UNC
SCHOOL OF MEDICINE
DEPARTMENT OF GENETICS

A: COVER LETTER

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Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health (OIR)
Food and Drug Administration
10903 New Hampshire Avenue
WO66, Room 5647
Silver Spring, MD 20993-0002

Re: Addendum to the Pre-submission IDE Review Request (Q140207)

Device Name: 1-U19-HD077632-01 (Powell and Berg co-PIs) 9/5/2013 - 8/31/2018

Funding by NICHD and NHGRI

Dear Dr. Shukla:

Please find attached an addendum to the NC NEXUS pre-submission enquiry (2 hard copies and 1 e-copy) that provides an overview of the ELSI considerations involved in pediatric genetic testing, our recruitment and ELSI research protocol, and description of the decision aid development.

The e-copy is an exact duplicate of the hard copies.

We look forward to your feedback regarding the addendum. Our specific questions are the same as in the original pre-submission: What level of risk is involved in the proposed study? Will our proposed study require an IDE? What modifications of the protocol are recommended by the FDA? During the course of the study, what changes to the protocol or IRB would require additional review by the FDA?

Thank you for considering this addendum as part of our complete pre-submission IDE enquiry. Please let us know if you have any additional questions.

Sincerely,

Cynthia M. Powell, MD

Jonathan S. Berg

Professor of Pediatrics and Genetics
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Attachment: Addendum to the pre-submission for an IDE (Q140207)

Addendum to Presubmission Enquiry

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C. Overview of ELSI considerations in pediatric genetic testing

Unlike many kinds of medical tests, which provide information of a transient, temporal nature, genetic testing typically can reveal information about an individual's past, present, and future medical conditions; this information may also have immediate implications for family members. These characteristics, combined with the complexity of genetic information, which ranges from probabilistic information to highly deterministic information, has led many to view genetic information as somehow different than other kinds of biomedical information ("genetic exceptionalism"). Consideration of the ethical, legal, and social implications of genetic knowledge has been an inherent component of the human genome project and other genomic research efforts (Greely, 1998), and inexorable advances in genetic testing have been accompanied by an immense societal discussion about the most appropriate uses of this information in healthcare, in human subjects research, and even in the setting of personal genomic exploration (Bunnik, et al., 2011). The thread of an individual's right to self-determination is woven tightly throughout the ethical considerations of genetic testing (eg. Nyrhinen, et al., 2009; Bunnik, et al., 2013).

Considerations of the benefits and risks of genetic testing are perhaps even more acute in children because of their special status as minors, under the guardianship of their parents for a period of time, after which they may achieve independence and acquire their own right to self-determination (Lantos, 2010). Although parents are given a significant amount of leeway in their decisions about how to raise their children, there are also limits on this guardianship when pertaining to that child's future autonomy. Parents have the responsibility to act in their child's best interests, which is the primary consideration in most approaches to pediatric genetic

testing. Further complicating matters, consideration of such testing inevitably occurs in the context of highly variable childhood developmental states and unique family settings (Fanos, 1997).

Expert panels have put forth various guidelines in order to delineate appropriate uses of genetic testing in children (Wertz et al., 1994; ASHG Board of Directors, ACMG Board of Directors, 1995; AAP Committee on Bioethics, 2001; Ross et al., 2013). These recommendations have traditionally been grounded in "best interests" being limited strictly to the impact of genetic information for the child in question. For example, it is generally agreed that we should avoid testing children for adult-onset conditions when the information would not directly impact medical management during childhood. This recommendation typically envisions the scenario in which a family is known to be segregating an adult-onset disorder and the information is expected to be available to the at-risk child when he or she becomes an adult and can make an informed decision about whether or not to learn whether the family mutation was inherited or not. The recommendation to avoid predictive genetic testing is based in the idea that such testing will not alter medical management of the child, and that there could be psychological harms associated with learning one's mutation status. However, it should be noted that substantial counter-arguments have been made on behalf of informed decision-making by parents, despite these concerns (Pelias, 2006; Rhodes, 2006).

Similarly, there is a view that testing for carrier status for recessive disorders is not likely to benefit the child and should thus be deferred until the individual is considering reproduction. Clinically, this often occurs in a scenario in which a child has a sibling with a diagnosed autosomal recessive or X-linked condition and/or one or both parents are carriers, so that the

unaffected child has an *a priori* carrier probability of 50-66%. Applying these same recommendations to the very different scenarios of population screening and incidental findings through genome-scale sequencing needs to be closely examined.

Diagnostic testing is an area in which genetic testing in children can more clearly be justified, especially when it allows a specific diagnosis to be identified and a management strategy implemented. That being said, in many cases a clinical diagnosis is established in the child and genetic testing is not actually required for the child's management; yet information about the molecular etiology can be enormously valuable to the parents for reproductive decision-making. Thus, even in the case of diagnostic testing, the main benefit of genetic testing may accrue to the parents or the family unit, not the child as an individual. And yet, such diagnostic testing is deemed justifiable.

In addition, modern sequencing technology greatly increases the efficiency of genetic testing, allowing analysis of broad panels of genes, or the entire genome. This genome-scale sequencing vastly increases the likelihood of "incidental findings" not related to the indication for sequencing, yet no less clinically relevant. Some incidental findings will provide information about adult-onset conditions, and other incidental findings will have implications for that individual's reproduction. How then should these types of information be handled? Earlier guidelines based on single gene testing or linkage analysis may not be as germane in the setting where genome-wide data is obtained during the course of a diagnostic test.

For example, the ACMG recommended (Green et al., 2013) that clinical laboratories routinely return incidental findings related to medically actionable adult-onset disorders when genome-scale diagnostic sequencing is performed in a child. At first glance, this

recommendation appears to be at odds with the previous restrictions on testing for adult-onset disorders, except that in the case of a child undergoing diagnostic genome-scale sequencing, there may be no knowledge in the family about a medically actionable adult-onset disorder (eg. a 25-year-old mother who inherited a BRCA1 mutation from her father, and has no family history of early-onset breast cancer). Such a finding, if not reported, could lead to irreparable harm to the child caused by the early death of a parent from a condition that might have been prevented. This type of incidental finding could therefore have direct psychological benefit to the child and be in the "best interests of the child," even though the revelation of the information may obviate that child's "right not to know" later in life. Clearly, there is equipoise about the balance of benefits and harms in this situation.

Newborn screening represents a special category of genetic testing in children (Levy, 2010). Although the testing is not usually carried out by molecular methods, the information provided is no less genetic in nature. The conditions represented on the recommended uniform screening panel represent inherited disorders that, when identified prior to onset of symptoms, can be effectively prevented or ameliorated. That being said, available interventions for these disorders may have varying efficacy, and some of the disorders have pleiotropic effects. Incorporation of genetic sequencing panels or even genome-scale sequencing into the newborn screening paradigm raises significant concerns about the management of such information (Bailey et al., 2008). In the recommendations made by the ACMG and AAP regarding the uniform screening panel (ACMG Newborn Screening Expert Group, 2006), the expert group made three recommendations that could have profound implications for newborn screening via genome-scale sequencing.

First, the expert group recommended that 25 additional conditions beyond the 29 conditions on the recommended panel be sought. These 25 conditions are "clinically significant and revealed by the screening technology but lack an efficacious treatment" and the expert group "thought it was important that such findings be communicated to the health care service community and to families" (ACMG Newborn Screening Expert Group, 2006). The direct implication of this recommendation is that ***any clinically relevant finding from NBS should be reported***, which in the case of genome-scale sequencing would include essentially any genetic condition – childhood onset, adult onset, medically actionable, or non-medically actionable. Presumably, the expert group was not envisioning the use of a genome-scale sequencing test for newborn screening when they made these recommendations, because many families would refuse such testing if they knew there was a possibility of learning about findings without any related preventive measures (Bombard et al., 2014), thus jeopardizing the immense value of the newborn screen at the population level.

