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Supporting Parental Decisions About Genomic Sequencing for Newborn Screening: The NC NEXUS Decision Aid

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Abstract

Advances in genomic sequencing technology have raised fundamental challenges to the traditional ways genomic information is communicated. These challenges will become increasingly complex and will affect a much larger population in the future if genomics is incorporated into standard newborn screening practice. Clinicians, public health officials, and other stakeholders will need to agree on the types of information that they should seek and communicate to parents. Currently, few evidence-based and validated tools are available to support parental informed decision-making. These tools will be necessary as genomics is integrated into clinical practice and public health systems. In this article we describe how the North Carolina Newborn Exome Sequencing for Universal Screening study is addressing the need to support parents in making informed decisions about the use of genomic testing in newborn screening. We outline the context for newborn screening and justify the need for parental decision support. We also describe the process of decision aid development and the data sources, processes, and best practices being used in development. By the end of the study, we will have an evidenced-based process and validated tools to support parental informed decision-making about the use of genomic sequencing in newborn screening. Data from the study will help answer important questions about which genomic information ought to be sought and communicated when testing newborns.

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The North Carolina Newborn Exome Sequencing for Universal Screening (NC NEXUS) study is 1 of 4 centers funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Human Genome Research Institute to study the implications and challenges of generating and using genomic sequencing information in the newborn period. The NC NEXUS study includes several interrelated projects that seek to evaluate whether genome-scale next-generation sequencing (NGS) can extend the utility of newborn screening (NBS) by using whole exome sequencing (WES) technology, devise and evaluate a clinically oriented framework for the analysis of next-generation sequencing newborn screening (NGS-NBS), and identify and investigate critical ethical, legal, and social implications (ELSI) that arise when families are asked to make decisions about which categories of information generated from this technology that they want to learn. Taken together, we expect that these projects will provide valuable empirical data that help clinicians and families make informed decisions about these complex issues.

Our investigation of the ELSI issues generated from the application of genomic sequencing in newborns includes studies to support the development of a decision aid for parents facing decisions about learning NGS-NBS results, development of a tablet-based decision aid based on best practices and user design principles, and implementation of the decision aid in a randomized controlled trial (RCT). Parents who have a newborn or a child aged 5 years that has been diagnosed with a genetic disorder will take part in the RCT and use the decision aid, in conjunction with clinical consultation, to help them decide whether they want to have their child's exome sequenced. If they agree to sequencing, they will also decide which types of genomic information they want to learn from this analysis. All parents electing to have their child's genes sequenced will learn clinically relevant genomic findings in genes implicated in the conditions currently screened for on standard NBS panels in the United States. In addition, genes implicated in other disorders with similar characteristics but for which screening is not currently available will also be analyzed and results returned. These disorders are all medically actionable during childhood and can potentially be prevented, ameliorated, or treated more effectively if detected early. A subgroup of parents will be randomly assigned to make decisions about learning additional genomic information for conditions that do not meet our criteria for actionability or age of onset. The 3 additional information categories being studied in NC NEXUS are carrier status for recessive disorders, adult-onset medically actionable conditions, and childhood-onset disorders that are not medically actionable. Parents randomly assigned to this "decision arm" of the study can decide to learn all, some, or none of these categories of additional findings. Parental outcomes will be monitored by standardized measures over a 3-month follow-up period to elucidate the effect of making these decisions.

In this article we provide the context for the NC NEXUS study, describe the development process of the parental decision aid, and analyze the key ELSI issues raised and addressed in the study (Table 1). Asking parents to make informed decisions about the types of information they want to learn and providing a decision aid to support them in this decision-making process are 2 unique aspects of the study. We highlight the key innovations of our approach, explain the theoretical bases for the decision aid, and describe the research and

formative work that have guided its development. We conclude with an overview of our plans for the next steps in the study.

THE NBS CONTEXT FOR NC NEXUS

The introduction of tandem mass spectrometry (MS/MS) significantly broadened the range of disorders that are detected by routine NBS. As a result, there are many conditions that can be detected with this biochemical screening that do not meet traditional screening criteria.¹ MS/MS provides a glimpse of the shifts in practice and policy that will be needed to accommodate population-level genome sequencing, albeit on a much smaller scale than what will be needed as sequencing technology becomes increasingly incorporated.

