Newborn screening in the genomics era

Shannon Rego*

Stanford University, CA 94305, USA.
Corresponding author. E-mail: srego@stanford.edu

ABSTRACT

Newborn screening (NBS) exists in every state for the purpose of testing newborns for genetic medical conditions that can be severe, may be treatable, and are often not clinically evident at birth. While almost all of the diseases screened for in newborns have underlying genetic causes, NBS in its current form is performed not by testing for genetic mutations, but by testing for biochemical markers that indicate a disorder. The potential use of whole-genome newborn screening (WG-NBS) as an alternative to the current biochemical testing utilized for NBS would dramatically expand the quantity and types of information parents could learn from screening and is likely to have many implications, both positive and negative. As whole-genome sequencing (WGS) becomes more economical, it probably will be used for the purposes of NBS. However, such an expansion of NBS would contradict many of the principles that have historically guided public health screening programs and, if implemented without sufficient preparation, could result in insufficient infrastructure to accommodate the health care and data management needs that would arise. This article will first look at the past and present of NBS, then the rise of whole genome sequencing, before considering the challenges of WG-NBS, and will end with some thoughts on the path forward.

KEYWORDS: newborn screening, whole-genome sequencing

NBS: PAST AND PRESENT

NBS began in the United States in the 1960s with screening for phenylketonuria (PKU), a rare genetic disorder for which early identification dramatically affects prognosis. The first screening test required collecting a drop of a newborn’s blood via a heel prick within 24–48 hours of birth and depositing it on a piece of filter paper. This test

* Shannon Rego is a genetic counselor working on genomics research at Stanford University.
was used for NBS when the states first began requiring it by law in 1963.\(^1\) The success of NBS for PKU led to questions about whether this screening method could be applied to other diseases as well. The list of diseases screened for has grown steadily since the 1970s. In the USA, states pass laws requiring NBS for various conditions—the USA is one of the only two industrialized nations without a national NBS program.\(^2,3\) As of 2000, there were significant differences in the diseases states were screening for, as well as a large range in the number of conditions screened for—between 3 and 36, depending on the state.\(^2\)

In 1968, only a few years after the USA first implemented PKU screening, the World Health Organization (WHO) released guidelines, written by James Maxwell Glover Wilson and Gunnar Junger, meant to guide population-based screening programs. These guidelines state that screening should be done for conditions that address important health problems for which an accepted treatment is available. These principles emphasize that the individual being screened should benefit from the screening program. This guideline was echoed in many reports that followed, including the 1994 report by the Institute of Medicine, *Assessing Genetic Risk: Implications for Health and Social Policy*, which stated that ‘a person should not be used as a means for the benefit of others’. This is a crucial point to consider in the context of whole-genome screening, as many (though not all) of the benefits of screening for conditions are for the family or society, not for the affected individual.\(^2\)

By 2003, the geographical disparities created by states’ differing laws on NBS led to the creation of a national task force, which recommended the development of a standardized list of conditions for NBS. The task force funded the American College of Medical Genetics (ACMG) to create a panel of experts. In 2005, the group released a report including 29 conditions.\(^4\) In creating this list, the panel considered several factors, including the incidence and burden of the condition, the availability and efficacy of the screening test, and the availability and efficacy of treatment.\(^5\) These 29 core conditions all result in serious medical complications, such as permanent cognitive impairment or death, if not recognized early, and all have some interventions that can improve outcomes if diagnosed early. Another 25 conditions were assigned to a secondary list because the corresponding metabolites are found incidentally as part of the process of screening for the core conditions, and in many cases their significance is not understood.\(^6,7\) The Secretary of Health and Human Services adopted the list as the nation’s

