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Newborn Sequencing in Genomic Medicine and Public Health

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The rapid development of genomic sequencing technologies has decreased the cost of genetic analysis to the extent that it seems plausible that genome-scale sequencing could have widespread availability in pediatric care. Genomic sequencing provides a powerful diagnostic modality for patients who manifest symptoms of monogenic disease and an opportunity to detect health conditions before their development. However, many technical, clinical, ethical, and societal challenges should be addressed before such technology is widely deployed in pediatric practice. This article provides an overview of the Newborn Sequencing in Genomic Medicine and Public Health Consortium, which is investigating the application of genome-scale sequencing in newborns for both diagnosis and screening.

Universal newborn screening (NBS) is an extraordinarily successful public health program, preventing morbidity and mortality through early diagnosis and management of conditions including rare inborn errors of metabolism.[1] Conditions such as phenylketonuria are not clinically evident at birth but lead to significant irreversible harm or death if not treated promptly.[2] NBS has saved countless lives and vastly improved the quality of children's lives by allowing timely therapeutic interventions, and technological advances such as the use of tandem mass spectrometry (MS/MS) have played a significant role in expansion of NBS.[3,4]

The ability to analyze many or all genes in the genome simultaneously provides new opportunities for genomic medicine. The capacity of genome-scale sequencing for disease gene discovery is well documented,[5] and it is increasingly being applied as a diagnostic test in children with suspected monogenic disorders.[6,7] The tangible potential of genomic sequencing more broadly in medicine, as part of "personalized" or "precision" medicine,[8] was foreshadowed in 1990 by Walter Gilbert, who extrapolated from the exponential growth of DNA sequencing that all newborns would have their genomes sequenced by 2030 or 2040. The idea that genomic sequencing will someday become part of the standard care of newborns is carried forward into today's dialogue:

> As we learn more about effective interventions for genetic risk factors, and recognize that interventions early in life provide significant advantages, it will become more and more compelling to determine this information at birth.
>
> —F. S. Collins, *The Language of Life: DNA and the Revolution in Personalized Medicine*. New York: Harper Perennial (2010)

abstract

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Dr Berg conceptualized and designed the study, drafted the initial manuscript, participated in data analysis, and reviewed and revised the manuscript; Drs Agrawal and Parad drafted the initial manuscript, supervised data collection at 1 of the sites, participated in data analysis, and reviewed

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Such predictions raise important questions: Could genomic sequencing become part of the universal standard NBS performed by each state, replacing conventional biochemical testing, or could it be offered as an optional supplement? How would sequencing be paid for, and how would parental informed consent be obtained? What impact would genomic sequencing in newborns have on children's health? What implications would it have for issues such as protecting an autonomous person's right not to know?

In the diagnostic setting, the goal of genome-scale sequencing is to identify genetic variants that provide a molecular etiology for the patient's symptoms. All other variants are considered incidental findings (or secondary findings when discovered through intentional analysis).[9] These additional findings differ widely with regard to predictive capacity and clinical actionability. Not surprisingly, there is disagreement about how much genomic information should be routinely returned in a pediatric setting,[10–14] and children and their parents are likely to express unique preferences.[15,16] Central challenges for clinical implementation thus revolve around the boundaries of professional responsibility and individual or parental choice, best practices for informed consent and determining parental preferences, standards regarding the types of findings that should be reported, long-term storage of genomic information so that it can be acted on at the appropriate time, and whether and how genomic data should be reanalyzed and reinterpreted.

The application of genomic sequencing in asymptomatic newborns intensifies many of these challenges and exposes deep societal questions about nonmaleficence, beneficence, autonomy, and the preservation of each child's open future.[17–19] Additionally, the economics of such screening must be considered before implementation on a population level. Although the technical features needed for rapid genomic sequencing appear feasible, interpretation of each asymptomatic person's variant profile will remain labor intensive for the foreseeable future, and clinically useful prediction of future disease may prove elusive. Recognizing these trends, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Human Genome Research Institute, and the Office of Rare Disease Research held a workshop in December 2010 to identify elements of a trans–National Institutes of Health research agenda that could inform the possible application of new genomic technologies to NBS and child health (https://www.nichd.nih.gov/about/meetings/2010-retired/ Documents/Newborn_Research_Agenda.pdf). A consensus finding was the need to examine the technical, clinical, social, and ethical issues related to sequencing in the newborn period in unison. Subsequently, the NICHD and the National Human Genome Research Institute issued a funding opportunity to develop a consortium to explore, in a limited but deliberate manner, opportunities to use genomic information for broadening our understanding of diseases identified in the newborn period, in the context of public health NBS or clinical sequencing of newborns. The consortium, called Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT), is addressing 3 key research questions:

