DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

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RE: Q140207/S001 and Q140207/S002
DEVICE: NC NEXUS
DATED: Q140207/S001: 7/02/14
Q140207/S002: 7/14/14
RECEIVED: Q140207/S001: 7/02/14
Q140207/S002: 7/14/14

DATE: August 27, 2014

Dear Dr. Milko,

Thank you for submitting the follow-up requested information for our review. The pre-submissions noted above seek FDA input regarding your clinical protocol.

This is an informal communication that represents the best judgment of the Office of In Vitro Diagnostics and Radiological Health staff and consultants who reviewed the protocols. It does

not constitute an advisory opinion and does not bind or otherwise obligate or commit the agency to the views expressed, as per 21 CFR 10.85(k). We have provided an evaluation of your proposed studies below.

Proposed Intended Use/Indications for Use (excerpted from the submission):

The NC NEXUS study will evaluate the use of exome sequencing as a potential means to augment newborn screening (NBS). The main technical outcome will be to examine the sensitivity and specificity of this technology in detecting conditions that are currently screened for in newborns. Another technical outcome will be to examine the capacity of exome sequencing to detect other conditions that would be beneficial to identify at an early age in children but for which there is currently no available diagnostic method.

Aim of Study (excerpted from the submission):

Carry out Whole Exome Sequencing (WES) from various target populations (see below) using DNA collected from buccal swabs (using Oragen Discover (OGR-250) sample collection kits. Key aim of study is how to divide the broad range of genomic variants into categories that will allow parents to make well-informed decisions about a) whether or not to pursue exome sequencing for their newborn; and b) what types of genomic information they are interested in learning. The study proposes a "binning" method of the results based on clinical validity and clinical actionability (see below) and the development of a standardized procedure for categorizing genomic loci into the binned categories (below). To assess the impact of non-medically actionable WES findings, parents will be randomized into 2 groups: control group (will receive all medically actionable results) and experimental group (will be asked to decide what, if any, of the non-medically actionable information they choose to learn about their child. A decision aid (see below) will be used to help parents make an informed decision about study participation and parental preference for return of results.

Binning Categories (excerpted from the submission):

- **Bin 1**: Findings that provide medically actionable incidental results, including conditions screened for in the current NBS context as well as other medical conditions that are not currently included in current NBS protocols. This category will represent the core results from NGS-NBS.
- **Bin 2**: Findings related to a childhood health condition with no specific medical intervention (non- medically actionable). (These findings, along with Bin R, will be returned to parents randomized to have the opportunity to learn them, if they request them after making an informed decision to do so)
  - Bin 2a: Findings selected by as likely to cause people very little distress
  - Bin 2b: Findings selected as likely to cause some people moderate distress
  - Bin 2c: Findings selected as likely to cause most people a considerable amount of stress
- **Bin R**: Findings about reproductive risks, likely to cause little to moderate stress
- **Bin X**: Findings related to untreatable adult-onset health conditions (not to be returned to parents)
- **Bin 3**: Findings that have no clear association with any genetic disorder (not to be returned to parents)

Decision Aid: You state that your study team has extensive experience in health communication, consent, health literacy, NBS and informed consent. Drawing on this experience the study team will develop and test an electronic Decision Aid tool that will explain the complexities of WES to parents and their options for return of results. The Decision Aid tool will be utilized by parents during the consent process and by those participating in a longitudinal study to investigate the acceptability of Next-Generation Sequencing (NGS)/WES for their children. 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. 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. Parents can opt to learn some, all, or none of the additional categories of information. More information regarding the target populations is shown in the table below:

Target Populations (excerpted from submission):

NC NEXUS Study Population and Recruitment Estimates				
	Cohorts	Estimated numbers of subjects available for recruitment		
		Current Patients (Age 0-5 years)	New cases* or births/yr	Total
Disorders currently detected through NBS	PKU	33	5-7	60
	MCADD	28	5-7	60
	CF confirmed	65	12-22	155
	CF with false positive NBS	N/A	130	500
	CRMS	10	1-3	20
	Hearing Loss	1800	200	2600
Disorders that currently cannot be detected by NBS	Other patients in Genetics & Metabolism Clinic, Neurology Clinic	20	5	50
	PCD	20	5	45
	Well Child	N/A	3500	5080

Disease cohorts are ascertained using current standard newborn screening methods

* New cases are identified in the newborn period and enrolled by 6 months of age

Confirmation of Results (excerpted from the submission):

Many of the variants, including rare variants, will be confirmed using Sanger sequencing. However, it is possible that WES may identify mutations for which clinical testing is currently available but for which Sanger sequencing is not ideal. If Sanger is not optimal, gold standard molecular diagnostics tests will be performed (for example, the Qiagen Pyromark MD (pyrosequencing) and Affymetrix GeneChip system (expression, copy number variation, etc) will be available). Clinical reports regarding any positive findings will be generated by the CLIA-based lab after confirmation through Sanger sequencing, which will then be provided to parents and placed in the electronic medical record. Research reports, describing the aggregate exome

sequencing results such as total number of variants identified in different categories (but no specific variant details), will be provided to all parents, but will NOT be placed in the electronic medical record.

Bioinformatics: You propose to develop and evaluate various bioinformatics approaches for the utilization in NGS-NBS. You also state that you will determine the types of variants that can reliably be detected using your current pipeline, and you will explore novel methods that promise to detect types of variants not readily detectable by current approaches to WES. Specifically, you propose to explore thresholds for selecting variants to be further analyzed in an effort to optimize the performance characteristics. In order to enhance the sensitivity of your approach, you will compare methods for calling single nucleotide variants and explore methods of detecting certain types of variants to determine those types that can or cannot be reliably detected. In order to enhance the specificity of your approach, you will investigate the application of a gene-specific mutational burden metric to help adjudicate and re-classify genetic variants (which may result in re-classification of bins for various incidental findings).

