2016 Progress Report

IDE G150258

NCNEXUS (North Carolina Newborn Exome Sequencing for Universal Screening)

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1 FDA FORM 3514

The use of this form is optional. If you choose not to use the form, ensure that the relevant information is contained in the cover letter:

- *Statement that this is an original IDE submission*
- *Device name and intended use*
- *Sponsor's contact information*
  - *Name, address, telephone number, fax number, email address*
- *Manufacturer information*
  - *Name, address, contact person, telephone number, fax*

Link to the form:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf

Commented [l1]: Amanda, do we need to use this?

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3 GENERAL INFORMATION

Please state your:

1) IDE number : G150258
2) Device name and indication(s) for use: NCNEXUS (North Carolina Newborn Exome Sequencing for Universal Screening)
3) Sponsor's name address, phone numbers, and fax
   Cynthia M. Powell, MD
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   Director, Medical Genetics Residency Program
   Division of Pediatric Genetics and Metabolism
   Department of Pediatrics
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   919-966-4202
4) Sponsor's email address: powellcm@med.unc.edu
5) Contact person: Cynthia M. Powell

Commented [I3]: Should this be me or you instead of Cindy?

Commented [WA4R3]: The contact person can be you or Cindy, a second contact is very useful in the event that the FDA needs to reach someone quickly if Cindy is out of town. If you decide to add yourself as the contact person, include your contact info in the same format as Cindy's above.

4 STUDY PROGRESS

4.1 Brief Summary of the Study Progress

Recruitment began in June, 2016, after we received FDA and UNC IRB approval to begin. We estimated that we would need to approach parents of 48 children per month for enrollment over 20 to 21 months to yield a sample of parents of 400 children completing the study, estimating 64% enrollment in the study. We are currently approaching approximately parents of 35 children per month, and our enrollment rate is currently 66% (see next section). At the current rate, we expect that we will have approximately parents of 266 children complete the study by the end of the award period (June 30, 2018). We are exploring ways to increase recruitment.

4.2 Number of Investigators/Investigational Sites

UNC-CH
Cynthia M. Powell, MD (contact PI)
Jonathan S. Berg, MD, PhD (co-PI)
Bradford Powell, MD, PhD
Myra Roche
Karen Weck, MD
Kirk Wilhelmsen, MD, PhD

RTI
Don Bailey, PhD
Megan Lewis, PhD

4.3 Number of Subject Enrolled

Table 1 summarize the status of enrollment as of the time of this report. Currently, 66% of families (i.e., mothers participating independently or couples including a mother and a father) approached for enrollment are successfully enrolled in Phase 1 of the project (57% in the diagnosed cohort and 76% in the well-child cohort). Enrollment in Phase 1 involves completing a baseline ("Time 1") questionnaire and completing the online decision aid to learn about NGS-NBS. We do not yet have enough data to reliably estimate how many of these families will elect to have their child undergo sequencing.

Table 1: *Status of family enrollment*

	Diagnosed	Well-child	Total
Approached	86	90	176
Enrolled in Phase 1	49	68	117
Completed Time 1 Questionnaire	31	29	60
Completed Online Decision Aid	27	21	48

Completed Visit 1	12	7	19
Sample Obtained	12	4	16
Results Returned	0	0	0

As summarized in *Table 1*, 48 families have completed the online decision aid to learn about sequencing for their child; each "family" is either a mother participating on her own or a couple that includes a mother and a father. Of these, six have decided not to have sequencing and who therefore have not been scheduled for a study visit. They are sent a follow-up survey about their decision; 75% of families have completed those. , Nineteen families have completed a study visit to speak with a counselor about sequencing and make a final decision about whether or not they will elect to have their child sequenced ("**Visit 1**"). Of these families, 19 have elected to have their child sequenced and 0 have decided against sequencing. An additional two families have scheduled their Visit 1. Samples have been obtained for 12 children in the diagnosed cohort and 4 in the well-child cohort (in which we must wait until the child is born before collecting a sample).

4.4 Number of Devices Shipped

N/A

4.5 Brief Summary of the Results

The NC NEXUS study is made up of a number of interrelated projects. To fulfill one aim of the study, we developed a decision aid designed to help parents make informed decisions about participating in the NC NEXUS randomized controlled trial (Lewis, Paquin et al, 2016); that is, this is the online decision aid that parents complete in Phase 1 of the randomized controlled trial. The goal of the trial is to understand parents' decisions about participating in the NEXUS study and having genomic sequencing for their child, as well as the choices parents make about return of results. Recruitment for the randomized controlled trial is underway and no results from that part of the project are yet available. However, we do have results from the formative research conducted as part of the decision aid development process. Insights learned from this research helped shape the content and design of the NC Nexus Decision Aid.