Second, the expert group recommended that states "mandate… reporting of any abnormal results that may be associated with clinically significant conditions, including the definitive identification of carrier status" (ACMG Newborn Screening Expert Group, 2006). This statement explicitly contradicts earlier recommendations against carrier screening in children, and in practice, carrier results for cystic fibrosis are now routinely returned as part of the newborn screen, just as carrier results for sickle cell disease have been for the past forty years. When one considers the use of a genome-scale sequencing assay for newborn screening, this recommendation by the expert group would essentially convert newborn screening from a program that detects rare, preventable disorders in a very small minority of cases into a carrier

screening test for all recessive disorders that would yield a handful findings in every individual screened. Indeed, the Hardy-Weinberg equilibrium dictates that the vast majority of results returned in such a scenario would involve carrier status for recessive conditions. Again, the expert group was clearly not considering the implications of this recommendation for genome-scale sequencing being used in newborn screening.

Finally, the expert group recommended that states "consider that the range of benefits realized by newborn screening includes treatments that go beyond an infant's mortality and morbidity" (ACMG Newborn Screening Expert Group, 2006). This statement was not very well developed in the executive summary, but seems to imply that there is value to newborn screening beyond preventable conditions – that personal utility (or perhaps the utility as perceived by the family unit) is just as valid a consideration in determining what information to learn about a child as are the traditional values of improving the health of the individual child. This recommendation is in many ways similar to the ACMG incidental findings recommendations regarding medically actionable adult-onset conditions, in which the benefit to the child is indirect and related to the overall health of the child's family members. This recommendation is also internally consistent with the expert group's recommendation about returning carrier findings, in that such information could allow couples to pursue additional genetic testing in order to avoid having an affected child in the future. Such information can be construed as being ultimately beneficial to the child whose screening results enabled prevention, because of the stress that families experience when they have a child affected with a genetic disorder. That being said, the expert group's recommendation, if taken to the logical

extreme, could be interpreted as meaning that any genetic information that is desired by the parents is justifiable if considered beneficial by the parents.

Clearly, these various expert recommendations for the return of genetic information in children are contradictory, at least at face value. However, one reason for the inconsistency is that the recommendations were written from entirely different contexts. Most people would agree that genetic information that is directly relevant to the child and would be expected to have direct benefit to the child should be returned, and that it would be unethical to withhold this information even if parents preferred not to learn it (Holm et al., 2014). This recommendation can be made regardless of how the information was discovered, whether through intentional diagnostic testing, as an incidental finding, or through newborn screening. Opinion seems to be split regarding the justification of revealing information about adult-onset medically actionable conditions in a child when the benefits are more theoretical (preventing the death of a parent) and less certain to accrue than the discovery of a condition with direct medical implications for the child (eg. Strong et al., 2014; Yu, et al., 2014).

Most people would also agree that when other types of information are available, parents should have a reasonable ability to learn such information if desired, and also to refuse information that they do not want. The challenge is in the qualifying term "reasonable" – herein lies the equipoise when considering the use of genome-scale sequencing in newborn screening. Some would argue that it is unethical to use the child as a means of carrier screening for the parents (one could ask, "why should the parents not simply undertake carrier screening themselves?"). Others would argue that learning about carrier status in a child is

highly unlikely to be harmful, and as such the balance of benefits and harms argues in favor of parents being able to learn such information.

Perhaps more complicated are genetic findings that indicate the presence of a childhood-onset disorder that has no effective prevention or treatment. It can be argued that parental prerogative is the primary consideration – parents are responsible for their child's health care, and learning information about such conditions could be considered part of this responsibility. On the other hand, such information could have terribly damaging effects on the child's own well-being if that knowledge interferes with parental bonding, creates family stress including divorce, or leads to abuse or abandonment. In addition, even the decision-making process regarding this type of information could lead to strife between parents if they were unable to agree about whether or not to learn such information. Who decides when the parents disagree?

Most would agree that adult-onset disorders with no effective prevention or treatment should be off-limits to parents and are most appropriate for informed decision-making by the individual when he or she becomes an adult. That being said, some argue that even these disorders fall within a parent's responsibility to raise their child to the best of their ability and prepare them for any eventuality, that the theoretical harms are less significant than initially supposed (Malpas, 2008) and that parents are in the best position to make decisions relative to their child's best interests (Robertson and Savulescu, 2001). Furthermore, in the case of a disabled child who will likely never be able to make an informed decision, why should a parent (who will be that child's guardian for their entire life) not be able to learn such information in order to adequately plan for the future? This extreme form of protectionism is unwelcome to

many parents, yet justified by a "black and white" interpretation of ethical guidelines as restricting such testing, when they were probably never intended to be interpreted in such a way.

Clearly, these questions raise a host of ELSI implications when considering the application of genome-scale sequencing in newborn screening (Tarini and Goldenberg, 2012). Challenges related to the use of genomic sequencing in newborns, both technical and ethical, formed the basis of the 2012 RFA posted jointly by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Human Genome Research Institute (NHGRI) of the National Institutes of Health. Addressing these multiple and complex research questions is the focus of our study, NC NEXUS, funded through a U19 Cooperative Agreement from NIH. The NC NEXUS study personnel have carefully considered all aspects of these questions and we have constructed a return of results framework that we feel appropriately reflects an ethical obligation to provide medically actionable information with a direct impact in childhood (the NGS-NBS panel) while grappling with the equipoise that exists around additional types of genetic information. We designed the randomization scheme as a way to detect differences in short term outcomes related to decision-making, and have planned focus groups and a discrete choice experiment to address some of these issues regarding parental choices. Since this is a research study, and parents will consent to the return of results framework and randomization, we feel that it is perfectly appropriate for some parents to be randomized to a group with results restricted to the NGS-NBS (and thus to not receive information about additional categories of information). This decision is in line with current consensus among members of several consortia involved in genomic research in human

participants (Jarvik et al., 2014). Parents can choose not to participate in the research study if they are not satisfied with the possibility of receiving only the NGS-NBS results (which nevertheless exceed the standard of care uniform screening panel), and they can choose not to have their child's DNA sequenced if they are uncomfortable with the potential to learn genetic information. In addition, we have planned a substantial panel of assessments that will measure psychosocial aspects of the project, including the parents' decisions about whether or not to accept whole exome sequencing for their child, their decision-making process regarding additional information that they may learn, and the impact of this information on the family. Finally, we will use best practices to develop a decision aid that may be broadly useful in future applications of genome-scale sequencing in newborn screening.

References:

1. AAP, Committee on Bioethics. Ethical issues with genetic testing in pediatrics. *Pediatrics* 107(6):1451–1455 (2001). Reaffirmed October 2004.

2. ACMG Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and system--executive summary. *Pediatrics* 117(5 Pt 2):S296-307 (2006).

3. ASHG Board of Directors, ACMG Board of Directors. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet*. 57:1233–1241 (1995).

4. Abdul-Karim R, Berkman BE, Wendler D, Rid A, Khan J, Badgett T, Hull SC. Disclosure of incidental findings from next-generation sequencing in pediatric genomic research. *Pediatrics*. 131(3):564-71 (2013).

5. Bailey DB Jr, Skinner D, Davis AM, Whitmarsh I, Powell C. Ethical, legal, and social concerns about expanded newborn screening: fragile X syndrome as a prototype for emerging issues. *Pediatrics*. 121(3):e693-704 (2008).

6. Bombard Y, Miller FA, Hayeems RZ, Barg C, Cressman C, Carroll JC, Wilson BJ, Little J, Avard D, Painter-Main M, Allanson J, Giguere Y, Chakraborty P. Public views on participating in newborn screening using genome sequencing. *Eur J Hum Genet*. 2014 Feb 19. doi: 10.1038/ejhg.2014.22. [Epub ahead of print]

7. Bunnik EM, Schermer MH, Janssens AC. Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. *BMC Med Ethics*. 12:11 (2011).