In response to the challenges raised by the use of MS/MS, a national committee convened by the American College of Medical Genetics and Genomics reached consensus on characteristics of disorders that would qualify them for inclusion on a state's NBS panel and recommended a panel of 29 conditions for which there was strong agreement on expected benefits.² They also recommended 25 additional "secondary targets," conditions for which there was less agreement about benefit (eg, very rare conditions, no current treatment) but that would also be identified by the use of MS/MS. This decision altered a fundamental precedent in NBS as information about a range of conditions, including those that did not meet criteria and that were incidental to the initial purpose of screening, would be returned to parents. The use of WES or other genomic technologies will inevitably produce an even greater amount of secondary information and, while enhancing the promise of more efficient disease identification,³ will raise concerns about a wide spectrum of issues.⁴⁻⁸

One central question is how to define which characteristics define an appropriate return of results, in light of the fact that genomescale sequencing will identify information that goes far beyond the original purpose of screening. Some of this information will be medically actionable, but most will not. Defining the criteria for determining what information will be sought and disclosed will be one of the most vexing challenges facing clinicians and policy makers, as will the inevitable need to provide parents with decision support to help them determine which types of information they want to learn. These issues, though relevant to the ethical application of NGS technologies to any age group, become particularly heightened and gain complexity when applied to newborns. Policy recommendations generally conclude that testing done in asymptomatic minors should occur only when timely identification can prevent harm and will directly benefit the infant.⁹

When those criteria are met, policymakers and courts in the United States have decided that NBS can be performed without explicit parental consent. The underlying assumption is that the urgent need to treat identified infants outweighs the ethical stipulation to obtain parental consent. But genome-scale testing such as WES challenges this "public health emergency" approach to NBS, leading many ethicists and clinicians to suggest that these technologies, and the breadth of information they can potentially provide, will force a reevaluation of current screening practice and strengthen the case for obtaining parental informed consent.^{4,10} Parents typically receive some information about NBS, and in many states they can opt out for religious or moral reasons. The fact that very few decline can be construed as

tacit acceptance of the need for rapid action at the cost of parental autonomy.¹¹ Asking parents to make informed decisions about a range of results for different categories of conditions before testing represents a fundamental shift in how public health NBS programs are conducted. The logistical constraints posed by the timing and context of NBS will require new models, tools, and data to accommodate this shift in practice. There are few investigations examining the impact of decision-making on parents, and little evidence exists to show how they respond after learning results. Empirical data on these topics are critical for informing policy and practice, and collecting and assessing them will be a major contribution of the project.

VALIDATED METHODS ARE NEEDED TO HELP PARENTS MAKE INFORMED DECISIONS

Validated methods to support parental decision-making are urgently needed to inform changes in policy and practice in NBS. Parents need to be actively engaged in decision-making to enable them to make decisions consistent with their personal values. One major challenge to developing such decision tools is that both the general population¹²⁻¹⁴ and most primary care physicians have limited knowledge about genomics¹⁵ and the kinds of information that can be learned. Existing materials describing NBS usually take the form of short brochures, which have generally not been subjected to formal evaluation to determine their effectiveness in conveying basic information about NBS¹⁶ or their value in educating parents about controversial topics such as blood spot retention for research purposes.¹⁷ Introducing genomescale sequencing in NBS would quickly render current informational materials obsolete. State programs could no longer ethically justify materials that simply list and describe the disorders included on a screening panel. Teaching parents how new sequencing technologies expand the amount and range of potential NBS results would be better achieved by a consent process that facilitates informed decisionmaking. Parental decisions about the kinds of information they want to learn about their child could be enabled by an online process that, in conjunction with clinical consultation when needed, would help them make decisions consistent with their beliefs and values. Decision aid design requires the flexibility to adapt to rapidly evolving knowledge about the conditions screened yet be easily disseminated to large populations. These specifications favor the development of electronically based tools that retain their usefulness across multiple digital platforms (eg, mobile phones, tablets, or personal computers), allowing a rapid response to changing information and making large-scale dissemination feasible.

OVERVIEW OF NC NEXUS DECISION AID DEVELOPMENT

The decision aid is a tablet-optimized, responsive Web application that dynamically delivers tailored multimedia content through an interface integrating animated multimedia, interactive tasks, and touchscreen gestural controls (eg, swipe, tap, drag, pinch). It is being developed based on communication principles, input from a multidisciplinary committee of experienced genomic clinicians who are “binning” (categorizing) variant information,^{18,19} data from qualitative interviews conducted with parents, findings from a discrete choice experiment, existing literature on user-centered design principles, and best practices for

developing decision aids. The NC NEXUS steering committee, composed of communication researchers, behavioral scientists, geneticists, genetic counselors, and ethicists, provides regular input on design and content. Here, we review some of the communication challenges and data sources that are helping us address the ELSI questions shown in Table 1 and that are informing development of the decision aid.

