NC NEXUS teleconference with the FDA - Q140207 Presubmission (1-U19-HD077632-01)
May 2, 2014, 11am -12pm

Attendees: Sunita Shukla (Scientific Reviewer, FDA CDRH/OIR/DCTD), Cynthia Powell (PI, UNC), Jonathan Berg (PI, UNC), Laura Milko (Project Manager, UNC), Courtney Lias (Division Director, FDA CDRH/OIR), Denise Johnson-Lyles (Toxicology Branch Chief, FDA CDRH/OIR/DCTD), David Litwack (Personalized Medicine, FDA CDRH/OIR), Zivana Tezak (Personalized Medicine, FDA), Kelliey Kelm (Scientific Reviewer, FDA CDRH/OIR/DCTD), Tiina Urv (NIH/NICHD), Anastasia Wise (NIH/NHGRI), Jonathan Gitlin (NIH/NHGRI)

Agenda:

- Sign-in and introduction (11:00 – 11:05 am)
- Presentation by Dr. Jonathan Berg (11:05 – 11:25 am)
- Clarification of study protocol for FDA feedback (11:25 – 11:50 am)
- Summary of FDA's feedback and action items (11:50am – 12pm)

Minutes:

- Clarification of study protocol for FDA feedback

  - **FDA Question: How and what results would be returned to the healthy newborn cohort?**

    NC NEXUS Answer: A significant effort of this project is to identify a core set of genes (referred to as the NGS-NBS panel) for return to all study participants. We expect that very few (1-3%) of the healthy group would receive positive results from the NGS-NBS. All healthy newborns will receive standard of care newborn screening (NBS) results from the State of North Carolina as well. Some parents of children in the healthy newborn cohort (and affected cohort) will also be randomized to an "experimental" arm in which parents will make decisions about additional information (from three categories: childhood-onset non-medically actionable, adult-onset medically actionable, and carrier status) that they would want to learn.

  - **FDA Question: Is NC NEXUS only sequencing a subset of genes?**

    NC NEXUS Answer: No. The process would best be described as "exome sequencing with focused informatics analysis." We will sequence exomes based on commercially available reagents (we are currently using Agilent SureSelect Human All Exon version 5, but will explore other options based on coverage, cost, and ease of use) and perform focused informatics analysis on a subset panel (NGS-NBS) that all study participants will receive. For the diagnosed cohort, we will also return indication-related diagnostic results; this is the only case where we would return VUS.

  - **FDA Question: A.) What access will the study participants have to genetic counseling? B.) What information will study participants receive to help them to make informed decisions about receiving results and placing them in the medical record and will this information be separated out for childhood vs. adult onset diseases?**

NC NEXUS Answer: A.) Parents of all participants will receive standard of care genetic counseling by board certified (American Board of Medical Genetics (ABMG) or American Board of Genetic Counseling (ABGC)) genetic counselors and medical geneticists during decision-making and return of results. One of the PI's (Dr. Powell) in addition to being a board-certified clinical geneticist is also a board certified genetic counselor. Additional genetic counselors are part of our study team and will participate in return of results sessions with study participants. This discussion will include the risks, benefits, and limitations of exome sequencing with focused informatics analysis. For example, parents will be told about the Genetic Information Nondiscrimination Act (GINA) and the types of insurance (eg. life and long-term care) that are not covered. Parents will be given information about the likelihood of any given type of results and the follow-up plan that would be put in place if such a result was present. Finally, parents will be educated about the limitations of the process, including the nuances of what a "negative" result would mean.

B.) A "decision aid" will be provided to parents that clearly outlines the pros and cons of choosing to learn different types of results, and there will be ample opportunities for questions. A similar decision aid was developed and used previously by Dr. Powell in the context of a Fragile X study. The NC NEXUS decision aid will be shown to focus groups to confirm clarity and ease of understanding before being given to the parents of NC NEXUS participants. The decision aid and counseling sessions will be divided up by the categories of choices that may be available. First, the choice to participate in the NC NEXUS study and receive the NGS-NBS panel, and second, the additional three categories of information that parents may choose to learn if they are randomized into the experimental arm of the study (as described above). Information will be provided in the decision aid that describes the legal consequences of placing results in the electronic medical record. Since all results will be subject to confirmation, clinical interpretation, and reporting by ABMG-certified molecular geneticists in the hospital's CLIA lab, such results could be made part of the official medical record. We do not yet have a determination from the Institutional Review Board as to whether parents will be required to sign an additional consent in order to place positive results in the medical record, or whether the consent to participate in the study will be sufficient.

- **FDA Question: Will parents of participants who choose only to get pathogenic results be able to get more information (e.g. a file of the full dataset of variants)?**

  NC NEXUS Answer: No. We do not have any plans to release complete variant datasets to parents. If parents disagree with the method of analysis they can elect not to participate in the study.

