RESEARCH PROJECT COOPERATIVE AGREEMENT **Issue Date:** 09/03/2013
Department of Health and Human Services
National Institutes of Health
EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH & HUMAN DEVELOPMENT

Grant Number: 1U19HD077693-01

Principal Investigator(s):
Stephen F Kingsmore, MB

Project Title: Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns

RE: **Q140271**
DEVICE: **Illumina HiSeq 2000/2500, NextSeq 500**
DATED: **March 4, 2014**
RESPONSE: **April 28, 2014**
Further clarifying information for FDA presubmission teleconference, May 1, 2014

Children's Mercy HOSPITALS & CLINICS Kansas City

Who we are

- A CLIA/CAP-approved molecular genetics laboratory
  - Director: Dr. Carol Saunders PhD FACMG
  - Conventional molecular diagnostic testing for URD
  - NGS-based clinical testing for URD (TaGSCAN)
  - Audited by CAP in 2013 with no deficiencies
  - Also do research testing in that facility, with that staff, under those guidelines, with those devices (e.g. this study)

This study

- Comparative effectiveness of WGS and standard testing in URD in acutely ill neonates
- 2 arms: standard testing, standard testing + trio WGS
- N=500
- Randomization
- Cost and clinical outcomes; short and long term

Page 3: Clarification 1

While your protocol states that confirmation of results by Sanger sequencing will be performed in most cases, it does allow for disclosure of results to clinicians *prior to* Sanger sequencing in cases that involve "…identification of a life-threatening, treatable condition

- Confirmatory testing will be performed in all cases prior to return of written results.
- A verbal provisional result will be disclosed to the physician of record only in cases where testing identifies high-likelihood, acutely actionable, diagnostic variants for a life-threatening, treatable condition in an acutely ill neonate in whom the risk of a delay in reporting significantly exceeds the risk of disclosure prior to Sanger sequencing (i.e. may result in patient death or serious harm).

Definition: High Likelihood Disease Causing Variants

- Occur in an established genetic disease gene (e.g. as defined by ACMG's guidelines for testing URDs) AND
- The features of that disease fit those of the acute illness present in the patient AND
- Determined to be pathogenic or likely pathogenic as per ACMG draft guidelines for evidence supporting pathogenicity
- Form a diagnostic genotype

Process for determining whether verbal disclosure of a provisional result to the physician of record is warranted

- The Laboratory Director (Carol Saunders PhD FACMG) and her team review:
  - The quality and quantity of the genome sequence and read alignment information at that nucleotide position(s)
  - The support for pathogenicity
- In conjunction with MDs on the team (esp. Laurie Smith, MD, Ph.D., FACMG), review
  - The literature support for a diagnosis being acutely "actionable" (i.e. likely to result in a material change in acute management of that disease)
  - The likelihood of death or significant harm if no disclosure occurs until Sanger confirmation is completed

Process for verbal disclosure of a provisional result to the physician of record

- The Laboratory Director (Carol Saunders PhD FACMG):
  - Requests confirmatory Sanger sequencing
  - Informs the treating physician verbally of
    - The putative diagnosis
    - The support for that diagnosis
    - The timeline for confirmatory testing
    - The potential, significant, acute "action" that prompted provisional reporting (i.e. a material change in the acute management of that disease)
  - Places a standard note in that patients Medical Record as follows:

"Whole sequencing research was performed on peripheral blood DNA from this patient and his/her parents on DD/MM/YYYY under Children's Mercy Hospital IRB Protocol XXXX for diagnosis of an acute neonatal disease. Testing disclosed acutely actionable information that was disclosed verbally to the physician of record prior to confirmation of results. For further information, please contact the Study Principal Investigator Dr. Stephen Kingsmore (816-854-0882, sfkingsmore@cmh.edu)."

Page 3: Clarification 2

While your protocol states that confirmation of results by Sanger sequencing will be performed in most cases, it does allow for disclosure of results to clinicians *prior to* Sanger sequencing in cases that involve "…identification of a life-threatening, treatable condition [and] novel variants of uncertain clinical significance" (p13).