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1. Robert Guthrie, *The Introduction of Newborn Screening for Phenylketonuria: A Personal History*, 155 EUR. J. PEDIATR. S4 (1996).
2. STEFAN TIMMERMANS & MARA BUCHBINDER, *SAVING BABIES? THE CONSEQUENCES OF NEWBORN GENETIC SCREENING* (2012).
3. Diane B. Paul, *Promoting Safe and Effective Genetic Testing in the United States*, National Institute of Health, National Human Genome Research Institute (2006), http://www.genome.gov/10002397 (last accessed September 2, 2014).
4. American College of Medical Genetics, *Newborn Screening: Towards a Uniform Screening Panel and System*, 8 GENET. MED. 15 (2006).
5. R. Howell, *Current Practices and Expansion of Newborn Screening*, Center for Disease Control (Aug. 18, 2011), http://www.cdc.gov/cdgrandrounds/pdf/grehrallfinal18aug2011.pdf (last accessed June 1, 2014).
6. National Institute of Child Health and Human Development, National Institutes of Health, *Brief History of Newborn Screening* (2013), http://www.nichd.nih.gov/health/topics/newborn/conditioninfo/pages/history.aspx (last accessed June 1, 2014).
7. Virginia A. Moyera et al., *On Behalf of the United States Preventive Services Task Force, Expanding Newborn Screening: Process, Policy, and Priorities*, 38 Hastings Center Re. 32 (2008).
Newborn screening in the genomics era

NBS standard in May 2010, although, again, state governments, not the federal government, actually decide which tests will be used. This report was important in providing, for the first time, national guidelines with recommended minimums for NBS in order to reduce inequities in screening programs among states. It would both encourage performance of useful screening tests and help prevent screening for conditions deemed inappropriate for NBS.

One of the driving forces of this shift was the dramatic technological improvements occurring concurrently. Around the same time the ACMG report came out, tandem mass spectrometry (MS/MS) technology was introduced and was adopted by most screening programs in the USA. This technology made screening faster and easier by allowing most screens to be run on the blood spot concurrently, rather than requiring a separate assay for each. It also reduced the number of false positives. MS/MS can screen for more than 40 inborn errors of metabolism, which comprise the majority of NBS panels in all states. Today, more than 4 million newborns are screened each year in the United States, and of them, 12,500 are diagnosed with one of the core conditions, of which there are now 31. The advent of MS/MS so dramatically impacted states’ capacity to screen for more diseases that, for the first time, the limiting factor determining which diseases were screened for was not necessarily the cost or time entailed to test, but rather, the disease characteristics and the disease’s suitability for screening based on several criteria, including the quality of the available screening test and the treatability of the disease. Finally, we were asking not only can we screen for this disorder, but should we?

In addition to state-by-state variation in the conditions that are screened for, states also vary among other dimensions, including treatment protocols, services available for follow-up, and to what extent those services are paid for by the state. In most states NBS is mandatory, and informed consent is not required or obtained. Some states allow parents to opt out of NBS, but parents rarely exercise this option and rarely even know that NBS is being done.

The current cost of NBS is difficult to assess, as the programs are funded differently state by state. However, in California, the cost of NBS between 2005 (when expanded NBS was implemented) and 2009 was about $231 million, making the average cost of screening a child about $115, but the cost of identifying a child with a true positive disorder more than $300,000. These numbers take into account neither additional follow-up testing nor the health-care savings resulting from early identification and possibly preventing severe disabilities.

In addition to the financial cost of NBS, there are other costs as well, including the time, money, and stress associated with false positives. False positives are an unavoidable part of screening programs, which struggle to balance sensitivity and specificity. Based on the statistics published from California’s newborns screening program between July 2005 and April 2009, 2,105,119 newborns were screened, and of those 4580 were referred to a metabolic clinic for follow-up. Ultimately, 754 of these infants (16%)

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8 Sam Crowe, A Brief History of Newborn Screening in the United States: Staff Discussion Paper, President’s Council on Bioethics (2008), https://bioethicsarchive.georgetown.edu/pcbe/background/newborn_screening_crowe.html (last accessed June 1, 2014).
9 Mary A. Baily & Thomas H. Murray, Ethics, Evidence, and Cost in Newborn Screening, 38 Hastings Center Re. 23 (2008).
were confirmed to have a disorder (true positive result), making the ratio of false positives to true positives more than 4:1.\(^2\)

**WHOLE-GENOME SEQUENCING**

Recent advances in technology have dramatically altered the landscape of genetic testing. The human genome was first sequenced in full in 2003. It took 13 years and cost nearly $3 billion.\(^{10}\) As of January 2014, a leading sequencing company is claiming to be able to sequence the whole genome (without interpretation) for $1000 in 24 hours.\(^{11}\) While $1000 per test is still prohibitively expensive for a program that tests more than 4 million infants a year, the precipitous drop in the cost of WGS has led many to wonder if, or when, this technology might be utilized for NBS.