- For disorders currently screened in newborns, how can genomic sequencing replicate or augment known NBS results? Can sequencing replace current screening modalities?
- What knowledge could genomic sequencing provide about conditions not currently screened for in newborns?
- What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

In 2014, 4 groups were funded to explore newborn sequencing in different clinical contexts by using unique study designs (Table 1 and Fig 1). Each study also included an aim examining ethical, legal, and social considerations. This article examines some of the challenges of newborn sequencing in 3 distinct clinical settings, describes the 4 projects, and puts this research in the context of current and future strategies for NBS and sequencing of newborns in clinical care settings.

CLINICAL SETTINGS FOR NEWBORN SEQUENCING RESEARCH: DIAGNOSTIC, PREVENTIVE, AND PREDICTIVE

The setting in which genomic sequencing is performed affects its technical performance, yield, and potential benefits and harms. In a diagnostic context, newborn sequencing is much like any other genetic diagnostic modality, and the ability to provide a molecular diagnosis depends on a number of factors including genetic architecture, phenotypic expressivity, locus heterogeneity and the fraction of cases accounted for by known disorders, mutational spectrum, the types of variants that are detectable by sequencing, and the quality of the assay performed in the patient. In contrast, the application of genomic sequencing in an asymptomatic newborn substantially depends on the power of genotype to predict disease status in the present or the future. Thus, a critical question is whether genomic variant data can be used to accurately predict disease when the pretest probability of disease is low, especially in cases where there may be no secondary

TABLE 1 NSIGHT Project Overviews

	BWH, BCH, Baylor College of Medicine	Rady, Children's Mercy Hospital	UCSF	University of North Carolina
Patient cohorts	Sick newborns (ICUs). Healthy newborns (well nursery).	Sick newborns (NICU)	Deidentified DBS samples from California NBS program Newborn DBS from consenting individuals with primary immunodeficiency	Children affected with known NBS findings Healthy newborns (prenatal recruitment)
Biospecimens	Whole blood (newborns) and saliva (newborns and parents).	Whole blood (parent–infant trios)	DBS retrieved from NBS program biobank	Cheek swabs
Sequencing	Exome sequencing. Illumina Content Exome. Illumina HiSeq. ≥100 × mean coverage.	WGS Illumina HiSeq 2500, rapid run mode	Exome sequencing Nimblegen v3 capture Illumina HiSeq 40–80 × average coverage	Exome sequencing Agilent V6.0 capture Illumina HiSeq 40–80 × average coverage
Informatics	All newborns: analysis of variants in genes responsible for childhood-onset disorders (<18 y). Sick newborns/Later-onset healthy and sick newborns: indication-based analysis of all variants in genes relevant to the phenotype (if applicable).	Clinical features translated into phenotype terms and differential diagnosis by Phenomizer (and custom lists)	Metabolic disease NBS samples: blinded assessment as an initial screen; second-tier analysis combining genomic, clinical, and MS/MS data Immunodeficiency cohort: analysis of genes relevant to patient's phenotype	All participants: primary analysis blinded to phenotype • Known diagnosis cohort: diagnostic or indication-based analysis based on phenotypic findings
Primary results returned	Diagnostic findings (ICU patients and others with clinical indications). Highly penetrant childhood-onset or childhood treatable conditions (all participants).	Diagnostic or likely diagnostic findings	No contact or return of results for metabolic NBS program cohort Offer clinical confirmatory testing to follow up likely pathogenic variants for immunodeficiency cohort	Childhood-onset medically actionable conditions (all participants) Diagnostic findings (affected cohort)
Secondary results returned	Carrier status for childhood-onset conditions and selected pharmacogenomics (all participants).	Incidental genetic disease diagnosis if life-threatening in childhood	None	Parents randomly assigned to decision group can select from 3 categories: • Childhood-onset non–medically actionable conditions • Carrier status for recessive conditions • Adult-onset medically actionable conditions

