Section 1 - Basic Information (Study 56875)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

North Carolina Newborn Exome Sequencing for Universal Screening

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	❍ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable NCT02826694

Section 2 - Study Population Characteristics (Study 56875)

2.1. Conditions or Focus of Study

- Metabolism, Inborn Errors
- Hearing Loss
- Hereditary Disease

2.2. Eligibility Criteria

Inclusion Criteria:

- Uncomplicated pregnancy and healthy newborn

Exclusion Criteria:

- Abnormalities such as major malformation or chromosomal disorder detected prenatally or significant complications during pregnancy or at the time of delivery.

2.3. Age Limits Min Age: N/A (No limit) Max Age: 5 Years

2.4. Inclusion of Women, Minorities, and Children

2.5. Recruitment and Retention Plan

2.6. Recruitment Status Completed

2.7. Study Timeline

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 56875	Domestic	

Inclusion Enrollment Report 56875

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s):

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	2	0	0	0	1	0	0	0	0	3
Asian	20	14	0	0	0	0	0	0	0	34
Native Hawaiian or Other Pacific Islander	1	0	0	0	0	0	0	0	0	1
Black or African American	41	42	0	3	3	0	0	0	0	89
White	149	129	0	18	26	0	0	0	0	322
More than One Race	5	11	0	7	1	0	0	0	0	24
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	218	196	0	28	31	0	0	0	0	473

Section 3 - Protection and Monitoring Plans (Study 56875)

3.1. Protection of Human Subjects

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site? ❍ Yes ❍ No ❍ N/A

If yes, describe the single IRB plan

3.3. Data and Safety Monitoring Plan

3.4. Will a Data and Safety Monitoring Board be appointed for this study? ❍ Yes ❍ No

3.5. Overall structure of the study team

Section 4 - Protocol Synopsis (Study 56875)

4.1. Brief Summary

The NC NEXUS research study is exploring the utility of next generation sequencing in newborn screening and parental decision making. The National Institutes of Health (NICHD and NHGRI) are co-funding this study under a single U-19.

4.2. Study Design

4.2.a. Narrative Study Description

The investigators will enroll and perform whole exome sequencing on two cohorts of patients. One cohort will consist of two hundred newborns with no known conditions whose parents will be recruited during the mother's pregnancy. The second cohort will include two hundred infants and children up to the age of five years with diagnosed conditions including conditions detected through standard newborn screening such as phenylketonuria and other inborn errors of metabolism, hearing loss and other rare conditions that may fit criteria for newborn screening in the future.

Parents will be introduced to the study by their clinician or a study recruiter. Those who agree to enroll in Phase I will review an online decision guide and be offered a study visit conducted by a genetic counselor to obtain informed consent for genomic sequencing of their child. Parents consenting to have their child's genome sequenced will be seen after the child's birth or at a convenient pre-arranged time and duplicate saliva samples will be collected from the children and one sample will be sent to the BioSpecimen Processing (BSP) Facility and to Dr. Jonathan Berg's laboratory for sequencing and the other sent to the Molecular Genetics Laboratory (MGL) for DNA extraction and storage until needed for clinical confirmation. Results will be returned for diagnostic (in the Diagnosed cohort) and medically actionable disorders of childhood (both cohorts). Two-thirds of parents who consent to sequencing will be randomly assigned to be eligible to request additional findings and use a supplement of the online decision aid. All results will be reported to parents by trained genetic professionals (genetic counselors and clinical geneticists)

4.2.b. Primary Purpose: Diagnostics

4.2.c. Interventions

Type	Name	Description
Genetic (including gene transfer, stem cell and recombinant DNA)	Well infant, whole exome sequencing	Whole exome sequencing will be performed in children with diagnosed conditions. Investigators will analyze results that are associated with their condition.
Genetic (including gene transfer, stem cell and recombinant DNA)	Diagnosed, whole exome sequencing	In addition to returning results of conditions associated with a child's phenotype, investigators will also analyze genes that are associated with conditions that have childhood onset and are medically actionable.

4.2.d. Study Phase: Other

N/A

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.2.e. Intervention Model: Parallel

4.2.f. Masking ❍ Yes ● No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation Randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	Parental decision making using decision aid.	average of 3-6 months.	Analysis of parents' decisions after they complete an on-line decision aid to see if they wish to participate in the study. Parent participants randomized to the decision group, after their child is sequenced, may decide what, if any, additional categories of conditions they wish to learn about. Options will be yes, no, or unsure.
Primary	Sensitivity of whole exome sequencing in detecting conditions by comparing results of sequencing to the appropriate genes associated with the child's underlying condition.	approximately 3-6 months after DNA sample obtained.	Investigators will analyze sequencing results in the diagnosed cohort to determine the ability of whole exome sequencing to detect pathogenic variants in genes related to phenotype.
Secondary	Participant characteristics and reactions to the study will be collected through surveys.	Baseline and 3 months after final return of results visit.	Surveys are administered at Time 1 (baseline), after parent participants decide to join phase I of the study, which involves agreeing to view the online decision aid about Next-Generation Sequencing Newborn Screening (NGS-NBS); at Time 2, after parent participants have viewed the decision aid and made a decision about accepting NGS-NBS for their child (yes/no/ need more information; note that the timing is variable, depending on when participants complete this task, but may range from hours to weeks); at Time 2a (for parent participants randomly assigned to learn/make decisions about additional information), after parent participants have made the decision to accept none, some, or all categories of additional information (note that the timing is variable depending on when parent participants complete this task, but occurs after return of NGS-NBS results); Time 3, which occurs 2 weeks after return of NGS-NBS results; and Time 4, which occurs 3 months after Time 3.

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 6 - Clinical Trial Milestone Plan (Study 56875)

6.1. Study Primary Completion Date	06/30/2019	Actual
6.2. Study Final Completion Date	06/30/2019	Actual
6.3. Enrollment and randomization		
Enrollment of the first subject	06/01/2016	Actual
25% of planned enrollment recruited by		
50% of planned enrollment recruited by		
75% of planned enrollment recruited by		
100% of planned enrollment recruited by		
6.4. Completion of primary endpoint data analyses		
6.5. Reporting of results in ClinicalTrials.gov		
6.6. Is this an applicable clinical trial under FDAAA?	❍ Yes ❍ No	