8. Bunnik EM, de Jong A, Nijsingh N, de Wert GM. The new genetics and informed consent: differentiating choice to preserve autonomy. *Bioethics*. 27(6):348-55 (2013).

9. Fanos JH. Developmental tasks of childhood and adolescence: implications for genetic testing. *Am J Med Genet*. 71(1):22-8 (1997).

10. Greely HT. Legal, ethical, and social issues in human genome research. *Annu Rev Anthropol*. 27:473-502 (1998).

11. Green RC, Berg JS, Grody WW, et al.; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 15(7):565-74 (2013).

12. Holm IA, Savage SK, Green RC, Juengst E, McGuire A, Kornetsky S, Brewster SJ, Joffe S, Taylor P. Guidelines for return of research results from pediatric genomic studies: deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board. *Genet Med*. 16(7):547-52 (2014).

13. Jarvik GP, Amendola LM, Berg JS, et al.; eMERGE Act-ROR Committee and CERC Committee; CSER Act-ROR Working Group, Burke W. Return of genomic results to research participants: the floor, the ceiling, and the choices in between. *Am J Hum Genet*. 94(6):818-26 (2014).

14. Lantos JD. Does pediatrics need its own bioethics? *Perspect Biol Med*. 53(4):613-24 (2010).

15. Levy HL. Newborn screening conditions: What we know, what we do not know, and how we will know it. *Genet Med*. 12(12 Suppl):S213-4 (2010).

16. Malpas PJ. Predictive genetic testing of children for adult-onset diseases and psychological harm. *J Med Ethics*. 34(4):275-8 (2008).

17. Nyrhinen T, Hietala M, Puukka P, Leino-Kilpi H. Are patient rights to information and self-determination in diagnostic genetic testing upheld? A comparison of patients' and providers' perceptions. *J Genet Couns*. 18(1):72-81. (2009).

18. Rhodes R. Why test children for adult-onset genetic diseases? *Mt Sinai J Med*. 73(3):609-16 (2006).

19. Robertson S, Savulescu J. Is there a case in favour of predictive genetic testing in young children? *Bioethics*. 15(1):26-49 (2001).

20. Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: Ethical and policy issues in genetic testing and screening of children. *Genet Med*. 15(3):234-45 (2013).

21. Pelias MK. Genetic testing of children for adult-onset diseases: is testing in the child's best interests? *Mt Sinai J Med*. 73(3):605-8 (2006).

22. Strong KA, Zusevics KL, Bick D, Veith R. Views of primary care providers regarding the return of genome sequencing incidental findings. *Clin Genet*. 2014 Mar 27. doi: 10.1111/cge.12390. [Epub ahead of print]

23. Tarini BA, Goldenberg AJ. Ethical issues with newborn screening in the genomics era. *Annu Rev Genomics Hum Genet*. 13:381-93 (2012).

24. Wertz DC, Fanos JH, Reilly PR. Genetic testing for children and adolescents. Who decides? *JAMA*. 272(11):875-81 (1994).

25. Yu JH, Harrell TM, Jamal SM, Tabor HK, Bamshad MJ. Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. *Am J Hum Genet*. 95(1):77-84 (2014).

D. NC NEXUS recruitment and ELSI research protocol

1. Cohorts to be studied

a) Healthy newborn cohort: Prospective parents with normal pregnancies ascertained prenatally. See Figure 1 for a summary of the study flow for this cohort.

i. **Site:** Obstetrics Clinic at UNC

ii. **Initial contact**: Pregnant women ("mothers") who are potential participants will be identified by a prenatal provider (nurse, OB, etc.). These mothers will be approached by a study recruiter and asked if they would like to hear about a research study. Fathers will also be recruited if they are reasonably available. Thus, these procedures discuss the involvement of "parents." However, when the baby's father is not reasonably available, the mother may participate on her own.

- **If they say NO**: Do not gather demographic information or reason for refusal (because they are not declining based on having any information)
- **If they say YES**: Recruiter provides a brief verbal description of the study and the **paper decision aid (brochure)** for mothers to read and take home to discuss with the baby's father. The brochure will include descriptions of WES, the four categories of findings, and the randomization. Mothers will be asked if they agree to a phone call from a research assistant (study scheduler). If they agree and give their phone number and other contact information including best time to contact, this information will be entered into the study database (a custom REDCap database

housed within the UNC Hospitals firewall). Recruiter provides a timeframe for the call (e.g., a week) and asks that both parents read the brochure before that time.

b) Diagnosed Cohort: Parents of children up to age 5 with conditions diagnosed through newborn screening or by other methods that include PKU, MCADD, hearing loss, cystic fibrosis, lysosomal storage disorders, primary ciliary dyskinesias and other miscellaneous genetic conditions. See Figure 2 for a summary of the study flow for this cohort.

i. **Site**: Specialty clinics at UNC (Metabolism, ENT/audiology, CF/Pulmonary, Neuro)

ii. **Initial contact:** Parents will be recruited in clinics or by phone. They will be contacted by a study recruiter and asked if they would like to hear about the study. Fathers will also be recruited if they are reasonably available. Thus, these procedures discuss the involvement of "parents." However, when a parent is not reasonably available, the other parent may participate on his or her own.

- **If they say NO**: Do not gather demographic information or reason for refusal (because they are not declining based on having any information)
- **If they say YES**: Recruiter provides a brief verbal description of the study and provides the **brochure** (either in person or by mail) for parents to read and discuss. The brochure will include descriptions of WES, the four categories of findings, and the randomization. Parents will be asked if they agree to a phone call from the study scheduler. If they agree and give their phone number and other contact information including best time to contact, this information will be entered into the study database. Recruiter provides a timeframe for the call (e.g., a week) and asks that both parents read the brochure before that time.

2. Enrollment

a) **Recruitment phone call**: The study scheduler will call parents who have agreed to a phone call, asking if they would like to continue in the study. If both parents have not read the brochure when the scheduler calls, the scheduler will ask if they need more time to read it, agreeing on how much time that will be. If parents have made a decision:

- **If they say NO**: Parents will be asked if they are willing to provide basic demographic information and their reason for declining.
- **If they say YES**: Scheduler schedules an in-person appointment for parents to meet in person with a genetic counselor to discuss the study, ideally coinciding with a planned visit to UNC (e.g., a prenatal care appointment for the healthy newborn cohort or an upcoming clinic visit for the diagnosed cohort). Parents will be sent a study informed consent form so they can read it before the visit.

b) **In-person appointment**: Parents will meet with a genetic counselor in the CTRC to discuss the study. This appointment will include informed consent procedures for being in the study, using the online decision aid to make a decision about sequencing, randomization into one of two groups, and basic information about the information that would potentially be returned to each group. The baby's father will be able to call in to this meeting and provide verbal consent, then mail a signed consent form.

- **If they DO NOT CONSENT to study**: Parents who do not consent to the study will be asked if they are willing to provide basic demographic information and their reason for declining.

- **If they CONSENT to the study**: Parents who consent to joining the study (and thus to using the decision aid to make a decision about whether to accept NGS-NBS for their baby and, if randomized to the experimental arm, to decide from among the additional categories of information), will sign the consent document at this visit. This consent will constitute participation in the overall study but not necessarily to having their child undergo sequencing. They will then complete the Time 1 (baseline) assessment. After consent and completion of the assessment, parents are randomized into one of two study groups (as described below) and given access to the online decision aid (see description, below).

3. Randomization

Parents who choose to participate in the study will be randomized into two groups using batch randomization. One group (one-third of total study parents, known as the "control group") will receive only the NGS-NBS results. The other group (two-thirds of total study parents, referred to as the "experimental group") will be asked to decide if they want to receive additional information in three categories: childhood onset non-medically actionable, adult onset medically actionable, and carrier status for recessive disorders. The decision to obtain additional categories of information can be made at any time during the course of the study. Parents will be able to obtain some, all, or none of the additional categories of information. After randomization, parents in each group will have access to the version of the online decision aid that corresponds to their group assignment.