TABLE 1 Continued

	BWH, BCH, Baylor College of Medicine	Rady, Children's Mercy Hospital	UCSF	University of North Carolina
Psychosocial and medical outcomes research	Surveys of parents and physicians assess impact of genomic sequencing across key domains: • Attitudes and preferences. • Health care utilization. • Health behaviors and intentions. • Decisional satisfaction. • Psychological impact. Psychosocial impact on the family.	Surveys of parents and physicians assess impact of genomic sequencing across key domains: • Attitudes and preferences • Health care utilization • Health behaviors and intentions • Decisional satisfaction • Psychological impact • Psychosocial impact on the family Correlation of parents' attitudes about test results with their health literacy, genomic literacy, anxiety, depression, and religiosity	Focus groups with: • Parents of immunodeficiency patients • Healthy pregnant women • Obstetric and pediatric clinicians	Surveys with parents assess decision-making about genomic sequencing and its effects on individual and dyadic parent outcomes: • Parents' collaborative decision-making and conflict • Prenatal anxiety (parents of healthy newborns only) • Parental bonding with child • Attitudes and beliefs about genomic sequencing • Decision conflict and regret • Test-related and general distress • Beliefs and concerns about the child's future health
Other project aims	Although Sanger confirmation is used for the main project, the study is exploring orthogonal sequencing by 2 NGS methods as an alternative for variant confirmation.	Comparison of rate of diagnosis and time to diagnosis in WGS and no-WGS groups Rates and types of actionability measured	Assess suitability of stored DBS as a source of DNA for deep sequencing	Semiquantitative metric to determine medical actionability Electronic decision aid for parental preference setting

gold standard clinical evaluation by which to validate the genomic prediction.

Sequencing in a NICU population of sick infants extends current molecular diagnostic strategies to a genomic scale, whereas sequencing otherwise healthy infants targets the prevention of future disease and is more akin to current NBS performed in a public health setting. Sequence information could also be used to guide a patient's care throughout life by predicting disease and directing management strategies for clinical scenarios that emerge, blending the predictive, reproductive, diagnostic, therapeutic, and prognostic value of genomic information. The NSIGHT projects differ in the clinical scenarios in which the use of genome-scale sequencing is being studied, spanning the areas described below.

Diagnostic Sequencing in the NICU

Level III and IV NICUs care for many neonates with genetic disorders, including metabolic disorders[20] and congenital malformations.[21,22] Indeed, genetic disorders and congenital anomalies are the leading cause of death in the NICU.[23] Current approaches for diagnosis of suspected genetic disorders in NICU patients include karyotyping, chromosomal microarrays, single-gene testing, and gene panels. In many cases, the etiologic diagnosis remains elusive despite several rounds of genetic testing, and clinical genome-scale sequencing is used for only a small fraction of cases. If genomic sequencing were used earlier in the diagnostic process, it could provide more timely definitive diagnoses and thereby increase the precision of treatments, whether therapeutic or palliative, and provide answers about prognosis and family recurrence risk. In addition, sequence data could aid in interpretation of the false-positive NBS results commonly reported in premature infants because of their immature organ systems, liver enzymatic activity, long-term parenteral nutrition requirement, and other comorbid conditions.[24]

Preliminary studies have shown potential cost reductions resulting from genomic sequencing in neonates with genetic disorders.[7,25,26] However, uptake has been impeded by concerns about clinical interpretation of ambiguous results, secondary findings and potential parental anxieties, economic factors including resistance on the part of third-party payers in the absence of definitive data on clinical utility

