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Newborn Screening in the Genomic Era: Setting a Research Agenda

December 13-14, 2010
Rockville, Maryland

Meeting Summary

Introduction

On December 13-14, 2010, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), and the NIH Office of Rare Diseases Research sponsored a workshop, *Newborn Screening in the Genomic Era: Setting a Research Agenda*. The purpose of the meeting was to identify elements of a trans-NIH research agenda that would lead to the application of new genomics concepts and technologies to newborn screening and child health. The meeting was attended by experts from academia, industry, and federal agencies in the fields of newborn screening and genomics, and chaired by Drs. David Valle (Johns Hopkins) and Piero Rinaldo (Mayo Clinic).

Discussion Overview

The first day of the meeting featured welcoming remarks by Dr. Alan Guttmacher (Director, NICHD) and Dr. Eric Green (Director, NHGRI) and a series of talks on the current state of newborn screening in the United States and elsewhere, emerging technologies that may have application in newborn screening, and some of the ethical, legal, and social implications of research involving newborn screening.

Dr. Rinaldo gave an introduction to the newborn screening system in the U.S. He explained that this system involves education, screening, diagnosis, management, follow-up, and evaluation; he noted that any future research agenda needs to consider all of these elements. As a public health program, newborn screening is subject to considerable cost pressure. He introduced the concept that newborn screening need not occur in isolation but might in the future be part of an integrated system of screening at several stages of life.

Dr. Valle followed with an overview of advances in the field of genomics in the post-Human Genome Project era. The opportunities for genomics to offer deep insights into the genetic determinants of disease are counterbalanced by the limitations of current capabilities for large-scale sequencing (analysis and computational infrastructure, accuracy vs. depth of coverage, difficulty in constructing long haplotypes, and the need to identify and interpret copy number variants (CNVs) from the sequence information).

Dr. Arthur Beaudet (Baylor College of Medicine) presented a talk on prenatal genetic testing, suggesting that diagnoses currently made via newborn screening will increasingly be made *in utero* or inferred from more widespread use of carrier screening. Illustrating this point, Dr. Beaudet discussed approaches such as Counsyl's chip-based Universal Carrier Screening Test that identifies mutations in genes that cause over 100 Mendelian disorders, as well as a next-generation sequencing-based approach to carrier testing for a large number (more than 440) of

severe recessive disorders (Bell et al, *Science Transl Med* 3:1, 2011). A consequence of these genome-wide approaches to heterozygote screening will be the identification of carrier status for one or more diseases in most individuals, each of whom may react to this information in different ways. Past experience from heterozygote screening (e.g., Tay-Sachs disease and thalassemias) predicts that this will lead to a significant reduction in the incidence of live born infants with severe recessive disease. As a research benefit, sequencing large numbers of carriers and creating a comprehensive database of deleterious mutations may prove highly valuable. Dr. Beaudet also discussed a recent report describing sequencing fetal DNA in maternal plasma samples, a technique which, when optimized, could have significant diagnostic implications (Lo et al, *Sci Transl Med* 2:61ra91, 2010). Finally, Dr. Beaudet predicted the possible impact of chromosomal microarrays that focus on CNVs on identifying deleterious chromosomal disorders *in utero*.

Dr. Ron Davis (Stanford Genome Technology Center) spoke on potential technological contenders for use in newborn screening, focusing mainly on targeted sequencing approaches (array-based exon-capture hybridization, RNA hybridization-mediated capture, and molecular inversion probe-based circularization). Dr. Davis stressed the importance of sequencing to detect individuals at high risk for immunologic disorders, as some of these are linked to human leukocyte antigens, although there are still significant technological problems in sequencing this region. He also emphasized that real-world application of genomic technologies to newborn screening will require much higher accuracy and speed than exist currently, as well as much lower costs. Targeted sequencing (sequencing only regions that can be interpreted, as opposed to whole genome sequencing) may be one possible strategy to address this challenge.