- No other results are disclosed to clinicians prior to Sanger sequencing
- VUS are not reported at all; we report only variants considered pathogenic

Page 3: Clarification 3

The protocol also appears to leave open the possibility that return of results without confirmation may occur in other, undefined situations.

- No results will be returned without confirmation in any other situation.

Page 3: Clarification 4

Finally, the protocol states that for negative study results a statement about the testing will be placed in patients' medical records. We are uncertain what kinds of results would be considered "negative" for this purpose.

- A negative case is one in which testing does not yield a diagnostic result.
- Upon completion of analysis of whole genome sequences of the familial trio, in the absence of a diagnostic genotype, a standard note will be placed in that patients Medical Record as follows:
  "Whole genome sequencing research was performed on peripheral blood DNA from this patient and his/her parents on DD/MM/YYYY under Children's Mercy Hospital IRB Protocol XXXX for diagnosis of an acute neonatal disease. Testing did not disclose the cause of this disease. For further information, please contact the Study Principal Investigator Dr. Stephen Kingsmore (816-854-0882, sfkingsmore@cmh.edu)."

Page 3: Clarification 5

Furthermore, we cannot make a determination that the blood collection does not pose added risk to study subjects. To make this determination, we will require information on volume when encountering conditions such as anemia.

1-3 ml of blood will be collected from neonates and parents at time of enrollment following the Children's Mercy Hospital Research Guidelines for blood draws.

Children's Mercy Hospital Guidelines for Blood Sampling Related to Research					
Body Wt (Kg)	**Body Wt (lbs)**	**Total blood volume (mL)**	**Maximum allowable volume (mL) in one blood draw (= 2.5% of total blood volume)**	**Total volume (clinical + research) maximum volume (mL) drawn in a 30-day period**	**Minimum Hgb required at time of blood draw if subject has respiratory/CV compromise**
1	2.2	100	2.5	5	9.0 -10.0
2	4.4	200	5	10	9.0-10.0
3	6.3	240	6	12	9.0-10.0
4	8.8	320	8	16	9.0-10.0
5	11	400	10	20	9.0-10.0
6	13.2	480	12	24	9.0-10.0
7	15.4	560	14	28	9.0-10.0
8	17.6	640	16	32	9.0-10.0
9	19.8	720	18	36	9.0-10.0
10	22	800	20	40	9.0-10.0
11-15	24-33	880-1200	22-30	44-60	9.0-10.0
16-20	35-44	1280-1600	32-40	64-80	9.0-10.0
21-25	46-55	1680-2000	42-50	64-100	9.0-10.0
26-30	57-66	2080-2400	52-60	104-120	9.0-10.0
31-35	68-77	2480-2800	62-70	124-140	9.0-10.0
36-40	79-88	2880-3200	72-80	144-160	9.0-10.0
41-45	90-99	3280-3600	82-90	164-180	9.0-10.0
46-50	101-110	3680-4000	92-100	184-200	9.0-10.0

Page 3: Clarification 6

encountering conditions such as anemia. Moreover, your protocol also provides for the possibility of collection of blood, urine, and tissue for future unspecified purposes, and it is unclear whether this would include invasive sampling outside of standard of care.

- Blood is collected at time of enrollment
- Collection of blood, urine, and tissue for future unspecified purposes will NOT include invasive sampling outside of standard of care.
- Blood or tissue retains from procedures performed as part of standard of care will be scavenged.

Do we require an IDE submission?

As such, your study appears to be significant risk, requiring the approval of an IDE submission unless you are able to provide further clarifying information or modifications to the protocol that allow for confirmation of all results with Sanger sequencing or an FDA cleared or approved test and, if necessary, allow for alternatives to any sample collection that is determined to pose a significant risk to subjects.

2) *What modifications/details in the protocol are recommended by the FDA prior to IDE submission if such submission is deemed necessary?*

FDA Response: The FDA does not have specific modifications to suggest.

- A verbal provisional result will be disclosed to the physician of record before Sanger sequencing only in cases where testing identifies high-likelihood, acutely actionable, diagnostic variants for a life-threatening, treatable condition in an acutely ill neonate in whom the risk of a delay in reporting significantly exceeds the risk of disclosure prior to Sanger sequencing (i.e. may result in patient death or serious harm).