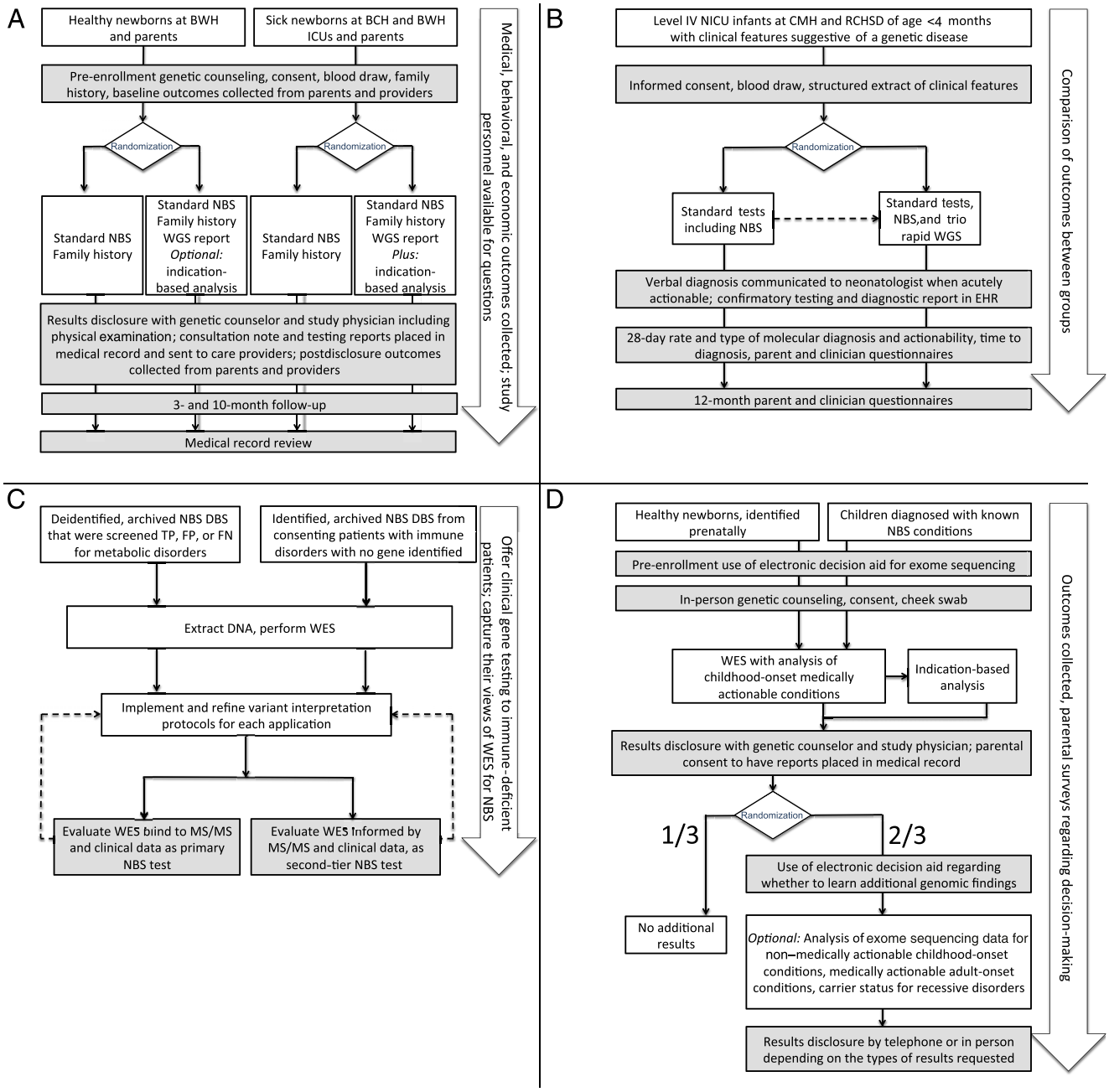

FIGURE 1

A, Diagram of the protocol in progress at BWH and BCH, Boston, Massachusetts. Infants are recruited from the well baby nursery at BWH and from the ICUs at BCH and BWH. After a pre-enrollment session with a study genetic counselor and completion of baseline outcomes, enrolled infants are randomly assigned to receive NBS and family history or NBS, family history, and exome sequencing. Results are disclosed to the family by a study genetic counselor and physician, and postdisclosure outcomes are collected. Follow-up is performed at 3 and 10 months after disclosure. Medical, behavioral, and economic outcomes are collected throughout the study from surveys, medical record reviews, and consultation with the families. B, Diagram of the protocol in progress at NICUs at Children's Mercy Hospital, Kansas City (CMH) and Rady Children's Hospital, San Diego (RCHSD). Eligible patients are infants <4 months old in whom a clinical genetic test or genetic consult was ordered, or those with 1 major anomaly or 3 minor structural anomalies, or an abnormal laboratory test suggestive of a genetic disease, or an abnormal response to standard therapy for a major underlying condition. Enrolled infants are randomly assigned to receive standard diagnostic testing or standard tests and rapid WGS of parent–infant trios. Diagnostic results are returned. Primary outcome measures are rate of molecular diagnosis in 28 days, time to diagnosis, and whether the diagnosis provided a change in clinical management. C, Diagram of the NBSeq protocol in progress at UCSF. NBSeq uses archived residual DBS from a very large and diverse population to examine the diagnostic utility of exome sequencing in 2 parallel projects. For metabolic disorders (left), DBS samples from deidentified true positives (TP), false positives (FP), and false negatives (FN) are subjected to exome sequencing, variant calling, and interpretation under blinded models for evaluation of first-tier screening and in conjunction with MS/MS and clinical data for evaluation of second-tier screening. A predetermined list of 93 genes relevant to the metabolic disorders is the basis for the exome assessment. Consented, identified patients with immune disorders with no gene identified (right) also undergo NBS DBS retrieval and exome sequencing and analysis, in this case with a pipeline restricted to immune system genes. Analysis protocols for both