Dr. Richard Gibbs (Baylor College of Medicine) followed Dr. Davis with a talk on applying current methods of sequencing to newborn screening. Dr. Gibbs proposed several "straw man" pilot studies to learn how to build a sequencing-based screening pipeline that will be most relevant to the needs of newborn screening. The pilot should include all the relevant steps including organizing the entire workflow from "samples in" to "data out" to relevant stakeholders, obtaining the Institutional Review Board (IRB) approval, securing consent of participants and collecting samples, sequencing the DNA, cataloging the variants, managing the data in the context of health records, and analyzing and interpreting them. Such a pilot study might not use a random newborn screening population because other populations might be more informative. Two alternative models could focus either on individuals who have modest genetic risk or on a larger number of newborns at modest to no genetic risk to build the organizational and analytic parts of the pipeline. Studies should include relatives, known variants, consideration of whether to include whole genome and exome components, and also a technology development component, and all of the elements of the pilot should be measureable.

During lunch there were presentations on new technologies that may have newborn screening applications. Dr. Vamsee Pamula (Advanced Liquid Logic) discussed digital microfluidics and lab-on-a-chip approaches that can multiplex enzymatic assays, immunoassays, or Polymerase Chain Reaction (PCR). Dr. Petri Huhtinen (PerkinElmer) discussed using time-resolved fluorescence resonance energy transfer (TR-FRET)-based end point PCR using dried bloodspots as samples. Dr. Keld Sorensen (Luminex) discussed the use of bead-based multiplexed assays to

conduct targeted genetic screens. Finally, Dr. Andre Marziali (University of British Columbia) discussed nanopore-based DNA and protein analysis.

The challenges of new technology in the ethical, legal, and social contexts were examined in a series of talks, beginning with Dr. Jeffrey Botkin (University of Utah School of Medicine).

Dr. Botkin began by pointing out that the newborn screening system is a low-cost, high-throughput, accurate system of tests, with a primary goal of improving the health of children. He also identified the difference between newborn screening and the screening of newborns, a distinction to which workshop participants would repeatedly return (see below). Dr. Botkin identified a number of ethical concerns with parental permission and education. Prenatal education has been widely endorsed as a way to ameliorate some of these problems, but faces major hurdles given obstetricians' lack of time, familiarity with, and commitment to newborn screening. He concluded his talk with a set of recommendations for developing effective methods for prenatal education about and permission for newborn screening, and recommendations for making parental choice information available to care providers.

Dr. Bent Nørgaard-Pederson discussed the Danish experience with newborn screening. Denmark has deposited all newborn screening blood spots in a biobank since 1982. Subjects can opt out of having their samples stored, or from having their samples used for research. The first priority for the use of newborn biobank material is to meet the needs of the parents and child. The second priority is the development and validation of new analytical methods for diagnosing congenital diseases, which might feed into newborn screening. The third priority is research. An IRB-like council ensures that guidelines are followed. In addition to providing critical medical information to families, biobank samples have contributed to assay improvements and cost reductions, and development of new tests and products.

Dr. Fred Lorey (California Department of Public Health) discussed the role of states and state legislation in newborn screening. He noted that legislative hurdles can cause significant delays or impediments to rolling out new technologies or even adding specific diseases to the newborn screening panels. Dr. Lorey identified partnering with groups such as disease advocacy organizations as a way to work with legislators, since state government employees are often banned from lobbying or even discussing legislation with bill authors. Dr. Lorey closed with vignettes on the effect of using consent for prenatal screening on the screening enterprise, researchers, and families.

During the discussion that followed presentations, a distinction was made repeatedly between newborn screening and the screening of newborns. The former is the current public health system used to identify a range of actionable childhood diseases, whereas the latter is far more encompassing, and could involve using sequencing (or other technologies) to identify adult-onset diseases and/or provide other information that would benefit patients throughout their lives. Screening of newborns (as opposed to newborn screening) lends itself well to answering research questions, both about specific diseases and conditions, and also whether and how genome sequencing affects a child's health over time.

Following these presentations, there were three breakout groups:

- New genomic technologies
- Education and expectations
- Scope and timing

These groups were charged with identifying new research opportunities by addressing the following three questions:

1. What are the most exciting areas of research that may emerge from the application of genomic approaches to newborn screening (organized by priority)?
    - How will these changes impact the fields of public health and research?
2. Gap analysis: what needs to happen to facilitate such research?
3. What are the greatest challenges to such projects, and how can those challenges be addressed?

The chairs of the workshops presented their recommendations on the second day. These presentations were followed by plenary discussion. The research agenda proposed by each breakout group is summarized below.