Were WGS to be adopted for NBS, it would dramatically increase the amount of information available from screening. With current methods for NBS, the output is simply biochemical levels for a few dozen analytes. A genome, on the other hand, comprises more than 3 billion base pairs, and can require more than 1.5 terabytes of data storage capacity. Of course, we only understand the functionality of a very small percentage of the genome, but even so, having this information would mean that in theory, we could give parents information about all genes known to have implications in disease, or even traits, and your knowledge of these correlations will only increase in time.

Anticipating the rapidly changing landscape of genetic testing, the NIH launched a pilot program in 2013 to explore the use of WGS for the purposes of NBS, giving $25 million to four grantees over five years to perform genomic sequencing and analysis on newborns; perform research related to patient care; and explore the ethical, legal, and social implications of using genomic information in the newborn period.\(^{12}\)

**DEFINING POTENTIAL IMPLICATIONS**

Needless to say, the potential implications of a change from the current biochemical-based screening method to WGS are significant. Such a change would also represent a major shift in the moral focus of NBS, which in its origins was aligned with the Wilson and Junger principles for screening, including that conditions screened for should represent a serious public health problem, have a well-understood natural history, and be diagnosable and treatable.\(^{13}\) Widespread adoption of WG-NBS will raise numerous difficult questions, including (1) what information should be returned to parents, (2) what to do about variants of unknown significance (VUSs), (3) what infrastructure will be needed, (4) privacy and research uses, and (5) informed consent.

\(^{10}\) National Human Genome Research Institute, National Institutes of Health, *The Human Genome Project: Frequently Asked Questions* (2010), [http://www.genome.gov/11006943](http://www.genome.gov/11006943) (last accessed June 1, 2014).

\(^{11}\) Matthew Herper, *The $1,000 Genome Arrives—For Real, This Time*, Forbes, Jan. 14, 2014, [http://www.forbes.com/sites/matthewherper/2014/01/14/the-1000-genome-arrives-for-real-this-time/](http://www.forbes.com/sites/matthewherper/2014/01/14/the-1000-genome-arrives-for-real-this-time/) (last accessed June 1, 2014).

\(^{12}\) National Human Genome Research Institute, National Institutes of Health, *Centers for Mendelian Genomics* (2013), [http://www.genome.gov/27546192](http://www.genome.gov/27546192) (last accessed September 2, 2014).

\(^{13}\) Anne Anderman et al., *Revisiting Wilson and Junger in the Genomic Age: A Review of Screening Criteria Over the Past 40 Years*, 86 BULL. WORLD HEALTH ORG. 317 (2008).
What information should be returned?

Few studies assess the types of information parents would want to know from WG-NBS, and only a handful have asked parents the same question regarding past expansions of NBS. Those that have been done on WG-NBS have shown parents to be strongly in favor of it.\textsuperscript{14,15} However, both studies were performed using surveys, and it is difficult to explain the magnitude of whole-exome and WGS to patients even with the benefit of time to have a conversation.

Most of the studies addressing the types of information parents do and do not want from NBS have been focused on previous expansions of NBS and do not address all the types of information WGS can provide, or the scale of the test and the quantities of information that could be returned. These studies generally found that parents err on the side of wanting more information, not less, from NBS. Parents prioritize the potential benefits of screening over the potential harms, with more controversy surrounding screening for later-onset conditions for which there are not preventative measures or treatment available.\textsuperscript{16,17,18,19}

This question of which types of information should be returned from whole-exome or whole-genome sequencing has been addressed formally by a professional organization, but not in the context of screening. As the ordering of whole-exome sequencing has become more commonplace in clinic, and WGS is done regularly on a research basis, the ACMG released guidelines for the return of incidental findings in 2013. These recommendations include a list of conditions/genes for which findings unrelated to the patient’s medical presentation should be reported—the list is primarily comprised of genes which cause cardiomyopathy or a predisposition to cancer.\textsuperscript{20} All of these conditions are serious and potentially life-threatening and there are preventative measures or treatment available, which would not be the case with the majority of the conditions detectable via WG-NBS.