and cost-effectiveness, and difficulty ordering tests due to institutional concerns over high costs. The process is also complicated by a need for detailed phenotypic information for optimal analysis by diagnostic laboratories. Provisional genomic diagnosis of genetic disease is technically feasible in as little as 26 hours.[27,28] However, cost is inversely related to the turnaround time, and the optimal balance of cost and clinical utility is unknown. Although some aspects of rapid turnaround time can be improved through technology, limits imposed by variant review and clinical interpretation standards will remain, including the need for communication between the clinical team and the laboratory for clinical genomic assessment. Parental acceptance of testing, given the unclear future implications for insurability and privacy, is not yet known. Finally, the responses of neonatologists and parents to genomic information warrant more study, and rigorous frameworks for translating such information into precision care plans in NICUs remain to be developed.

Preventive Sequencing in a Public Health Setting

Current NBS yields few false-negative results but does incur substantial numbers of false positives, with attendant emotional and financial costs.[29] For example, in a study of 176 186 specimens screened by MS/MS, there were 51 true positives, 2 false negatives, and 454 false positives that were ultimately resolved as nondisease after referral to a metabolic center.[30] Genomic sequencing could function as a multiplexed second-tier screen, increasing the specificity of current MS/MS screening tests by distinguishing false-positive results from true disease and aiding in the differential diagnosis of nonspecific biochemical profiles. Sequencing could also confirm conditions identified through other screening methods,[31–33] aid in providing prognosis and appropriate treatment,[34–37] determine the etiology of conditions identified through point-of-care testing,[38] and provide families with information about pathogenic variants that could be used for family testing. Such analyses could also increase knowledge of correlations between genotypes and phenotypes and might reveal possible genetic contributions to false positives, such as abnormal MS/MS screening data due to carrier status or hypomorphic variants. These goals will require longitudinal follow-up to obtain clinical data and examine genotype–phenotype correlations to ultimately determine the predictive capacity and clinical impact of genetic variants.

Genomic sequencing could also be deployed as a first-tier screen, particularly for rare disorders that currently lack methods for conventional biochemical NBS. In the public health context, selecting exactly which disorders to screen for requires careful consideration of factors such as age of onset, severity, penetrance, treatability, confirmatory testing, and opportunities for surveillance. Some genetic conditions will fulfill the original Wilson and Jungner criteria for screening,[39–41] but many will not. Thus, there is a need for scalable methods to determine which conditions would be appropriate for inclusion in a public health screening setting. In addition, the current practice of returning findings consistent with carrier status might be unsustainable given that nearly every person is likely to be a carrier for a handful of rare recessive conditions.

A significant challenge in the use of sequencing for NBS is the lack of data regarding the analytic and clinical performance of sequencing as a predictive test. Little is known about the positive or negative predictive value of genomic sequencing in asymptomatic people whose previous probability of disease is very small. Although it may seem self-evident that Mendelian diseases would be best identified from genetic sequence, this assumption remains to be demonstrated and may not be true. Monogenic illnesses are often influenced by additional and as-yet-unidentified genetic or environmental factors, whereas MS/MS measures analytes that are typically closer

FIGURE 1 Continued

applications undergo refinement based on integration of observed sensitivity and specificity with genome analysis tools. Enrollees with immune disorders can obtain confirmational clinical gene testing, and their assessment of risks, benefits, and uncertainties of exome sequencing for NBS are solicited. D, Diagram of the North Carolina Newborn Exome Sequencing for Universal Screening protocol in progress at the University of North Carolina at Chapel Hill. This study is enrolling healthy newborns, identified prenatally, and children affected with known conditions identified through standard NBS (metabolic disorders, hearing loss, pulmonary disorders). Parents use an electronic decision aid in addition to an in-person consultation with a genetic counselor to determine whether to have their child undergo sequencing. Exome sequencing is performed, with analysis of a panel of genes associated with childhood-onset medically actionable conditions (NGS-NBS) for all participants and indication-based analysis for patients from the diagnosed cohort. Participants are randomly assigned at the time of return of results. Parents in the control arm receive only the primary diagnostic findings and NGS-NBS results, whereas parents in the decision arm will use the electronic decision aid to choose between 3 additional categories of optional genomic information (adult-onset medically actionable conditions, childhood-onset non–medically actionable conditions, and carrier status for recessive conditions). Parents will also participate in longitudinal surveys to assess their responses to the genomic information.