Breakout Group 1: New Genomic Technologies

Group 1 proposed a research project that would involve whole genome sequencing of 1,000 trios (1,000 children along with each of their parents). The children would be selected on the basis of a true positive newborn screening test. By targeting children who have one of the disorders detected by current newborn screening, such a study could compare the biochemical and genomic approaches as well as investigate the role of possible modifier loci on the phenotype; by including trios, it would also provide information about de novo mutation rates. However, such a design—while dealing with practical issues (sample collection, consenting, analysis, data storage)—would not be optimal for issues related to detection of risk for adult onset disease, because the health of the sequenced newborns would be influenced in a significant way by the disease detected in the newborn screening and its management. Since the subjects would be identified by true positive newborn screening, it would be possible (and potentially preferable) to enroll the subjects in such a project beyond the newborn period, as phenotypic data would already have been collected as part of their medical care. Additionally, enrolling the cohort would be much faster. Parents of affected children would also be more likely to see the value of participation in a research study of this nature. Study design details for such a project would need further discussion, to determine the necessary sample size to detect relevant alleles.

Following consent of both parents, blood samples would be obtained to compare with dried blood spots. Other samples could also be obtained (e.g., saliva, cord blood in the newborn period), as these samples may be more accessible and more straightforward for use with some of the newer technologies (e.g., microfluidics). Point-of-care testing and point-of-care data generation could also be explored to provide immediate data for evaluations and feedback, which is critical in many metabolic disorders. The group also suggested that epigenomic factors or the newborn microbiome could be part of the research project. In addition, the group said that the proposed project should integrate electronic health records as a way to develop their use in research and clinical decision-making. A critical aspect of the design of the pilot study would be to establish metrics for false positive and false negative rates and the clinical validity of assays.

The group's gap analysis identified several areas that could be incorporated into the study. There is a need for higher accuracy and speed, and lower cost, than current sequencing technologies provide. Epigenomic analyses on newborn samples could detect individual differences that might correlate with genetic differences as well as variations in *in utero* experiences and would provide a baseline for repeated analysis of changes in the epigenome over the lifetime of the individual.

Currently, biochemical newborn screening tests are able to identify accurately most newborns who are at risk to develop certain diseases, so the aim of this study would be to determine whether or not genomic analysis would further inform clinicians and parents as to the molecular basis of the disease as well as predict its progression. Sequencing could also reveal insights into the pathways involved in the particular disease that may not be well understood currently, leading to novel therapeutic options.

Current projects such as 1,000 Genomes and the ENCODE (Encyclopedia of DNA Elements) were identified as good models for such a pilot project. Challenges included the need to think beyond the current newborn screening public health paradigm to scientific opportunities in personalized and predictive health, and issues of deployment, which will require research on the best methods of implementation.

Breakout Group 2: Education and Expectations

One proposed project would be to prospectively perform a genomic or exomic assessment and analysis of the principal causal gene for an individual known disorder in affected individuals and correlate this with comprehensive phenotypic data. Integrating this information with electronic health records might offer the development of new tools for clinicians in monitoring and predicting disease progression based on genotype-phenotype correlations. The group suggested that this project could provide a real-world test case for communication of genomic information to families and could expand to genome-wide testing.

A second important project could explore various cultural perspectives regarding what parents and clinicians want to know and expect to know about newborn screening. The group felt that newborn screening education is an important but an extremely difficult and challenging area in which to carry out projects. They noted, for example, that it is quite different to assess knowledge vs. competence vs. confidence. This project might result in the development of standardized educational tools (e.g., computer or Web-based educational programs, a guide for written or oral communication or face-to-face counseling with a variety of health care providers). This project would build upon the theoretical and empirical work that has already been done in this field.

A third project could focus on newborn screening education specifically. It would test methods to provide genomic health education to both children across their lifespan and older people who have not already received the education. Education would be tailored to the specific audience (health care providers, parents, patients, public, researchers, IRBs, insurance companies).

The breakout group also suggested incorporating CNV detection into one of the pilot studies to determine if prospective identification of medically significant CNVs would reduce delays in diagnosis and unnecessary diagnostic testing.

This breakout group provided a gap analysis as follows. First, they noted that tools for phenotyping are needed, including psychological assessment tools. Second, they asked, if genotyping is being done, what should be communicated? This could become the opportunity to look much more deeply at outcomes. Tools are needed to determine both long- and short-term outcomes and family functioning. Third, they observed that innovative educational tools and approaches (for both families and practitioners) are needed. Finally, they said that the gaps in IRBs' knowledge must be filled, noting that IRBs differ in levels of sophistication, and their members often need education themselves. They agreed that this would have to be a bi-directional process, with mutual education of both the IRBs and the research community.