One factor influencing which genetic tests providers order and which information is returned to patients is the issue of medical malpractice. Genetics health-care providers, and medical geneticists in particular, have increasingly become the target of lawsuits. There are several reasons for this—first, new medical technologies often lead to a wave of malpractice suits. The more that can be done to treat or prevent a particular condition, the more a physician could be at fault for failing to consider. Also, there is little consensus about the circumstances under which various genetic tests should be offered,

\textsuperscript{14} Yvonne Bombard et al., \textit{Public Views on Participating in Newborn Screening Using Genome Sequencing} \textit{EUR. J. HUM. GENET.} (2014), \url{http://www.ncbi.nlm.nih.gov/pubmed/?term=public+views+on+participating+in+newborn+screening+using} (last accessed June 1, 2014).
\textsuperscript{15} Aaron J. Goldenberg et al., \textit{Parents’ Interest in Whole-Genome Sequencing of Newborns}, \textit{16 GENET. MED.} 78 (2014).
\textsuperscript{16} H. Etchegary et al., \textit{Interest in Newborn Genetic Testing: A Survey of Prospective Parents and the General Public}, \textit{16 GENET. TEST. MOL. BIOMARKERS} 353 (2012).
\textsuperscript{17} H. Etchegary et al., \textit{Public Attitudes about Genetic Testing in the Newborn Period}, \textit{41 OBSTET. GYNECOL. NEONATAL NURS.} 191 (2012).
\textsuperscript{18} L. E. Hasegawa, et al., \textit{Parental Attitudes toward Ethical and Social Issues Surrounding the Expansion of Newborn Screening Using New Technologies}, \textit{14 PUB. HEALTH GENOM.} 298 (2011).
\textsuperscript{19} Robin Z. Hayeems et al., \textit{Expectations and Values about Expanded Newborn Screening: A Public Engagement Study}, \textit{HEALTH EXPECT.} (2013). DOI: 10.1111/hex.12047.
\textsuperscript{20} Robert C. Green, et al., \textit{ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing}, \textit{15 GENET. MED.} 565 (2013).
including which types of tests are ready for clinical application, as well as the clinical significance of the results. Even if there were a list of recommended information to return to parents from WG-NBS, there would still be an abundance of ambiguity in the test results. VUSs are common in genetic testing, and it is often unclear whether a mutation is likely to cause disease or not. The medical significance of many genes is also often unclear. Genetics professionals frequently make difficult judgement calls when deciding what to report back to patients.

Of course, genetics health-care providers are not the only ones who could be held liable for failing to order a genetic test or report back genetic testing information in a clinical context. Other types of physicians can and have been held liable for failing to order or interpret appropriate genetic testing, including a recent case in Connecticut in which a woman sued her physician for failing to warn her that her family history of breast cancer also implied a possible genetic risk for ovarian cancer. The Connecticut Supreme Court upheld a $4 million jury verdict after she developed ovarian cancer.21 Unfortunately, most medical schools have only recently started training students in genetics, and many physicians feel that they do not have sufficient training in this area.22

Also contributing to the increasing risk for medical malpractice suits in the medical genetics field is a recent shift away from a local custom standard for medical malpractice toward a more objective standard of ‘reasonableness’, or a national standard of care.23 This shift could increase the risk for physicians who have limited genetics background or work in clinics where genetic testing is not frequently offered due to a lack of training or financial resources.