to relevant phenotypes. Even for the best-studied diseases, there are substantial challenges in interpreting rare variants. Variant selection algorithms that maximize sensitivity necessarily sacrifice specificity, leading to increased false-positive results and potential downstream harms due to unnecessary medical interventions. A strategy of excluding "variants of uncertain significance" (which by definition have poor predictive value) from genomic screening results may be necessary. Historically, the focus of NBS on preventable disorders has led to low tolerance for false-negative screening results. With genomic sequencing it might be necessary to shift the screening paradigm from finding all affected individuals to finding an optimal proportion of cases for a larger number of potentially treatable conditions.

Predictive Sequencing of Newborns in Genomic Medicine

The broadest vision of genomic medicine, and potentially the most challenging for societal and practical reasons, involves the use of sequence data to guide a patient's care throughout life. Genomic sequencing reveals information well beyond the scope of conventional NBS. Some of this information could result in medical action, but most will not, raising questions of exactly what information should be reported and when.[42,43] Variant data could conceivably be held for future diagnostic analysis in the event that the patient develops symptoms of a genetic condition. Currently, our ability to interpret genetic variants is largely confined to simple monogenic and oligogenic conditions. As we learn to use multifactorial models for risk stratification or management in a clinically useful way, additional information will increasingly be available. Within this spectrum is the potential for genomic information to alert clinicians to reconsider the family history or interpret physical examination findings in a new light, and potentially the ability to benefit other family members before they develop a disease. Pharmacogenomic variants could guide the real-time selection and dosing of medications, yielding safer and more effective treatments. Recessive carrier traits detected in newborns could alert parents to genetic risks that provide information valuable to reproductive planning. Common variation for complex conditions may motivate families to be more vigilant about diet and other lifestyle choices. Finally, there is the potential for voluntary personal exploration of one's own genomic data.

If genomic sequence data are available, parents will need to make decisions about whether to learn about additional categories of information that may predict future events about their child with differing levels of certainty and ability to intervene, ranging from childhood-onset conditions that may not have direct interventions or preventive measures, adult-onset medically actionable conditions, or carrier status for recessive disorders. Studies suggest that parents are interested in their child's genetic variants, even when that information has no defined clinical utility,[44] although these preferences have largely been elicited in hypothetical scenarios and may not reflect real-life choices.

Genomic information may enable families to become aware of otherwise unsuspected familial risks, including potentially actionable adult-onset conditions in the infant that a parent is unknowingly carrying. However, some findings may be at odds with professional guidance that genetic testing in asymptomatic minors should generally be done only when identification before adulthood is needed to prevent harm and directly benefit the child.[11,13,17] The potential to query genome-scale data in children for secondary findings has elicited vigorous debate over the ethical boundaries of return of results. The argument has been made that benefit to family (eg, a parent who is unknowingly at risk) may be a valid consideration in decisions regarding return of results for actionable adult-onset conditions in children.[45,46] Genome-scale sequencing and analysis in newborns would probably require modification of current informed consent procedures[41,47] compared with a targeted screen focusing on a restricted number of conditions. If implemented across the entire population, genomic sequencing would fundamentally alter contemporary public health NBS procedures, necessitating innovative approaches to facilitate parental decision-making. Alternatively, such testing could be implemented through voluntary, out-of-pocket testing.

Expanding genomic sequencing in newborns to include a broad range of conditions demands a close partnership between clinical providers and parents, similar to other areas of medicine in which shared decision-making is becoming the norm.[48,49] Determining criteria for disclosure of information will be a challenge for clinicians and policymakers and will require development of decisional supports to help parents determine the information they want to learn.[50] The clinical interactions needed for support of parental decision-making would move this activity beyond the realm of current public health service

provision and into the clinical domain. Workforce shortages may present significant obstacles if genome-scale sequencing were to become widely available in the public health setting,[51] suggesting that new and more scalable materials and procedures for communicating the potential benefits and risks of learning such information would need to be developed, validated, and deployed. Systems may need to be established that enable parents to request certain results from their child's genomic information over time, allowing them to decide iteratively as their values and perceptions of risk change or as their child attains an age to assent or consent.

