with the conditions targeted. If we were to increase the amount of information by at least fivefold, it seems clear that primary care providers will be unlikely to effectively manage this flow, particularly given the complexity and uncertainty of genomic data. Further, the ACMG recommendations emphasize benefits to parents from GSS in children, so the newborn's results will lead to an expanded set of testing of parents and the kindred—this also must be understood and initially managed by primary care providers. Further, these calculations only consider the newborns with true positive results. The number of children with false positive and results of unknown clinical significance from sequencing would be orders of magnitude greater still. Simply put, the professional infrastructure is entirely inadequate for effectively managing genomic information on this scale.

Parental Education and Permission

It has long been recognized that the education of parents about NBS is limited and largely ineffective. New parents typically are given a brochure in the packet of information provided after a baby is born. Parents may or may not attend to the brochure because there are many other competing demands on their attention and the risk of having an affected child is low. Further, NBS is mandatory in all states except Wyoming and the District of Columbia, meaning that care providers need not get parental permission or even inform parents before obtaining the bloodspots. Most states permit parents to opt-out of screening for religious or philosophical reason, but parents typically are not made aware of this option.

The traditional justification for mandatory screening is that the benefits of this public health intervention are so substantial that the state can override parental decision-making. This justification has not been uniformly accepted. In 2013, the ACMG and American Academy of Pediatrics issued a report on ethical issues in genetic testing in children that recommends that the offer of NBS be mandatory but that screening only be conducted with parental permission [18]. Part of the justification for requiring parental permission in this context is that the benefits for NBS for many conditions on the panel are not nearly so dramatic as they are for the paradigm condition, PKU. The argument goes that, if there are uncertain benefits for some conditions and prospects of harm through false positive results, permission should be obtained for screening, just as permission is obtained for healthcare interventions for children in all other domains of medicine.

The newborn's results also will frequently have implications for the parent's health. Given the current ethical standards for the health care of children, testing on the genomic scale could not be conducted without the careful education and informed permission of the parents. The scope and magnitude of GSS is far too great to be considered on a mandatory basis even if selected conditions identifiable through sequencing would fit within the current justification for mandatory screening. Therefore, use of GSS as a primary screening tool would necessitate a transition to a full permission model for NBS. Here again, the manpower and resources necessary to support a thorough education and an informed decision-making process by new parents regarding sequencing would be monumental. Newborn nursery and/or OB staff would have to be entirely re-educated and services re-staffed to add this new responsibility for each and every set of new parents.

Conclusions

Although GSS is technical tour de force, it represents a halfway technology, in the scheme of Lewis Thomas, because its sophistication masks the fact that our understanding of genomic function remains limited. In this light, it should be clear that genome sequencing represents an inappropriate technology for population screening. The lack of specificity for sequencing will lead to an enormous volume of useful, marginally useful, useless, and misleading information on a large proportion of infants screened. The burdens, including cost, of analyzing, sorting, and responding to this flow of information would be enormous. Further, the psychological burden to parents of working through a detailed genomic report on their new baby, with all of its uncertainties, demands that the benefits be substantial. Indeed, such expansive testing might lead to a backlash from parents from screening overkill when continuing to target a modest list of treatable conditions would suffice for virtually all parents.

GSS may well have appropriate applications in newborns who have genetic conditions for which we need a greater understanding. Using sequencing in a research context can be justified with appropriate education and informed permission of the parents. But genome sequencing is entirely unsuited for use as a primary screening tool within mandatory public health programs.

Compliance with Ethics Guidelines

Disclosure Jeffrey R. Botkin and Erin Rothwell declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. • Dondorp W, de Wert G, Bombard Y, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Eur J Hum Genet. 2015;23:1438–50. *This highlights the ethical challenges of genome wide sequencing prenatally and raises similar challenges for genome wide sequencing in newborn screening.*
2. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med. 2014;6:265ra168.
3. Health NIo. Newborn screening in the genomic era: setting a research agenda. Newborn screening in the genomic era: setting a research agenda. Rockville: National Institute of Health; 2010.
4. Health NIo. NIH program explores the use of genomic sequencing in newborn healthcare. 2013.
5. Bamshad MJ, Ng SB, Bigham AW, et al. Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet. 2011;12:745–55.
6. Kitzman JO, Snyder MW, Ventura M, et al. Noninvasive whole-genome sequencing of a human fetus. Sci Transl Med. 2012;4:137.
7. • Botkin JR, Belmont JW, Berg JS, et al. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet. 2015;97:6–21. *This is an excellent review of the ethical, legal and psychosocial implications of genome wide sequencing in children and how it impacts the family and future reproductive decisions.*
8. Feuchtbaum L, Carter J, Dowray S, Currier R, Lorey F. Birth prevalence of disorders detectable through newborn screening by race/ethnicity. Genet Med. 2012;14:937–45.
9. Lewis M. Newborn screening controversy: past, present, and future. JAMA Pediatr. 2014;168:199–200.
10. Feutchbaum L, Cunningham G, Sciortino S. Questioning the need for informed consent: a case study of California's experience with

a pilot newborn screening research project. J Empir Res Hum Res Ethic. 2007;3:3–14.
11. Fant KE, Clark SJ, Kemper AR. Completeness and complexity of information available to parents from newborn-screening programs. Pediatrics. 2005;115:1268–72.
12. Fox C, Lloyd-Puryear M, Mann M. Serving the family from birth to the medical home. Newborn screening: a blueprint for the future—a call for a national agenda on state newborn screening programs. Pediatrics. 2000;106:389–422.
13. Wilcken B. Newborn screening: gaps in the evidence. Science. 2013;342:197–8.
14. Wilson J, Junger G. Principles and practice of screening for disease. Public health papers #34. Geneva: World Health Organization; 1968.
15. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008;86:317–9.
16. Lipstein EA, Perrin JM, Waisbren SE, Prosser LA. Impact of false-positive newborn metabolic screening results on early health care utilization. Genet Med. 2009;11:716–21.
17. • Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15:565–74. *This is foundational article about what type of incidental findings should be returned to adults as well as children.*
18. Fallat ME, Katz AL, Mercurio MR, Moon MR, Okun AL, Webb SA, Freedenberg DL. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013;131:620–2.