UNC SCHOOL OF MEDICINE
DEPARTMENT OF GENETICS

December 19, 2017

Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

IDE ANNUAL REPORT Annual Progress Report 002

Dear FDA Review Team:

Pursuant to 21 CFR 312, I am submitting an Annual Report for IDE# G150258.

- This is an original IDE submission.
- The device under review for this trial is the following: NC NEXUS (North Carolina Newborn Exome Sequencing for Universal Screening) research study and its intended use is to investigate the potential of genome scale next generation sequencing to augment and extend current newborn screening in a diverse pediatric population
- The sponsor of this IDE is Cynthia Powell, MD and her contact information is the following:
  Cynthia M. Powell, MD
  Professor of Pediatrics and Genetics
  Director, Medical Genetics Residency Program
  Division of Pediatric Genetics and Metabolism
  Department of Pediatrics
  University of North Carolina Medical Center
  Chapel Hill, NC 27599-7487
  919-966-4202 (phone)
  919 966-3025 (fax)
- The "device" is not manufactured, thus there is no manufacturer information.

Thank you in advance for the FDA's review of this annual report.

The e-copy is an exact duplicate of the paper copy

Sincerely,

Cynthia M. Powell

Cynthia M. Powell, MD

2017 Progress Report

IDE G150258

NCNEXUS (North Carolina Newborn Exome Sequencing for Universal Screening)
G150258

Cynthia M. Powell, MD
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Division of Pediatric Genetics and Metabolism
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University of North Carolina Medical Center
Chapel Hill, NC 27599-7487

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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

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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
   Professor of Pediatrics and Genetics
   Director, Medical Genetics Residency Program
   Division of Pediatric Genetics and Metabolism
   Department of Pediatrics
   University of North Carolina Medical Center
   Chapel Hill, NC 27599-7487
   919-966-4202
4) Sponsor's email address: powellcm@med.unc.edu
5) Contact person: Laura V. Milko, PhD
   NC NEXUS Program Director
   Department of Genetics University of North Carolina at Chapel Hill
   Chapel Hill, NC 27599-7264
   919-843-2878
   laura_milko@med.unc.edu

4 STUDY PROGRESS

(Data from the beginning of the study should be reported, unless otherwise indicated)

4.1 Brief Summary of the Study Progress

4.2 Number of Investigators/Investigational Sites

4.3 Number of Subjects Enrolled

4.4 Number of Devices Shipped N/A

4.5 Brief Summary of the Results

4.6 Deviations from the Investigational Plan

PROGRESS REPORT

4.1 Brief summary of study progress in relation to investigational plan.

Since recruitment began in June, 2016, we have approached 438 parents of children in both the "Healthy" and "Diagnosed" cohorts and enrolled 290 parents in Phase 1 of the study. In October we enrolled our first Spanish speaking family and currently have four Spanish speaking participants enrolled. Our enrollment rate is currently 66% (refer to Section 4.3) and, at the current rate, we expect that we will have parents of approximately 314 children complete the study by the end of the award period (June 30, 2018). We are currently exploring ways to increase recruitment.

The NC NEXUS binning committee has assessed a total of 814 gene-disease pairs, enriched for those with pediatric presentation of disease and suspected medical actionability (refer to Section 4.5). The final version of our gene panel has been applied to the sequencing analysis pipeline and a description of our process and list of categorized gene-disease pairs is in preparation for publication.

Sample sequencing and molecular analysis are underway. Currently, 63 samples have undergone next-generation sequencing and, of these, 39 (62%) have undergone molecular analysis of the gene panel list. An additional 24 samples have completed the sample preparation stage and have been transferred to the UNC High Throughput Sequencing Facility (HTSF) for sequencing on the Illumina HiSeq 2500. Molecular analysis has been completed for 13 patients in the health cohort, 10 patients in the metabolic cohort and 15 patients in the hearing loss cohort.

