Children's Mercy HOSPITALS & CLINICS
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Q140271: FDA/Children's Mercy Kansas City Teleconference

Meeting Minutes

Recorded by Nhu Bui
May 1, 2014
2:00pm-2:58pm EST

Present:

FDA
David Litwack, Ph.D, Personalized Medicine Staff
Sunita Shukla, Ph.D, Division of Chemistry and Toxicology Devices
Kellie Kelm, Ph.D, Division of Chemistry and Toxicology Devices
Yung Chan, Branch Chief, Division of Chemistry and Toxicology Devices
Denise Johnson-Lyles, Ph.D, Branch Chief, Division of Chemistry and Toxicology Devices
Aaron Schetter, Division of Molecular Genetics and Pathology

NIH/NHGRI
Tiina Urv, Ph.D, Program Director (U19)
Anastasia Wise, Ph.D, Project Scientist (U19)
Jonathan Gitlin, Ph.D, Science Policy Analyst

Center for Pediatric Genomic Medicine – Children's Mercy Hospital, Kansas City
Stephen Kingsmore, M.B., Ch.B., B.A.O., D.Sc., F.R.C.Path, Director
Carol Saunders, Ph.D, FACMG, Deputy Director and Laboratory Director
Laurel Willig, M.D., Assistant Medical Director and Project Lead on U19 Component 2
Josh Petrikin, M.D., Lead Neonatologist and Investigator on U19 Component 2

I. Introduction

Introduction of each attendee mentioned above.

II. Discussion

Stephen Kingsmore, Director of the Center for Pediatric Genomic Medicine at Children's Mercy Hospital, Kansas City, MO, confirmed the receipt of the Pre-IDE response letter from the FDA on April 28, 2014. This document was in response to the Pre-IDE submission packet sent by CMH to the FDA dated March 4, 2014. The documented dated April 28th was thoroughly reviewed by the CMH team involved in the NIH-sponsored U19 grant. Dr. Kingsmore and his team had provided a powerpoint document to the FDA immediately prior to the call to assist in providing clarifying information related to the questions and points that were mentioned in the letter.

The Center for Pediatric Genomic Medicine at Children's Mercy Hospital, Kansas City, is one of four grantees of an NIH U-19 opportunity entitled Genomic Sequencing and Newborn Screening Disorders. The title of our program is "Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns". Funding started September 3, 2013. The status of this program is that the study protocol is ready for submission to the local IRB for approval to conduct the study. In parallel we are seeking guidance from the FDA with regard to the need for an investigational device exemption (IDE) in order to undertake this study.

Hospital and Laboratory Background: Children's Mercy of Kansas City is the largest free-standing children's hospital between St. Louis, MO and Denver, CO. It has approximately half a million patient visits per year and has approximately 85% market share in the Kansas City metropolitan area. The Center for Pediatric Genomic Medicine at Children's Mercy Hospital, Kansas City, MO, is a CLIA/CAP-approved molecular genetics laboratory. Dr. Carol Saunders is the Laboratory Director and is in charge of ensuring CLIA/CAP accreditation and performance. The laboratory performs conventional molecular diagnostic testing for ultra rare diseases (URD), primarily serving the needs of physicians at the Children Mercy hospitals and clinics. It also offers a CLIA/CAP compliant LDT called TaGSCAN, which is a panel test for next generation sequencing of over 500 genetic disease associated genes. This test (TaGSCAN) has been available since January 2013. This is a regular billable test which physicians can order from both internal and external institutions. Our facility was audited by CAP in 2013 with no deficiencies. The audit included the Center for Pediatric Genomic Medicine, including next generation sequencing operations, TaGSCAN testing and associated documentation and proficiency testing. The next scheduled CAP inspection is in 2015. The Center also performs research testing in the same facility, with the same staff, under CLIA/CAP guidelines (as possible), with the same devices. The proposed U19 study is an example of such research.

Study design: This study has a simple design. It is a comparative effectiveness study of whole genome sequencing (WGS) and standard testing in URD in acutely ill neonates. It has 2 arms: standard testing with expanded newborn screening, and standard testing + expanded newborn screening + trio WGS of affected babies and parents. The site of this study is the CMH NICU (level 4) with approximately 76 beds and an approximate annual admission rate of 1000 patients. All patients enrolled are acutely ill and believed likely to have an ultra rare genetic disease as the cause of their acute illness. Each arm will enroll 500 patients and their parents. There is single blinded randomization of enrollees to these two arms. The study will collect data to allow determination of the comparative cost effectiveness and clinical outcomes in the two arms. Outcomes be both short term, such as 28-day diagnostic yield, and longer term, such as clinical effectiveness at one year.