While concerns about medical malpractice and a desire to be thorough might lead physicians and policy makers to favor returning more results, especially in the context of WG-NBS, it is also important to consider the negative impact of returning positive results. False positives will become more common as we look at yet more genetic information, and multiple studies have shown that abnormal NBS results requiring further testing lead to parental anxiety and/or depression, even when the follow-up testing is normal.24

**Variants of unknown significance**

Much of the variation we find with WGS does not fit neatly into the category of a known mutation. Every time WGS is performed, that genome is compared to a reference genome, and the number of differences between the reference genome and the patient’s genome usually reaches well into the millions. These differences, or variants, are pared down first by filters and computer algorithms, and then by a person who performs a review of the scientific literature. The variants are categorized by the likelihood that they are disease causing. Even after this process, the list of variants on the final report can number in the double digits and is usually comprised of a combination of variants in genes that may be related to the clinical presentation with varying degrees

21 Downs v. Trias, 49 A.3d 180 (Conn. 2012).
22 Richard R. Sharp, Michael E. Goldlust & Charis Eng, **Addressing Gaps in Physician Education using Personal Genomic Testing**, 13 G ENET. MED. 750 (2011).
23 Gary E. Marchant & Rachel A. Lindor, **Personalized Medicine and Genetic Malpractice**, 15 G ENET. MED. 921 (2013).
24 J. Hewlett et al., **A Review of the Psychosocial Effects of False-Positive Results on Parents and Current Communication Practices in Newborn Screening**, 29 J. INHERIT. METAB. DIS. 677 (2006).
of certainty, as well as variants that are clearly unrelated to the phenotype but are part of the ACMG list of incidental findings that are recommended to be reported. Often times they are VUSs, and it is not possible to advise patients as to their significance until years later, when that particular variant has been seen in enough people to know whether or not it correlates with disease.

VUSs have long been a challenge with clinical genetic testing—even single gene testing—but WGS presents a whole new level of problem. In its current iteration, NBS looks for a small number of well-understood conditions. WGS will give us orders of magnitude more information. Currently there is still more uncertainty than certainty about the human genome. For WG-NBS to work, we will need to determine how we want to address uncertain results—what kinds of VUSs will be returned to parents, if any? How will parents be notified of changes in the status of VUSs (which are generally re-classified over time), if at all?

**Infrastructure**

This issue of VUSs relates to the next complication of WG-NBS, which is the need for a great deal more infrastructure and funding than exists in our current form of NBS. WG-NBS will mean a dramatic increase in the number of ‘screen positives’, both true and false. Some will fall in a gray area between true and false—an infant, for example, who exhibits a genotype that sometimes correlates with a metabolic disease but who has no biochemical findings of the disease, but who may still need to follow up with genetics regularly and go on expensive medications as a precaution. Is this a good thing because it could prevent manifestation of disease, or bad because we would be overtreating healthy individuals?

The parents of these ‘screen positive’ infants will need to have the infants followed in a genetics clinic. In the event that they are true positives, they may need life-long follow-up care. Where will these families go for follow-up and who will pay for it? Who will obtain the consent of parents at the beginning of the WG-NBS process? Are there enough genetic counselors or other trained health-care professionals who are qualified to return WGS results to families? One recent study of genetic counselors shows that 82% do not feel prepared to counsel families on results of WG-NBS, implying that a great deal more education is needed for health-care providers, as well as for the public.\(^{25}\)

Additionally, significant infrastructure will be necessary to manage the massive quantities of data WG-NBS would generate. As well as having capacity to store the data, a system must be in place to control access to the data. If parents have a choice about the types of data they receive from WG-NBS, would they have the option of receiving information (such as information about adult-onset conditions) later in their child’s life? Or would the child himself have that option? If so, how would that information be conveyed at the appropriate age, especially if the individual has moved to another state?

**Privacy and research use**

Privacy implications are another major consideration with regard to WG-NBS. NBS in its current iteration is not a genetic test, and it looks for a discreet set of conditions. WG-NBS, however, would look at all of an infant’s genetic material, making it possible

\(^{25}\) Monica D. Nardini et al., *Genomic Counseling in the Newborn Period: Experiences and Views of Genetic Counselors*, 23 J GENET. COUNS. 506 (2014).
to know at birth if a baby will develop Huntington’s disease or if she is at increased risk for breast cancer. We could learn that her chromosomal gender does not match her phenotypic gender and that she will be infertile, or that her stated father is, in fact, highly unlikely to be her actual father. In the future, we will be able to tell much more.