How Will Information About Genomic Sequencing Be Presented to Parents in an Understandable Way That Leverages Clinician Experience?

One important challenge that must be addressed is how to communicate the enormous scope of information generated by genomic sequencing, when the majority is currently uninterpretable and therefore would not be returned to parents.²⁰ Even the loci clearly associated with recognizable phenotypes often lack clinical utility, especially when identified in childhood, which increases the complexity of both communicating this information to a lay audience and the decision-making by parents. Anticipating these challenges, we are using a framework that defines categories of information based on medical actionability and age of onset, which could potentially be returned in real-world settings in the future and outside a research context. We are building on a semiquantitative metric developed by investigators in our research group to help define medical actionability. The systematic evidence review and rating of variants by clinicians, geneticists, and genetic counselors characterize the actionability of a condition based on its potential severity, likelihood of occurrence, efficacy of interventions, acceptability or burdens of intervention, and knowledge base.¹⁹ Scores on these dimensions are combined in an algorithm to determine medical actionability. These actionability scores are plotted against the predicted age of onset of the disorder. This age-based metric system leads to variants being categorized in 4 “bins”: (1) conditions similar to those detected through NBS (ie, conditions that are medically actionable and have onset of symptoms or interventions in childhood); (2) conditions with a childhood onset that are *not* medically actionable; (3) conditions with an adult onset that are medically actionable; and (4) conditions with an adult onset that are *not* medically actionable. All parents who agree to sequencing can decide to learn results from bin 1; parents in the randomized group will be able to request information from bins 2 and 3 as well as findings consistent with carrier status for recessive disorders. Loci associated with bin 4 will not be analyzed. We anticipate that the systematic categorization of the vast amount of information potentially available in a way that accounts for age of onset and actionability will help address controversies about the information’s degree of clinical utility and the degree of personal utility; the latter may be of most relevance to parents making these decisions. This framework can accommodate an expanded knowledge base as conditions can be classified differently in the scheme without significant changes to the decision aid’s functioning.

How Can Parental Input Be Incorporated to Improve How Information About Genomic Sequencing Is Presented?

We are using a multimethod approach to ascertain parents’ values, beliefs, and knowledge about NGS, NBS, and genomic sequencing.

Formative Interviews With Parents—We recruited 33 couples who were married or in a committed relationship to participate in dyad-based interviews.²¹ Approximately half the couples were pregnant at the time of the interview or had a recent birth within the past 12 months. The other half had undergone genetic testing for their newborn or young child (ages 5 years). These 2 subgroups are similar to parents who will be recruited for the NC NEXUS RCT. The purpose of these semistructured interviews was to examine how couples communicate with each other and make decisions about genomic screening results for their child. We also used the interviews as a mechanism for gathering feedback on early drafts of decision aid materials.

A majority of parents showed individual variability in decisions across categories, NGS-NBS, medically actionable adult onset, carrier status, and non-medically actionable childhood conditions, suggesting that they saw meaningful differences between the types of conditions for which results might be returned.²² Regarding couple-level decisions, many couples described a deliberate, collaborative process of talking together and weighing the pros and cons before making joint decisions across all the results categories.²¹ The majority of participants said they would find the decision harder to make alone because their partner offered support, reassurance, input, or alternative perspectives.

With this in mind, we designed the decision aid to support a parental shared decision-making approach, where both members of the couple can complete the decision aid together and make joint decisions. Moreover, we organized the decision aid content around the same result categories that participants will be asked to decide about and allowed them to learn about and make separate decisions for each category. In addition, we used important values and concerns parents shared as content in the decision aid for a value clarification exercise.

Discrete Choice Experiment—To better understand how different characteristics of genetic disorders influence parental preferences for requesting additional non-medically actionable information about their child, we conducted a discrete choice experiment with 1289 parents of young children ages 5 years.²³ To facilitate subgroup analyses, we stratified the sample equally by race (white and African American) and gender. We randomly assigned each participant to complete a set of 8 choice tasks. In these tasks, we showed participants a pair of hypothetical profiles describing different kinds of sequencing results and asked them to select the profile they believed would be more important to know. The profiles in this experiment were designed by altering the levels of 7 characteristics: the likelihood the condition would develop given a true-positive result, the age of onset, level of mental disabilities, level of physical disabilities, the rate of disease progression, availability of options to improve quality of life, and the relative impact on life span of the child. This approach allowed us to estimate the relative influence of each characteristic by examining the choices that parents made in a controlled setting. Participants were also asked to complete basic demographic questions and questions that measured the level of distress they associated with specific characteristics of the genetic disorders.