The complexities of genomic result interpretation currently demand trained geneticists and genetic counselors to provide guidance and follow-up management. As genomic medicine becomes more mainstream in health care, a broader range of health care providers will need to interact with genetic information, which is likely to be increasingly viewed as 1 of many risk factors influencing future conditions; reports will have to be constructed with clarity that makes them useful for pediatricians and primary care providers. The potential use of this type of genomic information over time would necessitate development of new infrastructure to manage reporting, reanalysis, storage, and integration with electronic health records. Such data could be used for iterative phenotyping of the individual to define the clinical relevance of genetic variants. However, thresholds for reporting or acting on potentially relevant variants would have to be calibrated against the possible harms of false-positive results or overdiagnosis, which would lead to unnecessary, dangerous, or costly medical treatments.[52] The benefits of detecting true positives must therefore be balanced against the magnitude of harms.

NSIGHT RESEARCH GROUPS, STUDY DESIGNS, AND KEY QUESTIONS BEING ADDRESSED

Each of the 4 members of the NSIGHT Consortium independently designed and implemented study designs that focus on somewhat different populations and research questions (Fig 1 and Table 1).

Genome Sequence-Based Screening for Childhood Risk and Newborn Illness project (Fig 1A), led by Brigham and Women's Hospital (BWH) and Boston Children's Hospital (BCH) at Harvard Medical School and by Baylor College of Medicine, is a randomized controlled trial assessing the impact of providing genomic sequencing information to parents and physicians of newborns (clinicaltrials.gov identifier NCT02422511). The study is enrolling a cohort of healthy newborns approached in the postpartum period from the BWH Well Baby Nursery and a cohort of sick newborns from the BWH NICU and the ICUs at BCH. Within each cohort newborns are randomly assigned to either the control arm (conventional NBS results and a detailed family history) or the experimental arm (genomic sequencing in addition to conventional NBS and a detailed family history). Parents and physicians are surveyed to assess the impact of the genomic information across several key domains including attitudes and preferences, health care utilization, health behaviors and intentions, decisional satisfaction, and psychosocial impact on the family.[53]

The Clinical and Social Implications of 2-Day Genome Results in Acutely Ill Newborns project, led by Rady Children's Institute for Genomic Medicine and Children's Mercy Hospital, studies the use of rapid whole genome sequencing (WGS) at 2 large level-IV NICUs (~1000 admissions per year) in children's hospitals (Fig 1B). WGS was adapted for diagnosis of rare genetic diseases in NICUs, including shortening the minimum time to provisional diagnosis to 26 hours, increasing the analytic sensitivity and specificity of variant detection to >99.5%, and gaining US Food and Drug Administration approval to report a provisional diagnosis verbally to an attending neonatologist if death was imminent and the diagnosis would inform implementation of a treatment that could change the outcome.[27,28] The current study is a prospective, randomized controlled trial of the diagnostic utility, cost-effectiveness, and psychosocial implications of rapid WGS at the 2 NICUs (clinicaltrials.gov identifier NCT02225522). As part of this study, doctors and parents are surveyed about their perceptions of the risks and benefits of rapidly obtaining WGS results.

The goal of the Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening (NBSeq) project, led by the University of California, San Francisco (UCSF) and collaborating institutions, is to evaluate the potential application of exome sequencing to public health NBS by using dried blood spots (DBS) (Fig 1C). The project explores the feasibility of exome sequencing to augment or replace current MS/MS technologies in NBS. Exome sequencing is performed at UCSF on deidentified archival DBS from all California newborns found to have metabolic disorders in the

TABLE 2 Cross-Consortium Working Groups

Ethical, Legal, Economic, and Social Issues	Common Data Elements	Outcomes and Measure
Key questions • Differences in perceptions of benefits and risks of sequencing between symptomatic and asymptomatic populations • Parent willingness to accept sequencing and factors associated with parents' decisions • Extent to which parents are willing to accept uncertainties inherent in test interpretation • How key stakeholders make decisions about whom to test, how to share results, under what circumstances, and with what goals • Public policy regarding use of genome sequencing as part of mandated screening programs	Key questions • Identify common data elements in the NSIGHT projects to be collected systematically across the consortium • Collaboration with NBSTRN to use LPDR for individual cohort and combined cohort analysis where applicable • Define data elements to be shared more broadly, in a deidentified fashion, with other researchers in the NBSTRN	Key questions • Identify common outcome measures in the NSIGHT projects to be collected systematically across the consortium • Considerations of the overall cost/benefit ratio of newborn sequencing

LPDR, Longitudinal Pediatric Data Resource (https://www.nbstrn.org/research-tools/longitudinal-pediatric-data-resource).