To whom would this information be available? Parents? Physicians? Would the parents and, eventually, the child have the right not to be told certain types of information? If so, how would it be concealed from them? Would the state be allowed to keep samples used for WG-NBS for other research, a practice already controversial with newborn blood spots? These are important questions that should be answered before WG-NBS would be implemented.

**Informed consent**

Going hand in hand with this issue of privacy and the use of biological samples for research purposes is that of informed consent. As discussed earlier, most states mandate NBS and parents must be proactive to opt out or to prevent their child’s blood spot from being used in research. An opt-out policy for population-based screening that is looking for a small number of well-defined conditions seems reasonable, but informed consent for genetic testing has long been considered vital.²⁶ For WGS, informed consent is particularly important, due to the many different types of information it could provide and the potential significance of that information both on the individual screened and his family. Additionally, studies have shown that parents strongly support explicit informed consent for screening.¹⁶,¹⁷,¹⁸,¹⁹

**WHAT TO DO?**

I am not convinced that WG-NBS should be implemented, but I believe that it is inevitable. The question then turns to implementation. Because the implementation will be complicated, it will be tempting for policymakers to ignore it until it is not possible to ignore anymore. While ultimately viewed by most people as a success, the initial implementation of NBS with PKU screening many decades ago similarly went forward with little prior planning. The logistical and ethical consequences of making the same mistake with WG-NBS would scale with the magnitude of the test itself.

Above all, sufficient planning must go into the implementation of WG-NBS. One of the greatest improvements that could be made to NBS would for it to become a national program. The lack of standardization among states makes for confusion and for inequities in detection and care. Compound these problems with the complications of instituting a program as complex as WG-NBS, and it seems ridiculous to re-invent the wheel 50 times over. In addition to wasting resources, separate NBS programs in each state will complicate the care of those who are screened, making it harder for the information, useful throughout the lifetime of the screened children, to follow them across state lines.

Currently, few studies explore stakeholders’ viewpoints regarding WG-NBS. Such a dramatic expansion of NBS should not be implemented merely because it is possible—it should provide information that parents want, and it should fit into a revised list

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²⁶ Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Genetic Testing for Health Purposes* (2008), [http://conventions.coe.int/Treaty/en/Treaties/Html/203.htm](http://conventions.coe.int/Treaty/en/Treaties/Html/203.htm) (last accessed June 1, 2014).
of population-based screening principles that have buy-in from parents, health-care providers, and policymakers. When such studies are done, I believe we will find that while there are some strong common themes in the types of information parents want to know from WG-NBS (such as a desire to learn about clinically actionable diseases), there will be much more variation for other types of information (for example, non-actionable adult-onset conditions). To address this variation, we must develop an informed consent process that gives parents choices, with an option to have information revealed at a later date if, for example, they change their minds, the child’s health changes, or a VUS is reclassified. Information about non-preventable adult-onset conditions should not be reported to parents, but left to the child to decide when he comes of age, as information about what will happen to an adult should belong to that adult.

WG-NBS should be optional, and informed consent must be an integral part of the process. It makes sense for NBS in its current form to be mandatory because of the nature of the illnesses for which it screens. Today, NBS looks for a limited number of conditions, many of which have serious consequences that can be prevented if detected early. WGS is fundamentally different. It includes these same serious conditions, but also so much more—information families have a right not to know and not to test for. This kind of test should be offered on an opt-in basis only. If informed consent cannot be obtained, then screening should be limited to the diseases currently tested for by biochemical NBS.

CONCLUSION

WGS will replace the current biochemical method of NBS within my career. I only hope that it is done not because the technology exists to make it possible, but as a measured, well-planned answer to the desires of stakeholders. WG-NBS presents an opportunity to implement this technology thoughtfully, based on agreed-upon principles meant to strike an appropriate balance between cost and health outcomes. We must not waste it.