The group suggested that challenges to such projects begin with IRB review problems. A newborn screening pilot project of any breadth could have to deal with 50 or more state IRBs, not just a few regional committees. A study of the influence of state IRBs on newborn screening is planned, and federal agencies such as NICHD are exploring the feasibility of federated IRBs and common protocols. The outcome of protocols reviewed by an IRB is influenced by its membership. The group observed that a second challenge involves the fact that newborn screening takes place in a public health or state-run environment, and that segments of the public are mistrustful of the government having access to the level of information that would be afforded by genome sequencing. To overcome these issues and establish trust, the potential benefits and risks of the information and the plan for protection of privacy must be clearly spelled out. One key is to recognize that the information that may result from genome sequencing is valuable, but this information must be communicated effectively with individuals and family members and only when there is something important to communicate. The final challenge the group identified is how to link stored specimens to phenotypes so outcomes can be predicted.

Breakout Group 3: Scope and Timing

This breakout group considered the question of what samples to test and when to test them. Challenges identified by the group included: which conditions to focus on, and which variants (genetic, epigenetic, proteomic) to screen for; the breadth of genotyping information to be generated, and how it will be analyzed and stored in the medical record; and ensuring access to novel technologies by the underserved. In terms of source material, data from bloodspots could be compared to data generated from buccal swabs of newborns or fetal cells in maternal circulation. The group said that the timing of screening, during prenatal, perinatal, or postnatal periods should be considered and compared, with potentially different benefits accruing during each period.

The group also suggested that perinatal screening could focus on the genomics of the current set of screening disorders. This would allow the study of questions about phenotypic variation and modifiers, with follow-up to study the natural history under current standards of care.

The group added that postnatal screening could target monogenic or highly penetrant common diseases that are later in onset (examples include cystic fibrosis, type I diabetes, and cancer syndromes). The study could also look at high-risk populations. It would emphasize opportunities for intervention, treatment, or development of improved therapies. Other possible populations could include transplant patients or consanguineous populations.

One major opportunity the group identified for initiating research within a newborn screening context is the near-universal inclusion of U.S. newborns; this could serve as an "on-ramp" to more individualized genomic medicine down the road. This could also create the expectation that any new technology incorporated into the newborn screening framework be accessible to all. Ensuring accuracy, predictive utility, and rapid turnaround of the genomic information would be key requirements. In order to achieve this vision, several incremental opportunities could be pursued, such as standardizing and digitizing phenotypes present within the registry (for the disease or diseases being studied) and defining and measuring outcomes at all levels (e.g., benefits to the individual, clinician, society).

Summary

In the discussion that followed the presentations from breakout groups, there was consensus on the value of creating a pilot study that would evaluate genomic data in newborns, using newborn screening as a framework. Workshop participants felt that two considerations must be prioritized: clinical validity and clinical utility, not just analytical validity. Also, they suggested that the pilot look at costs and benefits in a broader way. The funding source must ultimately be considered. A final question they raised is how to move genomic screening into health care.

There was much discussion as to whether such a pilot study should take all comers (as with the current newborn screening model) or whether it should target a specific disease population (or several disease populations). Participants noted that both approaches have advantages, but the latter had broader support for a number of reasons; sequencing populations at known risk would likely make it possible to learn more about the disease in question, and may be better received. Also, the study population would not need to be as large, reflecting economic concerns.

An important idea that emerged from discussion was the concept of newborn screening (or screening of newborns) as an individual's first point of contact with the healthcare system, and a universal access point for lifetime personalized medicine. Because newborn screening is universal and therefore reaches across all socioeconomic backgrounds, it is less subject to health access disparities. Workshop participants commented that ensuring that newborn screening remains universal is vitally important for the public health system.

At the close of the meeting, Drs. Guttmacher and Green remarked on the quality of the discussion over the preceding two days. They noted that many of the concepts raised by the breakout groups lend themselves well to further study, and that the recommendations generated at the meeting will inform NICHD, NHGRI, and their collaborators as they develop future research initiatives on genomic applications for newborn screening.