Rationale: as discussed above, there is a state of equipoise regarding best practices for return of genome-scale results to infants and children, especially when those results are not expected to directly benefit the child.

- It is unknown whether being faced with such decision-making, particularly in the setting of a healthy newborn child, will create distress or cause discord between parents.
- It is unknown when and how parents will go about making such decisions, what information they feel that they need in order to make a confident decision, who they will consult regarding the decision, and what they will do with the information once received.
- It is unknown whether parents will experience short-term or long-term regret about information that they decide to learn.
- It is unknown whether the revelation of such information will have long-term adverse effects such as causing the child to become a "patient in waiting" or impacting parental bonding.
- It is unknown whether decisions made by the parents on behalf of a minor child will later be resented by the child when he or she reaches the age of majority.

Since this is a pilot study, we will not be able to generate enough data or follow the participants for long enough to fully answer all of these questions. However, this study will set the foundation for answering these questions over the long term and ultimately defining best practices for parental decision-making. The control arm will receive information that is analogous to (albeit more extensive than) the existing state newborn screen; this cohort effectively receives a targeted panel of information that surpasses a given threshold of medical

actionability. Such a restricted panel of genetic information is a plausible next step for sequencing-based newborn screening. Conversely, the experimental arm represents a scenario similar to the vision that has been articulated by many – that every person will have his or her genome sequenced at birth, and that the information will be used to guide their healthcare throughout their lives. Randomization allows us to directly compare the benefits and risks of these two visions of newborn screening.

4. Online decision aid

Those parents who formally consent to be in the study will be given access to the online decision aid (development and evaluation described in section E). The information parents get and the decisions they make depend on their randomization status**.** Parents can access the online decision aid at the enrollment meeting (with assistance from the genetic counselor) or at home on their own (with a way to contact us to get questions answered). In either case, the decision aid will begin with an introduction and brief tutorial parents can view in order to get the hang of it before viewing the rest of the decision aid.

a. **Control group:** The control group will be given access to a version of the online decision aid that provides information about sequencing and the NGS-NBS panel, and helps them decide whether they want to agree to sequencing, which for them would mean return of NGS-NBS results only.
b. **Experimental group:** The experimental group will be given access to a version of the online decision aid that provides information about sequencing, the NGS-NBS panel, and the **categories of additional information they can request to learn**. They may access the part of

the decision aid that discusses sequencing and the NGS-NBS panel at the enrollment meeting or at home (see "decision about sequencing," below). After they complete that part of the decision aid, the next part will help them decide whether they want any of the additional information; parents can opt to learn some, all, or none of the additional categories of information. They will complete the part of the online decision aid that discusses additional categories of information at home.

5. Decision about sequencing

All parents who have consented to participate in the overall study will decide whether or not they want to have their child undergo whole exome sequencing with focused analysis of the "NGS-NBS," with (experimental arm) or without (control arm) decision-making regarding additional findings.

a) **Timing:** The precise timing of this decision will depend on the cohort. For example, parents in the healthy newborn cohort will have up until the time of delivery to opt-in to sequencing. Parents in the diagnosed cohort are likely to make a decision at the time of the enrollment visit, but will also have the option of taking time to decide and returning to provide a sample at a future date.

b) **Mechanism:** To finalize decisions, we will provide a consent form for sequencing (this form will be similar to standard consent forms used in clinical genetic testing). Since parents will have had access to the decision aid, we expect the sequencing consent process to be accomplished in a short in-person encounter or via phone call. Parents in the diagnosed cohort who choose to make the decision at the enrollment meeting will review the decision

aid with the genetic counselor during the in-person visit and opt-in to sequencing by signing the sequencing consent form in person. Parents who choose to make the decision after returning home will complete consent procedures by phone and mail a signed consent form. All participants randomized to the experimental arm will be able to select additional categories of information at any time following (but not during) the enrollment visit so that they have time to review the additional information in the decision aid. They will call the study team if they decide they would like any or all of the additional information. Consent for this additional information will be obtained verbally (because it will have been discussed with experimental group parents as part of consent for sequencing) and the study team member will record their choices.

c) **Obtaining samples**: Samples will be obtained by buccal swab for all infants and children participating in the study. Parents will be given an information sheet with contact information and a brief summary of their participation in the study, the reason the sample is being obtained, and an estimate of when sequencing will be complete.

   i. For the healthy newborn cohort, an MD on the study will be alerted through UNC's electronic health record (EPIC) that the mother has been admitted to UNC and unless there is a complication (preterm, birth problems in infant for examples) a buccal swab will be obtained prior to infant being discharged from the hospital. If for some reason we could not obtain a sample from the baby before discharge after delivery we will arrange to obtain a sample when the mother returns for her next post-partum visit.

   ii. For the diagnosed cohort, the buccal swab sample will be obtained during an in-person meeting (either the initial enrollment visit or another pre-arranged visit).

6. Return of results

Parents will be notified when sequencing and analysis has been completed. They will be scheduled for an in-person appointment with a genetic counselor and an MD clinical geneticist to discuss the results. Parents can opt-out of the study at this point by not scheduling an appointment. Those in both groups will obtain NGS-NBS results. Those in the experimental group will also obtain any relevant results in the other categories that they have elected to receive based on the decision aid tool.

7. Assessments

Parents will complete a series of quantitative measures designed to assess a range of factors related to participation in the study (Table 1).

a) **For parents who CONSENT to NGS-NBS**: Parents will complete the Time 2 assessment. If the study consent and consent to NGS-NBS occurs at the same study visit (eg. for the diagnosed cohort) the Time 2 assessment will occur 2 weeks after the first visit.

b) **For parents who DO NOT CONSENT to NGS-NBS**: These parents will complete the Time 2 assessment, which ends their participation in the study.

c) **For parents who COMPLETE the results visit**: Parents will then complete the **Time 3 assessment** following the visit and **Time 4 assessment** three months after the results visit.