Revised Results: You state that over the course of time, association of more genes with diseases and the development of prevention or treatment will result in reassignment of loci and lead to changes in the interpretation of WES findings. When such reassignment occurs, parents will be re-contacted if the results they have received change during the period of the Project.

Specific questions for FDA:

UNC requests FDA feedback on the following questions:

1. *What level of risk is involved in the proposed study?*

- **FDA Response:** Based on the information provided, FDA has determined that your proposed clinical investigation is a Significant Risk device study and you will need to submit an IDE application for this investigation**.** This risk assessment is based on the following rationale:

  1) In your proposal (Q140207/S001), you have stated the following, "*The risk of parental anxiety due to return of unexpected incidental findings raises new and challenging human subjects issues. Further complicating the return of incidental findings is their heterogeneity with potential psychological and clinical impact on patients ranging from trivial to profound……How to handle the return of incidental findings is a central challenge to genomic medicine and will be particularly important in the use of WES and other forms of whole genome sequencing in children*." Thus, your study proposes to evaluate the risk associated with the return of incidental (investigational) findings (of varying degrees) to parents and the psychological impact this will have upon the parents and children over a given period of time. FDA agrees that this is an important study objective. In addition to the potential psychological risks, we also point out that there may also be physical and social risks to the children depending on what parents choose to do as a result of the research. The probability and magnitude of these risks cannot be quantified, especially in the cohort where children are not currently experiencing symptoms. Therefore, we cannot determine that these risks are non-significant.

As a mitigation for the risk, on page 155 you have stated that the binning strategy will "*allow for a systematic approach to parent education and informed consent as it relates to newborn screening…..Finally, the manner in which incidental findings are delivered (if parents so choose) will also be category-driven and risk-calibrated to protect them and their offspring from harm*." Although the decision aid tools will take the nature of the incidental findings into account, given the aim of your study, the risks of sharing all types of incidental findings cannot be fully anticipated. For example, parents may view children as "sick" or especially vulnerable as a result of the research findings, even if the incidental results have no known medical significance. Such unforeseen or unpredictable consequences for patients may warrant an ongoing relationship between the parents, researchers, and child advocates.

2) You state that: *Many of the variants, including rare variants, will be confirmed using Sanger sequencing. However, it is possible that WES may identify mutations for which clinical testing is currently available but for which Sanger sequencing is not ideal. If Sanger is not optimal, gold standard molecular diagnostics tests will be performed (for example, the Qiagen Pyromark MD (pyrosequencing) and Affymetrix GeneChip system (expression, copy number variation, etc) will be available).* We acknowledge that you state that investigational test results will be confirmed; however you also state that test results will be revised over time based on evolving bioinformatics approaches that you will develop. In such cases, this re-categorization of information will result in changes in the interpretation of WES findings, and will lead to re-contacting of parents to notify them of these changes. Since the bioinformatics approaches involved in potentially revising investigational results will be developed, modified, and evaluated throughout the course of the study, the probability and magnitude of the risk of re-analysis of results cannot be defined. Therefore, we cannot determine that such risk is non-significant.

3) We also point out that, as a result of this research, detailed information will be available in the child's medical record that may have long-term effects that are difficult to predict. The Agency is aware of circumstances where genetic information obtained in research has affected insurability, has been discoverable in legal proceedings or has otherwise been used against the research participant or a member of his/her family. We are particularly concerned because this information will be obtained about children who cannot consent or refuse for themselves. This risk is significant, and may not be mitigable.

2. Will our proposed study require an IDE?

- **FDA Response:** As outlined in our response to #1 above, the proposed study will require an IDE.

3. What modifications of the protocol are recommended by the FDA?

- **FDA Response:** We would like to emphasize that we believe you have proposed a study that may answer some important questions in the evolving field of NBS. FDA herein offers to work with you as your study evolves in order to suggest ways of mitigating potential risks and to expedite the IDE process. For example, review of informed consent forms is a part of the IDE process. Thus, it may be helpful to provide this information (as a supplement to this pre-submission) to us in advance of your IDE submission so that we can provide any suggested modifications at that time.

The following modifications are also recommended at this time:

1. Please provide details in your IDE submission or as a supplement to your pre-submission that outline the duration of follow-up of parents and children after parents are informed of research results. In addition, please provide information about who will be providing this follow-up, how often, and how this follow-up may help to mitigate any medical or social risks that may occur as a result of the research. Information on what actions will be taken to maintain contact with parents, and procedures for parents who wish to drop out of the study, should also be provided. In particular, it may be helpful to have the binning committee (or another body of experts) suggest additional precautions or safeguards for oversight before and after parents have been informed of the investigational findings.

*Please note that additional mitigations and safeguards may be recommended by FDA during the IDE process and/or as we continue to discuss your study proposal with you in any subsequent pre-submissions.

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

- **FDA Response:** Due to the evolving nature of the study components (such as binning categories, informatics changes, etc), FDA will provide further guidance regarding which modifications would result in a need for an IDE supplement prior to proceeding. We can discuss this in more detail in our upcoming teleconference on 8/28/14 from 1-2 PM ET.

Note that any revisions that you would like to submit in response to this letter (after the meeting) or new protocols for FDA feedback (called a pre-submission supplement) should be submitted as an eCopy[i] to the address below and should reference the pre-submission number above (Q140207) in the cover letter to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center – WO66-G609
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If you have any questions or comments regarding this review, please contact Sunita Shukla, at (301) 796-6406 or at sunita.shukla@fda.hhs.gov

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