We have prioritized the dissemination of results this year with articles in peer-reviewed journals and presentations (oral and poster) at annual professional meetings, invited platform sessions, and professional symposia. Principal Investigator, Jonathan Berg, led the publication of the NSIGHT consortium marker

paper [1] and several groups of NC NEXUS researchers, in addition have published or submitted their results for publication [2-4]. The Project 3: Ethical, Legal, and Social Implications (ELSI) group has submitted a manuscript that is currently in press describing the results of their discrete choice experiment about parental preferences toward genomic sequencing for non-medically actionable conditions in children [2]. The NC NEXUS Steering Committee has submitted a description of the study protocol to the journal *Trials* [3], and postdoctoral researcher, Lonna Mollison, and Jonathan Berg published an editorial outlining a proposal for age-based genetic screening [4]. Project members also presented results at the: 2017 American College of Medical Genetics and Genomics (ACMG) annual meeting in Phoenix, AZ [5,6,7]; invited pre-conference symposium at the 2017 National Society of Genetic Counseling in Columbus, OH [8], 2017 annual meeting of the Southeastern Regional Genetics Group, Asheville, NC [9], symposium conducted at the 2017 annual meeting of the Society for Behavioral Medicine, San Diego, CA [10], and at the 2017 Curating the Clinical Genome meeting in Washington, D.C [11].

4.2 List 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 subjects 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 (50% in the diagnosed cohort and 75% 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. Approximately half (49%) of families who complete the decision aid complete Visit 1 and consent to NGS-NBS (71% in the diagnosed cohort and 39% in the well-child cohort).

Table 1: *Status of family enrollment*

	Diagnosed	Well-child	Total
Approached	153	285	438
Enrolled in Phase 1	77	213	290
Completed Time 1 Questionnaire	55	134	189
Completed Online Decision Aid	51	98	149
Completed Visit 1	37	38	75
Sample Obtained	36	32	68
Results Returned	7	1	8

As summarized in *Table 1*, 149 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, 20 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; 95% of families have completed those. Seventeen families in the well-child cohort delivered their babies before the visit was scheduled and so were withdrawn from the study. Five families declined a visit and were sent the follow-up questionnaire; 3 completed it. Fourteen families have not responded to calls to schedule a visit. Seventy-four 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, 72 have elected to have their child sequenced and 2 have decided against sequencing. An additional two families have scheduled their Visit 1. Samples have been obtained for 36 children in the diagnosed cohort and 32 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 results.

The Next-Generation Sequencing Newborn Screen (NGS-NBS) category of childhood-onset, highly actionable conditions will be returned to all participants in the study [1, 5, 6, 11]. To determine which gene-disease pairs should be included in the NGS-NBS, we used an age-based metric that examines five criteria: severity and likelihood of disease, efficacy and acceptability of treatment, and knowledge base. We assessed a total of 814 gene-disease pairs, enriched for those with pediatric presentation of disease and suspected actionability. The first version of our gene panel is in preparation for publication and has been applied to the sequencing analysis pipeline. It includes the following results: 1) Four hundred sixty-one childhood-onset medically actionable gene-disease pairs were determined to be suitable for the NGS-NBS; 2) Three hundred fifty-three gene-

disease pairs did not meet the threshhold for inclusion in the NGS-NBS. Of those, parents randomized to the "decision" group will be asked to decide if they wish to learn additional findings from the following categories: 25 adult-onset medically actionable gene-disease pairs and/or 239 childhood-onset non-medically actionable genes-disease pairs associated with disorders with no known effective interventions; 3) Nineteen gene-disease pairs associated with adult-onset, non-medically actionable disorders (e.g. Huntington disease) will not be returned to anyone.