Figure 1:
Summary of Prospective Study for Healthy Newborn Cohort

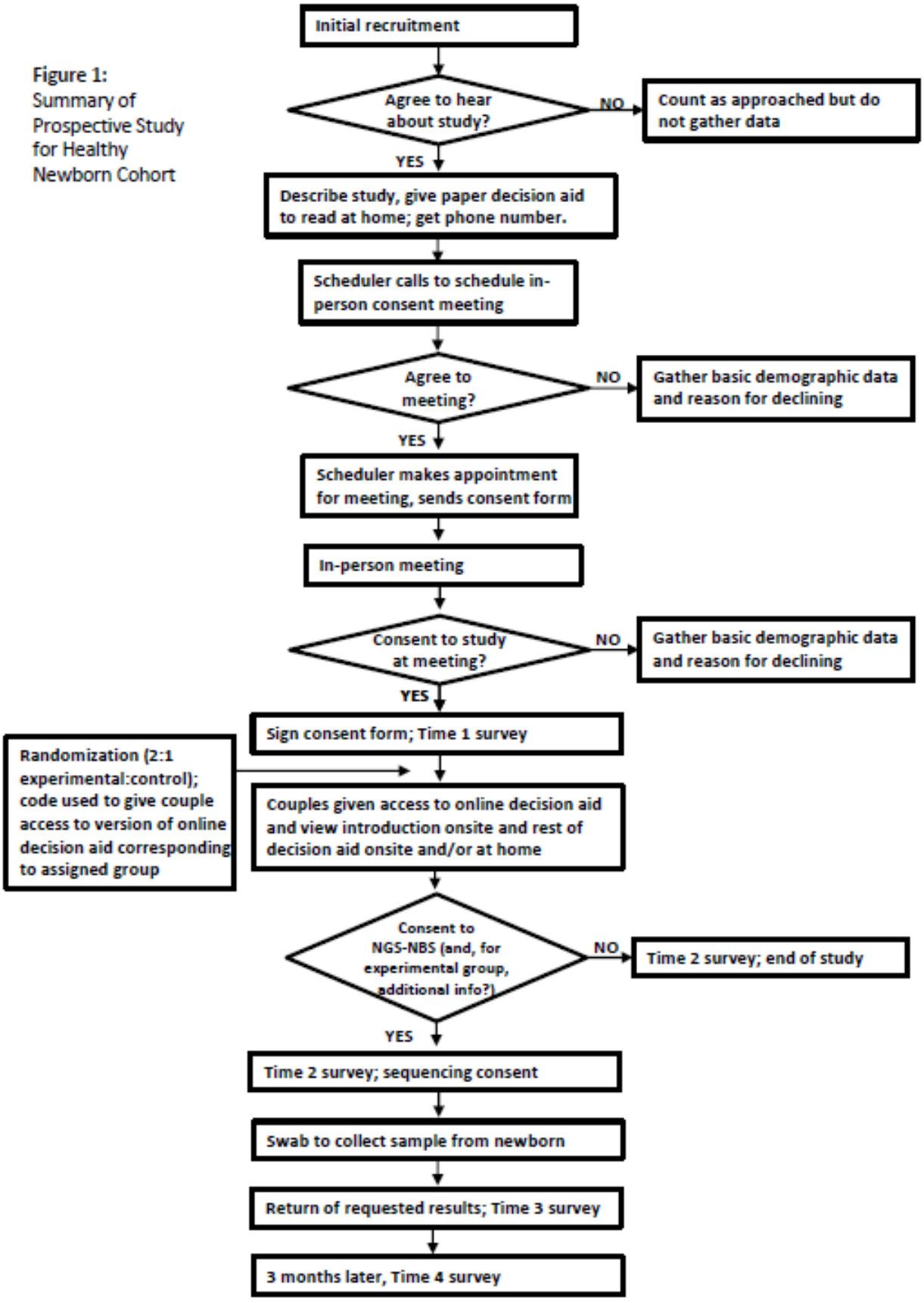

Figure 2:
Summary of Prospective Study for Diagnosed Child Cohort

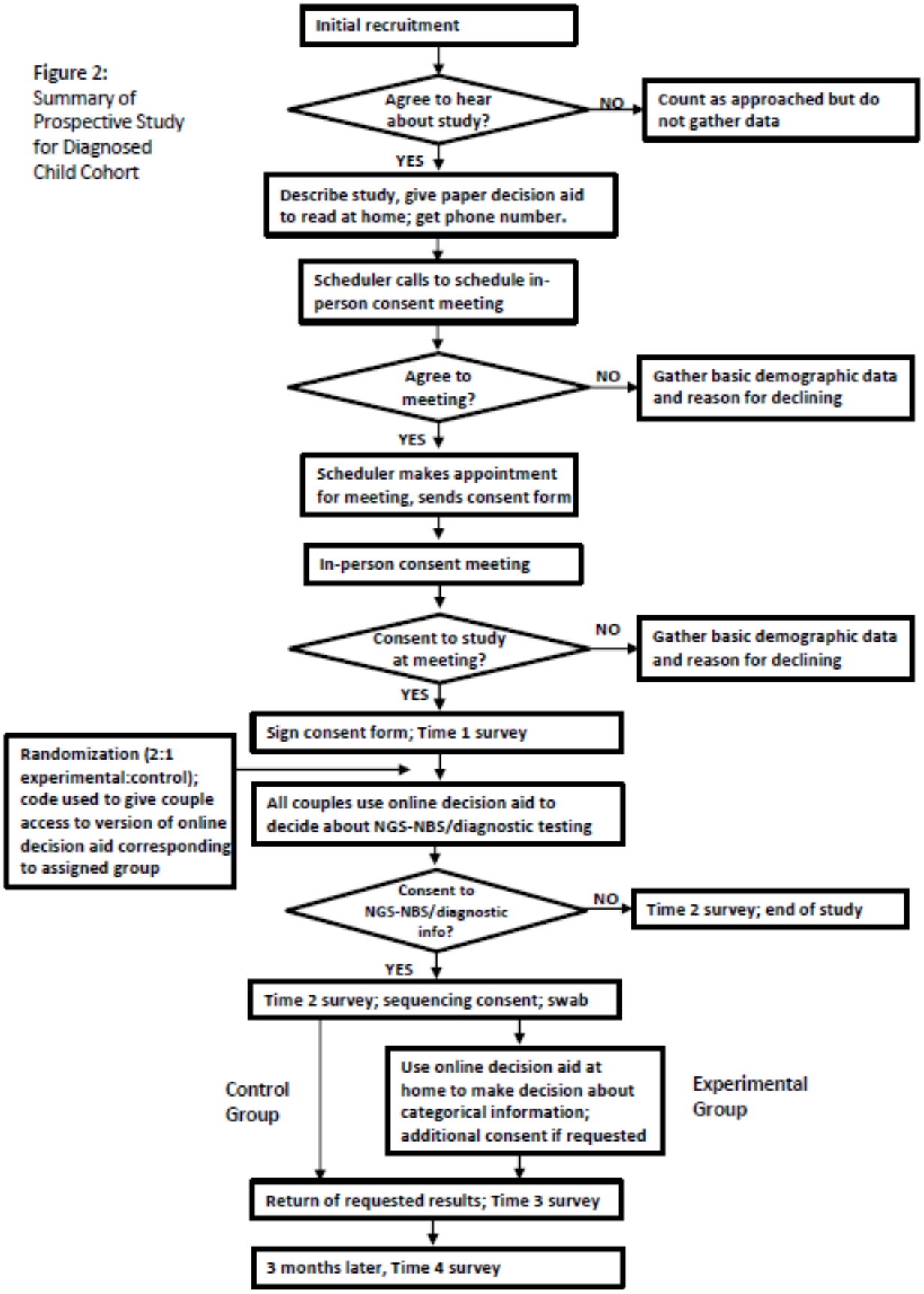

Table 1. Summary of Study Measures

Variable	Assessment Time			
	1	2	3	4
Selection/subject variables (e.g., race/ethnicity, gender, diagnosed-/well-child group, decision/control group)	**A**			
Health literacy (Test of Functional Health Literacy in Adults—Short Form)[1,2]	**A**			
Health Care System Distrust (Health Care System Distrust Scale—Revised) [3.4]	**A**			
Decision to consent for NGS-NBS	**n/a**[a]			
Decision to consent for each category of non-medically actionable incidental results				
Couple agreement about decision to consent for NGS-NBS (to be developed for this study)[5,6]		**A**		
Couple agreement about categories of non-medically actionable incidental results (to be developed for this study)				**E**
Reasons for accepting/declining NGS-NBS (to be developed for this study)		**A**		
Reasons for accepting/declining categories of non-medically actionable results (to be developed for this study)				**E**
Knowledge about NGS-NBS (NCGENES measure to be adapted for this study)	**A**	**A**		
Knowledge about non-medically actionable incidental results (NCGENES measure to be adapted for this study)			**E**	**E**
Decision conflict (Decision Conflict Scale)[7]	**A**	**A**	**A**	**A**
Test-related distress (Multidimensional Impact of Cancer Risk Assessment) [8]			**A**	**A**
Perceived risk and benefits of NGS-NBS (to be developed for this study based on validated existing measures)	**A**			**A**
Perceived risks and benefits of non-medically actionable incidental results (to be developed for this study based on validated existing measures)			**E**	**E**

Note: A = All participants; **E** = Participants randomized to experimental group only.

[a]These outcomes reflect participant behaviors rather than via self-report measures.

8. References

1. Parker, R. M., Baker, D. W., Williams, M. V., & Nurss, J. R. (1995). The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med, 10*(10), 537–541.