Early in the process, we conducted formative couples interviews (Fitzgerald et al., 2016). For these, we recruited 33 couples who were married or in a committed relationship. The interviews were semi-structured and conducted in-person with both members of the couple. We set out to examine how couples communicate with each other and make decisions about genomic screening results for their child. From the couples interviews, we learned that parents wanted to collaborate in their decision making. By and large, they looked to one another for support and to arrive at a joint understanding of the choice options. As a result, we treated couple-status as a tailoring variable in the decision aid. In effect, we developed two alternative

versions of the decision aid. One designed for single parents to complete on their own, and one for couples to complete together. We also asked parents to share reasons they would or would not choose to learn their child's sequencing results, as well as the kinds of information they would be interested in learning. These discussions revealed potential benefits and concerns that were especially important to parents, and we used these as narrative anchors and examples in the educational portions of the decision aid.

We also conducted an online, discrete choice experiment with over 1200 parents of young children ages 5 or younger (Lewis, Stine et al., 2016). Discrete choice experiments are quantitative methods for eliciting preferences and to systematically understand choices. We specifically focused on identifying which characteristics of genetic health conditions are important to parents' preferences, and what factors might drive decisions to receive different kinds of sequencing results. Parents' preferred learning results about genetic disorders with more severe manifestations (e.g., earlier age of onset, more severe disability, shorter lifespan, etc.), even though this knowledge was associated with increased distress. We found that participants' preferences for sequencing results related to genetic conditions differed as a function of the condition's medical actionability and age of onset. As a result, we organized the decision aid around different results categories defined along those dimensions (e.g., childhood onset actionable), in effect building out separate decision modules for each.

4.6 Summary of Anticipated and Unanticipated Adverse Effects / Deviations from the Investigational Plan

On Wednesday, June 8, 2016, the project 3 staff were contacted by email by our first recruited participant who was having trouble accessing the Decision Aid web site. On Thursday, June 9, the message was forwarded to Megan Lewis (RTI) and Dylan Young (RENCI) (both members of our research team) so that they could determine the source of the problem. The email included not only the link that was not functioning but it also contained the participant's name and email address. This email message was forwarded to the technical staff at RTI who are not listed as personnel on our IRB application. This error was noticed very quickly and everyone was instructed to delete the email messages from their accounts. We have re-stated, to the relevant staff, of the need to use the participant ID number as the identifier when communicating with other project members. Email messages will be created that have the relevant, non-PHI information and original emails from participants will not be forwarded.

References

Fitzgerald, T. M., Lewis, M. A., Moultrie, R. R., Zulkiewicz, B. A., Rini, C., Roche, M., & Bailey, D. B. (2016, February). *Couple dynamics in decisions about newborn screening via whole exome sequencing*. Poster presented at 2016 APHL Newborn Screening and Genetic Testing Symposium, St. Louis, MO.

Lewis, M. A., Paquin, R. S., Roche, M., Furberg, R. D., Rini, C., Berg, J. S., Powell, C., & Bailey, D. B. (2016). Supporting parental decisions about genomic sequencing for newborn screening: The NC NEXUS decision aid. *Pediatrics, 137*(Supplement 1), S16–S23. doi:http://dx.doi.org/10.1542/peds.2015-3731

Lewis, M. A., Stine, A., Paquin, R. S., Mansfield, C., Wood, D., Rini, C., Roche, M. I., Powell, C. M., Berg, J. S., & Bailey, D. B., Jr. (2016). *Parental preferences toward genomic sequencing for non-medically actionable conditions in children: a discrete choice experiment.* Manuscript submitted for publication.

5 RISK ANALYSIS

N/A

6 OTHER CHANGES

IRB-approved changes to study protocol:

1. We expanded our recruitment criteria to include couples who receive their OB care elsewhere but who have had consultations with the UNC prenatal clinic and/or who deliver outside of UNC Hospitals.

2. We are obtaining signed consent via an iPAD so signed forms can be stored in REDCap.

3. If only one parent is present at the time of recruitment and agrees to join, we will gather contact information for both members of the couple and send them separate links to the questionnaire. The partner will receive an email explaining the study and can provide consent by completing the T1 Questionnaire. This consent process is explained on the first page of the T1Q.

Pending modifications:

1. In the well-child cohort, the recruiter will offer access to the first questionnaire (T1Q) in either paper form or electronic links to those who agree to join so they can begin or complete this during their visit. Couples who wish could also view the decision guide on a tablet during the visit. We will continue to email the links to both the T1Q and the decision guide to those who prefer to do these at home.

2. In cases when one parent is unable to attend the study visit, we will use Skype or telephone for the counseling and consent. The counseling and consent will be done in the CTRC and will be conducted by the clinical geneticist and/or genetic counselor. The partner who is unable to attend will sign the consent form during the encounter and return it to the study office.

3. In cases where both parents cannot return for an in-person visit we may return results by telephone or Skype. The reports will be emailed securely before the call so parent can review it prior to our discussion.

7 FUTURE PLANS

We are working on a supplemental application to perform parental sequencing and to change the library capture kit to XT2.

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