Dr. Litwack asked, "How exactly do you define acutely ill?"

Dr. Stephen Kingsmore indicated that the study enrollment is only of infants in the CMH level-4 NICU or PICU, and enrollees must be receiving intensive care for an acute medical condition that lacks a molecular diagnosis. There is a high mortality rate in these children. These are typically unexpected admissions and there is extreme urgency in the need to make a diagnosis. Failure to make a timely diagnosis in these children is associated with a high likelihood of death. Genetic diseases are the leading cause of NICU deaths. Conventional testing using serial Sanger sequencing of individual candidate genes typically does not have a turnaround time that is useful in terms of guiding clinical management of these children. Conventional molecular diagnostic test results are typically returned after eight to twelve weeks, by which time the child has been discharged or has died. In addition, conventional molecular diagnostic testing has relatively low yield since the clinical features evident in an acutely ill newborn often differ from those of the full-blown genetic disease. Thus the target for single gene Sanger sequencing tests is either unclear or incorrect.

Dr. Litwack asked, "What percentage of patients who are admitted to the NICU die?"

Malformations and genetic disorders are the leading cause of infant mortality in the US[1,2]. One study in a university-affiliated children's hospital reported 51.0% infants deaths were from a malformation and/or genetic disorder[3]. 19.0% of deaths during a 5-year period in the PICU of a university-affiliated hospital were in patients with heritable disorders[4].

1. National Vital Statistics Reports: Infant Mortality Statistics from the 2010 Period Linked Birth/Infant Death Data Set. NVSR Volume 62, Number 8. 53 pp. (PHS) 2014-1120. http://www.cdc.gov/nchs/products/nvsr.htm#vol62
2. Steward & Hersh. J Ky Med Assoc. 1995 93:329;
3. Stevenson DA, Carey JC. Contribution of malformations and genetic disorders to mortality in a children's hospital. Am J Med Genet A. 2004 May 1;126A(4):393-7.
4. Cunniff C, Carmack JL, Kirby RS, Fiser DH. Contribution of heritable disorders to mortality in the pediatric intensive care unit. Pediatrics. 1995 May;95(5):678-81.

Dr. Kingsmore suggested that for the remainder of the call, he would provide clarifying information related to the points that were raised in the April 28, 2014 document from the FDA. Dr. Litwack concurred. These points were as follows:

Point raised on page 3 of document (clarification 1):
"...it does allow for disclosure of results to clinician *prior to* Sanger sequencing in cases that involve identification of a life-threatening, treatable condition..." First, confirmatory testing will be performed in <u>all</u> cases <u>prior</u> to return of **written** results. However, there is one, uncommon situation where a verbal provisional result is returned. In this, the provisional diagnostic result was disclosed to the physician of record <u>only</u> in cases where testing identifies <u>high-likelihood, acutely actionable, diagnostic variants</u> for a <u>life-threatening</u>, <u>treatable</u> condition in an <u>acutely ill neonate</u> 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. Details of this are as follows:

How does one define the High Likelihood Disease Causing Variants?

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

What is the process for determining whether verbal disclosure of a provisional result to the physician of record is warranted?

- The Laboratory Director (Carol Saunders, Ph.D., FACMG) and her team review:
  - The quality and quantity of the genome sequence and read alignment information at that nucleotide position(s)
  - The literature and database support for pathogenicity (as per the recent draft guidelines of the ACMG)
- In conjunction with MD's 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.

What is the process for verbal disclosure of a provisional result to the physician of record?

- The Laboratory Director (Carol Saunders, Ph.D., 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 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 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)."

Dr. Litwack asked, "What percentage of children qualify for return of a provisional diagnostic result prior to confirmation?"

Stephen Kingsmore shared that we have been running STATseq (50 hour whole genome sequencing) in our NICU under a prior research protocol that is outside of the proposed U19 study for about 2 years. We published a paper approximately 15 months ago with initial experience, and since have increased that experience to a total of ~35 families. There was only one case, among 35, that met these criteria and whose physician received a provisional verbal test result prior to confirmatory testing. This was a 2-month old baby with acute liver failure who was near to death. Dr. Josh Petrikin, the neonatologist caring for the baby, informed family on three different occasions that baby was likely to die imminently. Whole genome sequencing was ordered for baby after a period of attempted diagnosis with standard testing. WGS identified compound heterozygosity for two variants with high-likelihood for being causative of liver failure. The provisional diagnosis of hemophagocytic lymphohistiocytosis type 2 was reported to Dr. Josh Petrikin, and resulted in a change in management (initiation of intravenous corticosteroids and immunoglobulin). The provisional diagnosis was not on Dr. Petrikin's differential diagnosis list due to the incomplete presentation of this diagnosis in the newborn. In response to treatment, the baby's liver function recovered, and the newborn was subsequently discharged to home. Confirmatory testing was performed and confirmed the diagnosis.