2. Baker, D. W., Williams, M. V., Parker, R. M., Gazmararian, J. A., & Nurss, J. (1999). Development of a brief test to measure functional health literacy. *Patient Education and Counseling, 38*(1), 33–42. PMID: 14528569

3. Shea, J. A., Micco, E., Dean, L. T., McMurphy, S., Schwartz, J. S., & Armstrong, K. (2008). Development of a revised Health Care System Distrust scale. *J Gen Intern Med, 23*(6), 727–732. PMID: 2517896

4. Rose, A., Peters, N., Shea, J. A., & Armstrong, K. (2004). Development and testing of the health care system distrust scale. *J Gen Intern Med, 19*(1), 57–63. PMID: 1494688

5. Bailey, D. B., Bann, C., Bishop, M. S., Guarda, S., Barnum, L., & Roche, M. (2012). Can a decision aid enable informed decisions in neonatal nursery recruitment for a fragile X newborn screening study? *Genetics in Medicine*, Advance online publication. doi:10.1038/gim.2012.1135

6. Skinner, D., Choudhury, S., Sideris, J., Guarda, S., Buansi, A., Roche, M., et al. (2011). Parents' decisions to screen newborns for FMR1 gene expansions in a pilot research project. *Pediatrics, 127*(6), e1455–e1463. PMID: 3103273

7. O'Connor, A. M. (1995). Validation of a decisional conflict scale. *Med Decis Making, 15*(1), 25–30.

8. Cella, D., Hughes, C., Peterman, A., Chang, C.-H., Peshkin, B. N., Schwartz, M. D., et al. (2002). A brief assessment of concerns associated with genetic testing for cancer: The Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychology, 21*(6), 564-572.

E. Development and evaluation of the decision aid

Project 3 employs a multi-method approach to develop a comprehensive decision aid (DA) to help parents decide if they want to 1) participate in the study; 2) receive genetic information about their newborn or child that would be presented to the NGS-NBS control group; and 3) receive other genetic information about their newborn or child that would be presented to the experimental group. We are using expert review, semi-structured interviews, and two different experiments to help us develop a DA for parents that supports informed decision-making.

1. Decision aid overview

We are developing three DAs for use in the study. Each DA focuses on key decisions that parents will need to make to obtain genetic information about their child or newborn.

a) **Participation in the study:** The first DA will help parents decide whether or not they want to participate in the study. This DA will be a paper-based brochure so that it can be easily distributed in recruitment clinics. The brochure will provide parents with information about the study, an overview of NGS-NBS, and a list of reasons for or against participating in the study. The brochure covers information about what parents would have to do to participate in the study and describes information they might receive.

   Prior experience with decision aids for participation in genomic research. We used a DA similar to the one we are developing for NC NEXUS in a previous study of parents deciding to have their newborn screened for fragile X syndrome (Bailey, et al., 2013). The fragile X DA described complicated concepts such as carrier status, chances that a result would be

positive, and chances of false negative or positive findings. In addition it provided pros and cons for obtaining fragile X screening and an opportunity for values clarification. We tested the fragile X DA in a simulation study (Bailey, Lewis, et al., 2013) and an implementation study (Bailey, Bann, et al., 2013). In the simulation study, parents' gained knowledge about fragile X, thought the DA was easy to understand and found the information to be helpful for decision making. Sixty-one percent of parents in this simulation study said that after reading the DA they would choose to participate in a study that screened their child for fragile X if they were presented with that opportunity. The implementation study tested whether the DA was better than a traditional study recruitment brochure for supporting informed decision making about study participation. Seven-hundred and sixteen parents received the traditional recruitment brochure over a 7-month period, and 607 families received the DA over a 6-month period. Families found the DA more helpful than the traditional recruitment brochure, particularly African American families. Seventy-two percent of mothers who read the traditional brochure agreed to participate in the screening study, compared with 50% of those who read the DA. These findings suggest to us that the DA approach is effective at supporting informed decision making about study participation. We are using a similar approach and organization in developing the recruitment portion of the DA for the NC NEXUS study.

b) **Deciding to have NGS-NBS for a child or newborn:** The second step in parental decision-making will be supported by an electronic DA delivered via the Internet. This DA will be accessible in-person via tablets, or via any computer with access to the Internet. In this part of the DA parents will learn more detailed information about how genes work, NGS-NBS,

and reasons for or against obtaining NGS-NBS genetic information. At this stage, they would be consenting to have NGS-NBS done for their child or newborn. The final organization and wording are still in development and will be informed by the parent interviews and the studies described below.

c) **Deciding whether or not to receive additional genetic information for a child or newborn.** The third step of the DA will also be electronic and will support decision making for parents randomized to the experimental group. These parents will be asked to decide whether or not to receive additional genetic information about their child or newborn, and the DA will support decision making about the kinds of other genetic information they may want to receive about their newborn or child. The content of the DA to be presented at this stage is still in development. The interview and conjoint studies described below will help us determine the content organization and the types of information parents need to help support a decision at this stage.

2. Methodological approach to decision aid development

Our comprehensive and multi-method approach for developing the DA consists of expert review and consultation, semi-structured interviews with parents, and two experimental studies using different designs. We are following best practices in DA development (Elwyn, et al., 2006), health communication, health literacy and plain language (McCaffery, et al., 2013), as well as social and behavioral science theory (Glanz, Rimer & Viswanath, 2008) to develop a DA that supports parent decision making throughout multiple stages of participation. We will also use principles from user-centered design in our creative approach to programming the electronic DA that ensures the information presented is understandable, accessible, and helpful

to parent decision making (Gulliksen, et al., 2003). Below we discuss each of the methods underlying the DA development.

a) **Expert consultation and review**: In March 2014, we convened a multi-disciplinary panel of experts to consult on DA development and Project 3 methods. These experts provided input on the design and implementation of all Project 3 aims. Based on their experience in genetics, genetic counseling, newborn screening, and development of interventions to support decision making, they have provided input on the approach to categorizing genomic findings, the types of questions we should probe with parents, the study design and measures for Aim 3, and the organization for the content for the DA at each step.

Once the DA is developed, we will obtain expert review by the International Patient Decision Aid Standards (IPDAS) quality standards rating group. This organization independently evaluates the quality of a DA on multiple dimensions and the quality expectations shown in ***Table 1***. We are also using these requirements as a framework for ensuring the DA developed for NC NEXUS is being systematically developed with quality standards in mind. This checklist is based on an international consensus conference (Elwyn, O'Conner, Stacey, et al., 2006).

Table 1: IPDAS rating domains and quality expectations.

IPDASi Domain	Domain Description / Expectations
1) Information	Assesses the format of the DA informational content. Eight items scored. • Describes the health condition/problem, decision to be made and the options available. • Presents positive and negative features of each option using equal detail in a format that allows fair comparison.
2) Test	*Only applicable if the DA considers an investigation or screening procedure. Nine items scored.* • *Includes what the test is designed to measure, information about true and false positive/negative result, and next steps typically taken.* • *Explains chances that the disease is detected with and without the use of the test, and consequences of detecting the condition or disease that would never have caused problems if screening had not been done (lead time bias).*
3) Probabilities	Assesses the way in which probabilistic information is provided. Eight items scored. • Provides precise and balanced information about the outcome probabilities associated with the (multiple) options and states the levels of uncertainty. • Presents information in a way that facilitates understanding and accounts for individual differences in processing complex information.
4) Values	Assesses whether the DA facilitates the expression and clarification of user' values and attitudes regarding the options available. Four items scored. • Provides information about the physical, psychological and social effect of each option (through personal stories or in the main narrative). • Engage users in the decision making process by asking them which positive and negative features of the options matter most to them.
5) Guidance	Assesses whether the DA provides structured guidance towards making a decision. Two items scored. • Provides a step-by-step way to making a decision and tools to use with a practitioner when making a decision.
6) Development	Assesses whether the DA was designed using a systematic development process. Six items scored. • Systematic development process includes a needs assessment, expert review and field-testing with patients and health professionals.
7) Evidence	Assesses the quality of the scientific evidence used to develop the DA. Five items scored. • Provide citations to the studies selected, describes how research evidence was synthesized, and justifies the quality of the research evidence used. • Displays a production or publication date and provides information about the proposed update policy.
8) Disclosure	Assesses transparency regarding the funding used for development and the authors involved (including credentials or qualifications). Two items scored.
9) Plain Language	Assesses whether the DA reports readability levels. One item scored.
10) Evaluation	Assesses whether the DA (after evaluation) helped users to make an informed choice and improved their knowledge about the features of the options. Two items scored.

b) **Semi-structured interviews with parents**: We will conduct semi-structured interviews with parents during the summer of 2014 to understand their concerns, test DA content, and

obtain input on DA organization and function. Obtaining parental input on the DA design is critical to ensuring the final DA meets parent needs.