Sample sequencing and molecular analysis are underway. Currently, 63 samples have undergone next-generation sequencing, and 39 have undergone molecular analysis of the NGS-NBS list. Additionally, for participants in the diagnosed cohort, we evaluated variants in genes on a diagnostic list related to the participant's phenotype. In total, the analyzed samples include 14 participants in the well-child cohort and 25 participants in the diagnosed cohort. We found that analysis of the NGS-NBS list did not identify any reportable pathogenic or likely pathogenic variants in 13/14 participants in the well-child cohort; the results of the 14th participant are still pending. In the diagnosed cohort, analysis of the NGS-NBS list identified reportable pathogenic or likely pathogenic variants in 7/10 participants with a clinical diagnosis of a metabolic disorder. Clinical confirmation of one sample is still pending, which is expected to increase the yield to 8/10. These same variants were identified by the inborn errors of metabolism diagnostic list. In addition, diagnostic analysis in the remaining 2 participants that were "negative" on the NGS-NBS analysis identified genetic variants potentially consistent with their diagnoses, highlighting the role of prior probability in guiding the clinical interpretation of genetic variants. Analysis of the NGS-NBS list identified reportable likely pathogenic or pathogenic variants in 4/15 participants with a clinical diagnosis of hearing loss; these same variants were identified by the hearing loss diagnostic list [5], while 6/15 hearing loss patients were "negative" on both NGS-NBS and diagnostic analysis, which is not entirely unexpected given that approximately half of cases of congenital hearing loss are currently thought to be due to non-genetic factors. The remaining 5 hearing loss cases gave somewhat more complicated results. In one case, the NGS-NBS screen was considered "positive" due to a suspected homozygous variant that was then determined to be heterozygous by Sanger sequencing in the CLIA lab. In two other cases, the NGS-NBS screen was negative, but similar to the metabolic cases an "uncertain" type of result was identified by the diagnostic analysis. Interestingly, for two other participants in the hearing loss cohort, analysis of the NGS-NBS list identified reportable pathogenic variants in different genes associated with clinically-actionable conditions unrelated to the participants' hearing loss. In both cases, the NGS-NBS screen and indication-based analysis did not identify the cause of the participant's hearing loss.

4.6 Deviations from the Investigational Plan:

1. In January of 2017 a mother enrolled as a single parent but the child's father also came to the consent visit. Both parents provided consent, a sample was obtained, and the family was reclassified as a couple. After that visit, the father failed to participate further by answering the T2 questionnaire. We allowed the family to remain classified as a couple even though data will be missing from the father.

2. Due to procedural changes in University accounts services that occurred suddenly and without notice, a significant lag time occurred between when we requested funds for gift cards and when those funds were approved. Our study protocol was to send gift cards soon after participants completed the questionnaire. However, for a few months, many participants did not receive these until several weeks later. Currently, all participants have received their gift cards.

3. In April of 2017, two letters to two participants were switched and placed into each other's envelopes, resulting in each participant receiving a letter that included the name and address of the other participant. After being alerted by one of the participants, we spoke to both participants and neither expressed concern about this error. The research assistant was informed of the error and now double checks that the names on the letters ad the envelopes match. This was reported to the IRB on 4/1/17 , who did not require any further action.

4. A family who declined sequencing changed their minds and are in the queue for scheduling. The father had already completed the questionnaire that follows this decision. We will request that he complete it again following the consent visit.

References:

Peer-reviewed publications:

1. Berg JS, Agrawal PB, Bailey, DB Jr., Beggs AH, Brenner SE, Brower AM, Butler I, Cakici J, Ceyhan-Birsoy O, Chan K, Chen F, Currier RJ, Dukhovny D, Green RC, Harris-Wai J, Holm IA, Iglesias B, Joseph G, Kingsmore SF, Koenig BA, Kwok P-Y, Lantos J, Leeder JS, Lewis MA, McGuire AL, Milko LV, Parad RB, Pereira S, Petrikin J, Powell BC, Powell CM, Puck JM, Rehm HL, Risch N, Roche M, Shieh JT, Watson MS, Willig L, Yu TW, Urv T, Wise AL. Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT). Pediatr. 2017; 139:2016-2252. [Epub ahead of print] PMID: 28096516. doi:10.1542/peds.2016-2252.

2. Lewis, MA, Stine, A, Paquin, RS, Mansfield, C, Wood, D, Rini, C, Roche MI, Powell, CM, Berg, JS & Bailey, DB, Jr. (in press). Parental preferences toward genomic sequencing for non-medically actionable conditions in children: A discrete choice experiment. GenetMed.

3. Milko LV, Rini C, Lewis MA, Butterfield RM, Paquin RS, Powell BC, Roche MI, Souris KJ, Bailey, DB Jr., Berg JS, Powell CM. Evaluating parents' decisions about next generation sequencing for their child in the NC NEXUS (North Carolina Newborn Exome Sequencing for Universal Screening) study: a randomized controlled trial protocol. Manuscript submitted for publication

4. Mollison, L., Berg, JS. Genetic Screening: birthright or earned with age? Expert Rev Mol Diagn. 2017;17: 735-738. [Epub ahead of print] PMID: 28641021. doi: 10.1080/14737159.2017.1346473.