past decade, as well as samples that were false positives on the MS/MS screening. Sequence data from newborn DBS[54] are also being interrogated in a cohort of 50 patients who have been clinically diagnosed with immunodeficiency disorders to determine whether sequencing DBS as part of NBS could facilitate early diagnosis and optimal management of non–severe combined immunodeficiency immune defects. Stakeholder views, perspectives, and value preferences about the potential expansion of NBS are being evaluated through focus groups.[55] In addition, legal and constitutional issues surrounding the potential use of genome-scale analysis in NBS are being examined.[56]

The North Carolina Newborn Exome Sequencing for Universal Screening study at the University of North Carolina at Chapel Hill evaluates exome sequencing from saliva samples in 2 groups: children and infants affected with conditions identified through standard NBS and a cohort of healthy newborns whose parents are approached for participation prenatally (Fig 1D). Parents will use an electronic decision aid to assist in decisions about exome sequencing.[57] After providing informed consent at an in-person study visit, those who accept sequencing will receive results from a "next-generation sequencing newborn screening (NGS-NBS)" panel of genes implicated in childhood-onset medically actionable conditions.[58] Parents will also be enrolled in a randomized trial of decision-making regarding whether to learn about 3 types of additional genomic findings in their child by using the electronic decision aid (clinicaltrials.gov identifier NCT02826694). The study seeks to understand how parents think about and consider different categories of information,[59] and, combined with longitudinal quantitative surveys, the study will reveal the spectrum of results parents decide to learn, issues surrounding returning these findings, and consequences of decision-making and results disclosure.

CROSS-CUTTING CONSORTIUM ACTIVITIES

Although the research projects address distinct research questions and have unique study designs, the 4 NSIGHT groups participate in consortium activities that build on the strengths at each site and harmonize data collection to improve cross-cutting analysis (Table 2). An ethical, legal, and social implications workgroup brings together the perspectives of each project regarding the responses of clinicians, families, payers, and other stakeholders; parental informed consent and decision-making; and implications for public health NBS programs.[19,60] The Common Data Elements workgroup is charged with creating a common set of data elements collected across the 4 research groups to enable data sharing and combined data analysis. The Outcomes and Measures workgroup examines the standardized instruments being used by each group to assess stakeholder responses to newborn sequencing to facilitate cross-consortium analyses. The NSIGHT Consortium is working closely with the Newborn Screening Translational Research Network (NBSTRN) Coordinating Center, housed at the American College of Medical Genetics and Genomics. The NBSTRN, created as part of the NICHD's Hunter Kelly Newborn Screening Research Program to create a shared research infrastructure to support NBS researchers, provides a mechanism to increase understanding of conditions that

are currently part of routine NBS or may be future candidates for screening. The NBSTRN resources, tools, and network of experts are used in population-based pilots of new screening technologies and natural history studies of screened conditions. NSIGHT Consortium investigators also maintain close ties with other National Institutes of Health–funded consortia including the Clinical Sequencing Exploratory Research consortium[61] and Clinical Genome Resource consortium.[62]

CONCLUSIONS

Data gathered from the projects in the NSIGHT Consortium will address technical, clinical, and ethical questions that are fundamental to the future consideration of sequencing in newborns. The projects will determine the feasibility and utility of this technology in critical care and public health settings. Design and implementation of rapid high-throughput methods will be essential to maximize the benefit of sequencing for certain conditions in the neonatal population. Longitudinal follow-up of parents will allow the study of parental decision-making, measure parental preferences in real-world settings, and assess test-related stress or anxiety. Medical outcomes of the children who undergo sequencing will need to be monitored over many years. Ultimately, these data will aid in the development of best clinical practices and provide guidance on the implementation of sequencing in newborns. Although genomic sequencing will expand our ability to diagnose conditions and offer personalized treatments, health care providers and public health entities must be good stewards of this technology, ensuring careful attention to ethical standards and evidence-based outcomes in making recommendations about its use.

ABBREVIATIONS

BCH: Boston Children's Hospital
BWH: Brigham and Women's Hospital
DBS: dried blood spots
MS/MS: tandem mass spectrometry
NBS: newborn screening
NBSeq: Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening
NBSTRN: Newborn Screening Translational Research Network
NGS-NBS: next-generation sequencing newborn screening
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NSIGHT: Newborn Sequencing in Genomic Medicine and Public Health
UCSF: the University of California, San Francisco
WGS: whole genome sequencing

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