- Forty couples of child-bearing age who are either pregnant, recent parents, or have had genetic testing done for their child will participate in interviews that will last about 1.5 hours. The interview will present DA content to gauge their reaction, determine understanding of the content, probe important factors affecting decisions to obtain genetic information about one's child, explore concerns parents may have in making decisions related to NGS-NBS and other genetic information, and examine how partners would resolve situations in which one parent wants to have genetic sequencing for their child or newborn and the other parent does not.
- Analysis of qualitative data generated from these interviews will follow Framework Analysis (Ritchie & Spencer, 1994), a systematic method for coding, analyzing and interpreting qualitative data. Using this approach will help us understand parent concerns and proactively address those in the DA. It will also provide relevant content for the DA. For example, in our fragile X DA study, responses from parents formed the basis for the "reasons for or against" section of the DA.

c) **Experimental conjoint survey**: "Conjoint" is a word derived from the phrase 'considered jointly.' This approach capitalizes on experimental design to simultaneously test multiple attributes that might be important in decision-making (Marshall et al., 2010).

- In many complex decision-making contexts there is usually not a single important consideration that defines a decision. We will vary important attributes of a child's genetic information to better understand which attributes are important drivers of

parent decision making. Conjoint surveys are also referred to as discrete choice methods or stated preference methods. They are commonly used to understand complex decision-making. This method also has been used to understand how people weigh attributes important for predictive genetic testing (Huang, Huston, & Perri, 2014). This approach will allow us to learn what parents value when deciding what kind of genetic information they want about their child, particularly information to be presented to the experimental group.

- In July 2014 we will begin cognitive testing of the survey with a group of 10 parents to ensure it is understandable and provides valid responses. The survey content was derived from several sources including a systematic review of issues related to parental decision making related to newborn screening (Sweeny, et al., 2014; Whitehead 2010), input from the expert panel for the project, and the review by the NC NEXUS steering committee. ***Table 2*** outlines an overview of the attributes that will be studied as part of the conjoint survey. These attributes and levels will be systematically compared across our sample of parents via random assignment to a series of decision-making scenarios.
- The conjoint survey will be fielded in August 2014, over a two-week period, with an online sample of 1200 parents of childbearing age (18-44 years) that is equally stratified by race (White/Black) and gender (male/female). Analysis using Sawtooth software will allow us to understand which configuration of attributes are most important for decision making and the relative weight of attributes. This information

will allow us to tailor the DA content to address priorities that parents themselves have identified as important. Analysis will begin in September 2014.

Table 2: Attributes and levels examined in the conjoint study.

Likelihood of Outcome	
10%	10 out of 100 (10%) of children develop symptoms related to the condition
50%	50 out of 100 (50%) of children develop symptoms related to the condition
75%	75 out of 100 (75%) of children develop symptoms related to the condition
90%	90 out of 100 (90%) of children develop symptoms related to the condition

Age of Onset	
Less than one year	Signs and symptoms start between birth and 12 months
1-5 years old	Signs and symptoms start between age 1 and 5 years
6-12 years old	Signs and symptoms start between age 6 and 12 years
13-18 years old	Signs and symptoms start between age 13 and 18 years

Rate that the Condition May Get Worse	
Stable	Once signs and symptoms appear, the health condition does not get worse.
Slow	Once signs and symptoms begin, the health condition gets worse slowly over time. It may be 15 years or more before the condition reaches its maximum severity of mental and/or physical disabilities.
Moderate	Once signs and symptoms begin, the condition gets worse at a moderate pace over time. It may be 5 to 15 years before the condition reaches its maximum severity of mental and/or physical disabilities.
Rapid	Once signs and symptoms begin, the condition gets worse rapidly over time. It may be 5 years or less before the condition reaches its maximum severity of mental and/or physical disabilities.

Options to Improve Day-to-Day Functioning	
None	There are no options that can slow the rate that the condition may get worse or improve the quality of life.
Improves Quality of Life	Options can help reduce symptoms of the health condition, such as pain, discomfort, or stress. These options can also help a child's physical and mental development.
Slows the Rate that the Condition may get Worse	Options can delay the onset and/or slow the rate that the condition may get worse. This could potentially double the number of years it takes for the condition to reach its most severe mental and/or physical disabilities.

Slows the Rate that the Condition may get Worse and Improves Quality of Life	Options can help reduce symptoms of the health condition, help a child's physical and mental development, and delay the onset and/or slow the rate that the condition may get worse. This could double the number of years for the condition to reach its most severe mental and/or physical disabilities.

Severity of Physical Disabilities	
None	No physical disabilities are associated with the condition.
Mild to Moderate	The child experiences lasting physical changes as a result of the disease. The level of disability could range from very little difficulty to moderate difficulty functioning independently.
Severe	The child experiences lasting and severe physical consequences. These disabilities would make it almost impossible for the child to function independently and could drastically threaten a child's overall health.

Severity of Mental Disabilities	
None	No mental disabilities are associated with the health condition.
Mild to Moderate	The child experiences lasting learning, social, and/or emotional disabilities. These could make it somewhat to very difficult for the child to learn information, interact with other people, or control emotions.
Severe	The child experiences lasting and severe learning, social, and/or emotional disabilities. These would make it extremely difficult for the child to learn information, interact with other people, or control emotions.

Risk of a Shortened Lifespan	
Low	This health condition is rarely fatal and rarely decreases a child's lifespan.
High	This health condition is fatal and will likely decrease a child's lifespan.

d) **Experimental Simulation Study**: In the spring of 2015, we will test a version of the DA in an online simulation experiment with parents of childbearing age, before we use the DA in the Aim 3 longitudinal RCT. We will evaluate its utility using an ethnically diverse sample of 100 expectant couples randomly selected on the basis of race/ethnicity by an online survey

panel. Mothers and fathers will independently work through the decision aid, ultimately coming to a hypothetical decision about study participation and return of results.

- The simulation study will be conducted with three ethnic groups (White, Black, and Hispanic). Each parent will first complete two measures assessing trust or mistrust in the medical system and health literacy, as we hypothesize that both constructs will be associated with willingness to participate and desired return of results.

  Health Care System Distrust Scale—Revised (Rose, et al., 2004; Shea et al., 2008). This rating scale contains 9 items measuring two factors of health care distrust: technical competence and value congruence. It has demonstrated reliability and validity.

  Test of Functional Health Literacy in Adults—Short Form (Baker, et al, 1999; Parker, et al., 1995). This brief measure of health literacy includes 4 numeracy items and a timed reading comprehension test in which every 5th to 7th word in a passage is omitted. Respondents select a word to fit into the blank spaces from 4 multiple-choice options. Health literacy scores range from 0 to 36, categorized as adequate (23–36), marginal (17–22), and inadequate (0– 16). This test demonstrates high correlations with other well-validated literacy measures (Baker, et al., 1999).

- Each parent will then work through an online version of the decision aid and complete three measures:

  Knowledge about the project and possible return of results. Knowledge assessment is widely recognized as a central component of decision aid evaluation, especially in the context of consent processes (Mullen, et al., 2006). We will create a 10- to 15-item true-false test to assess recall and understanding of information received. We developed a similar scale that worked well in our fragile

X newborn screening study (Bailey, et al., 2013) and will develop a new test about this specific study and the potential return of results.