Dr. Kelm asked, "Out of the 30 children, one result was helpful. What happened to the other 29 children?"

Stephen Kingsmore said that in 16 of 25 families, a molecular diagnosis was made. In all cases, the findings by whole genome sequencing were confirmed by Sanger sequencing. None were found to be false positives. Only in the one case was the result reported verbally prior to confirmatory testing. In seven families, the diagnosis resulted in a potential change in clinical management. In three families, a likely novel disease gene was identified. The latter were not reported and are under further study. In six families, no causative genotype was identified and no report was generated.

In response to a question by Dr. Kelm, Stephen Kingsmore indicated that there was one case of a verbal report prior to the result of the confirmatory test. In all cases, confirmatory testing was completed. In all cases, causative variant genotypes identified by whole genome sequencing were confirmed upon Sanger sequencing. We have not had a single case to date where we identified variants (diagnostic) that did not confirm upon Sanger sequencing.

A member of the FDA team indicated that "this is helpful information. This answers the question of having a false positive and risk the mismanagement of the baby."

Dr. Kingsmore agreed that this was an important point, which had been corroborated by experience in offering a CLIA/CAP-compliant Next Generation sequencing clinical test for 15 months. While this test (TaGSCAN) differs from whole genome sequencing, the devices used were the same. TaGSCAN has given our team

experience in the interpretation of Next Generation Sequencing based diagnostic test results for URD in over 300 patients.

Dr. Kelm requested additional information and the difference of experience with prior and current tests.

Dr. Kingsmore indicated that over a two-year period, he and his team developed a LDT test (TaGSCAN) and went through thorough validation, looking specifically at precision, sensitivity, and specificity measures. That analysis involved more than 300 samples and compared TaGSCAN both with array-based genotypes and standard Sanger sequencing clinical tests, and was able to calculate precision, sensitivity, and specificity and create documents for each of the component steps with detailed protocols. This information was placed in a repository and underwent CLIA/CAP inspection last year. There were no deficiencies. Since that time, we have built a second version of that test. We are in the final stages of completing validation of the second test version. Both of these are panel tests for ~500 genes. WGS is similar to these panel tests but has several significant differences. Many of the components of device for WGS are identical to those of the clinical TaGSCAN panel test, but the validation process is for the test as whole rather than individual components. Again, we are looking at precision, sensitivity, and specificity. There are a number of gold-standard benchmarks that we use for these comparisons, such as sample NA12878, which has been adopted by National Institutes (NIST) as a "gold standard" 2.8 billion genotype set. Overall, sensitivity for nucleotide variants when compared with NA12878 standard genotypes, is greater 98%, and specificity is 99.98% using current protocols and whole genome sequencing. These metrics are superior to those of our current clinical panel test (TaGSCAN). However, the panel test has been formally validated, while the whole genome sequencing has not yet and remains a research use only test. We do not have enough information yet to speak to precision of whole genome sequencing. Also, we have insufficient data to date in recapitulating known diagnoses in samples prospectively by whole genome sequencing.

Dr. Litwack asked, "Are you in process of validating of WGS to be used in this study?
Do you anticipate changing the platform throughout the course of study?"

Dr. Kingsmore said, "Yes, we are validating the WGS device. This is Year 1 of U19 grant's major aim, and we've been working on it since September 2013. We have locked down a majority of the components. There will be modification of whole genome sequencing testing during the course of the study, but changes will be documented per protocols, and performance of protocol changes will be assessed.

Point raised on page 3 of document (clarification 2):
".....it does allow for disclosure of results to clinician *prior to* Sanger sequencing in cases that involve identification of a life-threatening, treatable condition (and) novel variants of uncertain clinical significance (VUS)."

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

Point raised on page 3 of document (clarification 3):
"The protocol also appears to leave open the possibility that return of results without confirmation may occur in other, unidentified situations."

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

Point raised on page 3 of document (clarification 4):
"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)."

Point raised on page 3 of document (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

Point raised on page 3 of document (clarification 5):
"Moreover, your protocol also provides for the possibility of collection of blood, urine and tissue for the 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.

Dr. Litwack indicated that he and his team will come to final determination and respond to whether an IDE submission is required. He mentioned that the meeting minutes are to be submitted within 15 days from the time of the telephone conference of May 1, 2014.

The call was adjourned at 2:58pm EST.