We found that among the 7 characteristics parents considered, the likelihood the condition would develop given a true-positive test result was the most important characteristic in predicting whether a parent thought the information was important to know. The availability

of options to improve quality of life was the only characteristic that did not significantly influence which profiles were chosen. Also, within each characteristic, participants rated the more severe levels as more distressing (eg, a rapid vs slow progression of the disease). This information is helping us choose exemplary disorders to use in the decision aid.

How Can Parental Informed Decision-Making in the NC NEXUS Study Be Best Supported?

Our study asks parents to make decisions about potential future health events that are uncertain. These are difficult, and possibly emotional, decisions for parents to make. Theories of decision-making^{24,25} suggest that in these circumstances it is more important that people understand the gist of the information than being able to recall verbatim the risk estimates or other information presented. However, a balanced presentation of the pros and cons of sequencing and the risk of disease is still needed. These decisions are akin to many current medical decision-making scenarios for which evidence for the best course of treatment or action is equivocal. In these cases, an optimal decision can be reached by informed and shared decision-making processes.²⁶

Decision aids are educational interventions that can help parents make better decisions by providing information and helping to clarify values and preferences. They are particularly helpful when there is no clear best choice for action.²⁷ Evidence shows that decision aids increase knowledge,^{28,29} promote more accurate risk perceptions,³⁰ support value-congruent decisions when there is a value clarification component, and reduce decisional conflict while increasing decision confidence.³¹

Decision aids can be designed to promote informed decisions that do not necessarily involve a clinician or promote shared decision-making between a parent and clinician.³² Our decision aid exemplifies the latter type, because parents will have the opportunity to consult with a genetic counselor to answer questions and to discuss their decisions about genomic sequencing for their child and the types of information they decide to learn. Informed decision-making by parents is a necessary component of shared decision-making that might occur in these interactions.³²

The process of informed decision-making requires that parents understand the potential application of NGS to future health conditions, understand the evidence about the risks and benefits for all decision options, and consider their own values and preferences when deciding on a course of action.^{33,34} The NC NEXUS decision aid applied standards described by the International Patient Decision Aid Standards checklist (http://www.ipdas.ohri.ca/IPDAS_checklist.pdf). One challenge of applying these standards is that some of the dimensions required by the International Patient Decision Aid Standards are not currently known and will require additional study by the NC NEXUS study and others. Another challenge is that the standards are usually applied to decisions about a single piece of information rather than decisions about categories of information (eg, carrier status). Future iterations of the decision aid can be updated as evidence from NC NEXUS and other studies emerges.

We are also developing and testing a new model for informed decisionmaking that includes both members of a couple in the decision-making process by integrating traditional notions of shared decision-making between clinicians and patients^{35,36} with dyadic theories of decision-making and behavior that are typically applied to close relationships.³⁷ This integration is important because genomic sequencing has great potential to provide results with implications for both sides of the family. In our previous study of fragile X NBS, our institutional review board required consent from both parents; consequently, we conducted an extensive investigation of the fathers' role in these decisions and developed an algorithm for applying the institutional review board's "reasonably available" guideline for fathers' consent.³⁸ There are few theoretical accounts to help guide collaborative joint decisions between parents and inform future research and practice. Our study will assess whether the processes of shared, informed decision-making helps to attenuate potential negative psychological consequences of being asked to make decisions about genomic information. However, we will also recruit single participants (when the father or mother is not "reasonably available") and samegender couples to understand decision-making and consequences, regardless of relationship type.

User-Centered Design Principles—Principles of user-centered design require iterative audience involvement and pretesting³⁹ throughout the decision aid development process, which typically consists of 4 major activities: content development, decision aid design and programming, pretesting, and experimental study. We used a feature-driven development approach in which major components of the decision aid were initially developed and tested, then refined, progressively integrated, and tested again under controlled conditions throughout the development life cycle. First, we created the content for the decision aid that was extensively reviewed by the steering committee. We then developed artwork, audio narration, and other multimedia elements that were integrated into the application. This process used key user interface and user experience design principles such as giving the user control, empowering the user, and allowing exploration and browsing; reducing the user's memory load by providing context and reminders, with minimal reliance on the need for recall; providing immediate feedback and the option of help at any point, including defining the terminology used; and keeping the interface consistent, with active buttons or menus in the same place throughout.⁴⁰ The NC NEXUS decision aid allows users to go at their own pace, repeating and reviewing information as needed. All content uses plain-language principles to address the varying health literacy levels of the audience.