- **FDA Question: Will people understand that they may be getting back unanticipated results?**

NC NEXUS Answer: Yes, this will be clearly stated in the consent documents that parents of subjects will be given prior to enrollment in any part of the study. If they do not wish to receive any unanticipated results they will have the option of not participating in the study. In the group randomized to decide whether or not to learn additional results (beyond those related to their child's condition and/or those that are included in the NGS-NBS panel results) the decision aid tool that is being developed as part of the research study will enable them to learn more about these options and decide what, if any, additional results they wish to learn.

- **FDA Question: How will negative results be reported?**

  NC NEXUS Answer: We propose to return negative results to parents in the form of a "research report" that will summarize the test process, including coverage metrics, genes tested, aggregate information about the number of variants, and a disclaimer about the limitations of whole exome sequencing. The research report would not be placed in the medical record.

- **FDA Question: Is Cohort 2 already diagnosed with a medical condition?**

  NC NEXUS Answer: Yes, Cohort 2 will have been clinically diagnosed with a genetic disorder (eg. via biochemical assay or other clinical work-up). Parents will already be aware that their child is affected with a medical condition, even though the genetic etiology (specific gene mutations) may not be known. One important aspect of the NC NEXUS project is evaluating the performance of NGS-NBS in predicting and diagnosing the causal genetic factor underlying rare disorders as well as disorders with known genetic and environmentally-induced components (e.g. hearing loss).

- **FDA Question: How does Cohort 3 factor into the ELSI research about decision-making by parents?**

  NC NEXUS Answer: The healthy newborn cohort provides information about parental decision-making in a "real world" setting, as would be expected for pregnant couples who are at no increased risk for genetic disorders. The ELSI component of the NC NEXUS project is comprised of a series of questionnaires and surveys as part of a longitudinal study to look at hopes, expectations, and anxieties associated with making choices about the return of NGS-NBS results.

- **FDA Question: How are threshold cut-offs and actionability scores determined?**

  NC Nexus Answer: The actionability score will be based on an algorithm, which incorporates factors such as severity and knowledge of the disease and intervention. The actionability score along with age of onset will help to determine which bin the disease will be categorized in to. Along with informatics, an expert panel will also help set the threshold and decision making process. For example, Duchene's Muscular Dystrophy would be

categorized in the childhood onset non-medically actionable bin, however treatment can delay the onset of disease, thus this may be categorized in the NGS-NBS bin.

- Summary of FDA's feedback and action items

NC NEXUS provided an informative ~~satisfactory level of information to~~ presentation to help clarify some of the issues in the "Q140207 Memo to Sponsor – FINAL" that arose from the presubmission questions below. Further internal discussions within the FDA will be required before answers can be provided. NC NEXUS will send draft meeting minutes within two weeks of the teleconference. The FDA will request any additional information that is necessary, and conduct internal meetings to provide updated ~~answers~~ responses to the NC NEXUS presubmission questions. The FDA will respond in the context of the presentation and make specific suggestions about what, if any, aspect(s) of the proposed study might trigger a determination of significant risk. The FDA will also provide specific feedback about any changes, if necessary, that would ameliorate the need for an IDE and provide helpful information for future studies. NC NEXUS and the FDA will maintain open communication via email and teleconference(s), as needed, in a timely fashion. ~~The FDA expects to be able to get back to NC NEXUS fairly soon.~~ Some additional discussion points regarding the study and associated risk are noted below:

1. **What level of risk is involved in the proposed study?**
   - More specific details on the information/reports that will be returned to parents and placed in the medical file.
   - Examples of diagnostic methods besides Sanger sequencing that may be needed to confirm certain types of mutations, such as large deletions, that may be detected by WES were provided to the FDA. NC Nexus stated that the~~These~~ confirmatory tests will also be done in a CLIA-approved laboratory.

2. **Will our proposed study require an IDE?**
   a. Which results will be returned to parents?
   b. Which results will be placed in patient's electronic file and associated ethical implications regarding the children?
   - Other confirmatory methods besides Sanger
   - Examples of diseases in the distinct binning categories ~~(~~FDA requested a list of all diseases, if available, that will be included in the study).

3. **What modifications of the protocol are recommended by the FDA?**
   - More information on the proposed study, including ethical implications regarding how data generated in the study will be used is needed for the FDA to understand the risks of the study and the mitigations that could be put in place to address these risks. The addition of mitigations is an example of protocol modifications. ~~Modifications based on feedback about reporting negative results~~

4. **During the course of the study, what changes to the protocol or IRB would require additional review by the FDA**?

a. Changes to study (e.g. software) reviewed by both the PI and the IRB