Presentations: Oral and Poster

5. Crowley, S. B., DeCristo, D. M., Wallace, K. E., O'Daniel, J. M., Powell, C. M., & Berg, J. S. (2017, March). *Listening to the Data: an Expert-Curated Gene List to Screen for Hearing Loss in Newborns*. Poster presented at 2017 ACMG Annual Clinical Genetics Meeting, Phoenix, AZ

6. DeCristo D, Crowley S, Mollison L, Wallace K, Metcalf F, O'Daniel D, Powell C, Berg J. (2017, March). *Better Together: Integrating Genetic Analysis with Biochemical Newborn Screening.* Poster presented at the 2017 ACMG Annual Clinical Genetics Meeting, Phoenix, AR.

7. Mollison, L., Crowley, S., DeCristo, D., Wallace, K., O'Daniel, J., Powell, C., Berg, J. (March 2017). *Explicitly Defining Age of Onset and Age of Intervention to Develop Age-Based Targeted Gene Panels for Screening Newborns and Children.* Poster presented at 2017 ACMG Conference, Phoenix, AZ.

8. O'Daniel, JM and Fayer, S. (September 13, 2017*) Newborn Sequencing In Genomic Medicine and Public Health (NSIGHT): Perspectives from BabySeq and NCGENES.* Invited preconference session presented at the National Society of Genetic Counseling Annual Education Conference, Columbus, OH.

9. Powell, CM, Roche, MI, Rini C, Lewis, MA, Paquin, RS, Bailey, DB, Margolis, M, Butterfield, R, Milko, L, Powell, B, Berg JS: "The NC NEXUS Project of Newborn Exome Sequencing", platform presentation, 35th Annual Meeting of the Southeastern Regional Genetics Group, Asheville, NC July 21, 2017.

10. Rini, C. (2017, March) Health Decision Making SIG Presents: Ethical Considerations for Using Online Strategies for Recruiting and Informing Participants in Genomic Sequencing Studies .Symposium conducted at the meeting of the Society for Behavioral Medicine, San Diego, CA.

11. Wallace, K. E., Crowley, S. B., DeCristo, D. M., Foreman, A. K. M. , Milko, L. V., Mollison, L., O'Daniel, J. M., Powell, B. C., Powell, C. M., & Berg, J. S. (2017, June). *Defining the pediatric actionability of genetic conditions for utility in newborn screening*. Poster presented at 2017 Curating the Clinical Genome, Washington, D.C.

5 RISK ANALYSIS

A thorough risk analysis and risk mitigation strategies are critical for the FDA's decision to allow a study to continue. Update the risk analysis from your initial application with any relevant changes. Include a summary of any new adverse information (since the last progress report) that may affect the risk analysis. This includes preclinical data, animal studies, foreign data, clinical studies, etc. For more details on what to include in the risk analysis, please see the DTMI original IDE template.

Also, please attach the reprints of any articles published from data collection from this study.

Present a new risk analysis, if necessary, based on any new information and study progress.

N/A

6 OTHER CHANGES

Summary of any changes in the manufacturing process and quality control, including changes that have not been submitted as a supplemental application.

Summary of all changes in the investigational plan that were not required to be submitted in a supplemental application.

1. In January, we received IRB approval to consent one parent by phone at the time of the consent visit with the other parent, and we also received IRB approval for the well-child cohort recruiter to offer paper copies of the first questionnaire instead of a link to the electronic version. We also began mailing a paper copy of the questionnaire with a stamped return envelope to parents who had not completed it within two weeks of their enrollment.

2. In June, the clinic recruiter began to call families who had not responded to reminders about completing the questionnaire.

3. In July we began sending exit letters to parents who had not been able to be scheduled for a consent visit requesting that they complete the second questionnaire. An exit letter informs the parents that we have been trying to reach them unsuccessfully and asks them to contact us if they would like to continue in the study.

7 FUTURE PLANS

Progress towards product approval, including a projected date for PMA or 510(k) submission.

If there are any plans to change the investigation, e.g., to expand the study size or indications, to discontinue portions of the investigation or to change manufacturing practices, please state in this section. (NOTE: Actual proposals for these changes should be made in a separate supplemental application since they may require prior approval).

N/A