Usability testing of the decision aid has involved conducting interviews with a small group of people who are in the same age range as our intended end users, using a think-aloud interviewing method⁴¹ to solicit feedback and assess the technical functionality. Results from these interviews informed decision aid development to make it more understandable and engaging.

Expert and Clinician Input for Accuracy

At various stages during the development of the decision aid, we have sought input and advice from experts and experienced clinicians. Stakeholder engagement with key groups of experts has provided critical feedback on issues to be discussed with parents and guidance

on decision aid content. For example, we have established a continuous dialogue with the NC NEXUS steering committee, comprising researchers with expertise in communication and behavioral science, medical genetics, genetic counseling, pediatrics, and bioethics. In addition to informing the research questions explored through other formative research projects already described, the steering committee has directly shaped the structure and content of the decision aid. In the early phases of development, we met with the steering committee to review a general outline of the decision aid content and established the technical requirements needed for data transfer and participant tracking throughout the study. Later, the steering committee played instrumental roles in editing the decision aid's content for technical accuracy and expected patient literacy and in finalizing a complete draft of the shooting script, including full text of the audio narration and detailed notes describing multimedia elements to appear on screen. The steering committee's input proved invaluable for striking a balance in crafting a factual overview of the complex topics of genomic sequencing and issues related to returning different kinds of results while using plain-language principles.

NC NEXUS NEXT STEPS

The NC NEXUS study will allow us to test the extent to which a decision aid supports informed decision-making; reduces decision conflict, regret, or distress; and increases decision confidence. It will also allow us to evaluate whether there are differences in these outcomes for parents who receive information from the categories of additional information available to them: conditions that have childhood onset but are *not* medically actionable, disorders that have adult onset and are medically actionable, and carrier status findings. We will also be able to detect differences between parents who make decisions about a newborn child versus an older child with a previously diagnosed genetic disorder.

Because the decision aid is electronically based, it will be adaptable as new evidence emerges about genetic conditions. It will be easily updateable to keep pace with best practices in decision aid development and the communication of genomic information. We will also gain a much greater understanding of how parents understand genomic sequencing, their perceptions of the decisions they make, the role and impact of a decision aid in clinical interactions, and the ramifications of result disclosure for family adaptation. This information will be used to update and refine the content presented.

After the project is completed, we will have validated materials produced by an evidence-based process that could be used in other studies and in clinical care to support parents and pediatricians as they make decisions about genomic sequencing. We will also have collected evidence to address key questions about the degree to which parents and children are harmed by or have benefitted from learning the information offered in NC NEXUS. Answering these questions will be critical to help inform policy and clinical practice about how genomic information is best communicated in various clinical, public health, and research settings.

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ABBREVIATIONS

ELSI	ethical, legal, and social implications
MS/MS	tandem mass spectrometry
NBS	newborn screening
NC NEXUS	North Carolina Newborn Exome Sequencing for Universal Screening
NGS	next-generation sequencing
NGS-NBS	next-generation sequencing newborn screening
RCT	randomized controlled trial
WES	whole exome sequencing

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TABLE 1**ELSI Questions Raised by the Use of Genome-Scale Sequencing in NBS and How They Are Addressed in NC NEXUS**

ELSI Question	NC NEXUS Approach
How can the vast amount of genomic information be categorized into meaningful units to facilitate parental decision-making and support clinicians?	Categorize disparate conditions based on age of onset and medical actionability.
How can parental input be incorporated to improve how information about genomic sequencing is presented?	Conduct multimethod research (qualitative methods and discrete choice experiment) and triangulate data to understand parental needs, preferences, values, and the impact of their decisions.
How can parental informed decision-making in the NC NEXUS study be best supported?	Develop a decision aid to support parental decision-making that incorporates best practices and is scalable to a broad population.
To what degree will parents and their children be harmed or benefited when asked to make decisions about which information to learn following genome-scale sequencing?	Conduct an RCT to understand the short- and long-term effects of parental decision-making about a broad range of information spanning a spectrum of age of onset and actionability.