Decision Conflict Scale (O'Conner, et al., 1995). The DCS is a 16-item scale measuring decision uncertainty, factors contributing to uncertainty, and perceived effective decision-making. Since its original validation in 1995, the scale has been widely used in studies of decision aids in many different health care contexts and has confirmed reliability, utility, and validity of the scale (de Achaval, et al., 2012; Katapodi, et al., 2011; Knapp, et al., 2009; Knops, et al., 2012) and have also demonstrated its usefulness in assessing decision conflict in dyads (LeBlanc, et al., 2009; Legare, et al, 2012; Lorenzo, et al., 2012) important because of our focus on couples.

Decision aid quality. Perceptions of decision aid quality are important for formative feedback and for interpreting findings. With our fragile X decision aid, we found that greater perceived quality was associated with greater trust in the information, and women who gave high quality ratings and those who trusted the information more were more likely to agree to screening and reported greater decisional confidence. In the present study we will use the same measure we developed for the fragile X project (Bailey, et al., 2013), a survey containing 31 statements rated on a 5-point scale from Strongly Agree to Strongly Disagree, assessing reactions to multiple dimensions of the decision aid (e.g., I like the way this brochure looks; I trust the information).

- After administering those measures, we will assess five primary outcomes:

Decision to participate. Each parent will make an independent hypothetical decision as to whether he or she would choose to allow his or her child to participate in a NGS-NBS study, a binary yes/no choice.

Desired return of results. The parents who would agree to allow their child to participate will choose whether they would like to know only medically actionable results (necessarily returned for all families) or whether they would like to know results that might not be medically actionable.

Couple agreement. From these independent ratings we will classify couple agreement in two ways: agreement on study participation and agreement on desired return of results.

Reasons for decision. Open-ended options will ask reasons for the choices they made; reasons will be coded and categorized following approaches we have used in previous studies (Bailey, et al., 2013).

Decisional confidence. Each parent will complete a single-item rating of decisional confidence ranging from 0 (not at all) to 10 (completely) (Frosh, et al., 2011). This study showed the scale was effective in assessing effects of two methods to facilitate shared decision making for men considering prostate testing.

3. References

1. Bailey, D. B., Lewis, M. A., Harris, S. L., Grant, T., Bann, C., Bishop, E., Roche, M., Guarda, S., Barnum, L., Powell, C., & Therrell, B. L. Design and evaluation of a decision aid for inviting parents to participate in a fragile X newborn screening pilot study. *Journal of Genetic Counseling, 22*(1), 108–117. (2013).

2. Bailey, D. B., Bann, C. M., Bishop, E., Guarda, S., Barnum, L., & Roche, M. Can a decision aid enable informed decisions in neonatal nursery recruitment for a fragile X newborn screening study? *Genetics in Medicine, 15*(4), 299–306. (2013).

3. Baker, D. W., Williams, M. V., Parker, R. M., Gazmararian, J. A. & Nurss, J. Development of a brief test to measure functional health literacy. Patient Educ. Couns. 38, 33–42, doi:10.1016/S0738-3991(98)00116-5 (1999).

4. de Achaval, S., Fraenkel, L., Volk, R. J., Cox, V. & Suarez-Almazor, M. E. Impact of educational and patient decision aids on decisional conflict associated with total knee arthroplasty. Arthritis Care & Research64, 229-237, doi:10.1002/acr.20646 (2012).

5. Elwyn, G., O'Connor, A., Stacey, D., Volk, R., Edwards, A.,….on behalf of the International Patient Decision Aids Standards (IPDAS) Collaboration. Developing a quality criteria framework for patient decision aids: Online international Delphi consensus process. BMJ, 333(7565); 417. (2006).

6. Frosch, D. L., Kaplan, R. M. & Felitti, V. The evaluation of two methods to facilitate shared decision making for men considering the prostate-specific antigen test. J. Gen. Intern. Med. 16, 391–398 (2001).

7. Glanz, K., Rimer, B.K., & Viswanath, K. Health behavior and health education: Theory, research, and practice. San Francisco: Jossey-Bass.

8. Gulliksen, J., Goransson, B., Boivie, I., Blomkvist, S., Persson, J., & Cajander, A. Key principles in user-centered systems design. Behaviour and Information Technology, 22(6), 397-409. (2003).

9. Huang, M., Huston, S.A., & Perri, M. Consumer preferences for the predictive genetic test for Alzheimer disease. Journal of Genetic Counseling, 23, 172-178. (2014).

10. Katapodi, M. C., Munro, M. L., Pierce, P. F. & Williams, R. A. Psychometric Testing of the Decisional Conflict Scale: Genetic Testing Hereditary Breast and Ovarian Cancer. Nurs. Res. 60, 368-377 310.1097/NNR.1090b1013e3182337dad (2011).

11. Knapp, C. et al. An evaluation of two decision-making scales for children with life-limiting illnesses. Palliative Medicine 23, 518-525, doi:10.1177/0269216309104892 (2009).

12. Knops, A. M. et al. Interpreting Patient Decisional Conflict Scores: Behavior and Emotions in Decisions about Treatment. Med. Decis. Making, doi:10.1177/0272989x12453500 (2012).

13. LeBlanc, A., Kenny, D. A., O'Connor, A. M. & Légaré, F. Decisional Conflict in Patients and Their Physicians: A Dyadic Approach to Shared Decision Making. Med. Decis. Making 29, 61-68, doi:10.1177/0272989x08327067 (2009).

14. Légaré, F. et al. Some but not all dyadic measures in shared decision making research have satisfactory psychometric properties. J. Clin. Epidemiol. 65, 1310-1320.e1313, doi:10.1016/j.jclinepi.2012.06.019 (2012).

15. Lorenzo, A. J. et al. Analysis of Decisional Conflict Among Parents Who Consent to Hypospadias Repair: Single Institution Prospective Study of 100 Couples. The Journal of urology 188, 571-575 (2012).

16. Marshall D, Bridges JFP, Hauber AB, et al. Conjoint analysis applications in health–how are studies being designed and reported? An update on current practice in the published literature between 2005 and 2008. Patient;3:249-56. (2010).

17. McCaffery, K.J., Homes-Rover, M., Smith, S.K., Rover, D., Nutbeam, D., et al. Addressing health literacy in patient decision aids. BMC Medical Informatics & Decision Making, 13(Suppl 2):S10. 2013.

18. Mullen, P. D. et al. Measures used in studies of informed decision making about cancer screening: a systematic review. Ann. Behav. Med. 32, 188–201, doi:10.1207/s15324796abm3203_4 (2006).

19. O'Connor, A. M. Validation of a decisional conflict scale. Med. Decis. Making 15, 25–30 (1995).

20. Parker, R. M., Baker, D. W., Williams, M. V. & Nurss, J. R. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. J. Gen. Intern. Med. 10, 537–541 (1995).

21. Ritchie, J., & Spencer, L. (1994). Qualitative data analysis for applied policy research. In A. Bryman & R. Burgess (Eds.), *Analysing qualitative data* (pp. 173-194). London: Routledge.

22. Rose, A., Peters, N., Shea, J. A. & Armstrong, K. Development and testing of the health care system distrust scale. J. Gen. Intern. Med. 19, 57–63 (2004).

23. Shea, J. A. et al. Development of a revised Health Care System Distrust scale. J. Gen. Intern. Med. 23, 727–732, doi:10.1007/s11606-008-0575-3 (2008).

24. Sweeny, K, Ghane, A., Legg, A.M., Huynh, H.P., Andrews, S.E. Predictors of genetic testing decisions: A systematic review and critique of the literature. Journal of Genetic Counseling. 23, 263-288. (2014).

25. Whitehead, N. S., Brown, D. S., & Layton, C. M. (2010, March). *Developing a conjoint analysis survey of parental attitudes regarding voluntary newborn screening*. RTI Press Publication No. MR-0014-1003.