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April 10, 2014

Dr. Kellie Kelm
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health (OIR)
Food and Drug Administration
10903 New Hampshire Avenue WO66, Room 5648
Silver Spring, MD 20993-0002

Re: Amendment to a Pre-Submission for an IDE

Dear Dr. Kellie Kelm:

As required, please find the minutes from our Pre-IDE Submission feedback teleconference that took place on Tuesday, April 9, 2014, as well as the slides that were presented. The eCopy is an exact duplicate of the paper copy.

Sincerely,

Robert L Nussbaum MD

Robert L. Nussbaum, MD, FACP, FACMG,
Chief, Division of Genomic Medicine

Enclosure

Minutes
UCSF/FDA IDE Pre-submission Teleconference
Regarding an NIH U19-funded Research Study
On Newborn Screening
April 8, 2014
12:00 – 12:43 PM

Action Items:	1) Robert Nussbaum to provide PCR/Sanger and CLIA reference (page 4) 2) Robert Nussbaum to confirm use of AmpliChip at SFGH (page 4) 3) Robert Nussbaum to provide more information on the service that GeneDx will provide (page 4)
Attendees, UCSF Team:	*Robert L. Nussbaum*, M.D., PI, Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening; Chief, Division of Genomic Medicine *Barbara Koenig*, Ph.D., PI, Project 3, UCSF U19 NBS Grant *Robert Currier*, Ph.D., Collaborator, UCSF U19 NBS Grant; Genetic Disease Screening Program, California Dept. of Health *Steven Brenner*, Ph.D., Co-Investigator, UCSF U19 NBS Grant, Professor, University of California, Berkeley *Cristina Kapustij*, Program Manager, U19 NBS Grant *Tiina Urv*, Ph.D., NIH Program Director, U19 NBS Grants *Jonathan Gitlin*, Ph.D., Science Policy Analyst, National Human Genome Research Institute, NIH
FDA Team:	*Kellie Kelm*, Ph.D., Lead Scientific Reviewer, Division of Chemistry and Toxicology Devices *Courtney Lias*, Ph.D., Division Director, Division of Chemistry and Toxicology Devices *Yung Chan*, Branch Chief, Clinical Chemistry Devices Branch

Kellie Kelm introduced the members of her team; Dr. Nussbaum introduced the UCSF Team.

Dr. Nussbaum began the presentation of the slide set that accompanied this call, starting with slide 5, Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening. The notice of the award was September 3, 2013, and the project start date was September 5, 2013. [Slide 6] The aim of the project is to compare whole exome sequencing to tandem mass spectroscopy currently used for the diagnosis of >40 biochemical markers for disorders of amino acid or organic acid metabolism or fatty acid

oxidation. We will also compare whole exome sequencing to diagnose primary immunodeficiency diseases that are not detected by TREC assay and for which newborn screening might be appropriate. We also intend to explore parental attitudes toward receiving genetic information beyond what is normally returned through newborn screening. Such "extra" genetic information will include certain pharmacogenetic variants that we wil actively search for as well as possible "incidental" findings we may find in one or more of the 56 genes that the ACMG believes are currently "actionable" treatments, and we will consider whether to report these back. We will also develop legal and ethical frameworks to make sure that testing by WGA (whole genome analysis) can be done to the benefit of all stakeholders. In this case, WGA refers to the whole exome work that UCSF will be doing.

[Slide 7] Whole exome sequencing and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiency will be examined. We will request de-identified newborn blood spots from the California Department of Public Health from all true positives and all false negative screens over the past five years, as well as two control sets of infants, half representing false positive and half representing true negative blood spots. We will analyze the five year follow-up records the CDPH has regarding hospitalizations, ER visits, weight, growth and development, and whether diseases recur in the long term.

[Slides 8, 9, 10, Project 1, continued] We will obtain 1357 true positives and 13 false negatives as well as 100 confirmed false positives and 100 confirmed true negatives. We will extract DNA using the protocol set out in Section C using phenol extraction. We will use the data obtained from the HiSeq 2500, and annotate variants found in a set of 44 primary metabolic disorder genes and 200 additional genes associated with the primary genes by network analysis and pathway analysis. The data will be stored in a HIPAA-compliant database, and we will obtain the 5-year follow-up information and look at sequence variants to determine sensitivity and specificity and correlate that information to clinical outcome. There will be no return of results; the aim is just to learn, and we don't have information on the identities of the patients.

[Slides 11 and 12, Project 2] We will examine variants in selected immunodeficiency, pharmacogenetic, and other "ACMG incidental finding genes" obtained by whole exome sequencing of patients who are suspected of having primary immunodeficiencies not identified by the TREC test. We will ascertain patients in Primary Immunodeficiency clinic here at UCSF, obtain informed consent (in conjunction with Project 3) for the California Department of Public Health to give us the patients' original blood spots for extraction and find the primary gene, but also look at other genetic variants. The pharmacogenetic genes are a particularly interesting area because of the variety of infections in immunodeficient patients that may need to be treated by medications whose metabolism is affected by pharmacogenetic variants. It's also an interesting area to explore patient attitudes and desires, and also about how much could be used for patient care later on. We will also examine 56 genes proposed by the ACMG to look for known pathogenic variants in predominantly autosomal-dominant cardiovascular or neoplasia conditions, as well as a few others, such as malignant hyperthermia.

[Slides 12 and 13, Project 2, continued] We will obtain consent from parents for exome sequencing and analysis. All DNA sequencing will be performed in the Institute for Human Genetics sequencing lab on HiSeq 2500 machines, and the lab pipeline will be CLIA-certified by July 1, 2014. We will return results for which consent was obtained. At the current time, this whole field of research is up in the air regarding whether next-generation sequencing calls with high quality score generated in a CLIA lab can be reported without Sanger sequencing for confirmation. Some clinical labs that are CLIA- and CAP-certified report results that are not confirmed by the Sanger method. Indels are more difficult to detect – if one is missed, we won't know to look, but if we do find indels, that need to be confirmed. We can have mutations we find verified by GeneDx. GeneDx will set up a test for any mutation we find, not just the ones routinely offered. For known pharmacogenetic mutations, we propose to use the D-met chip that San Francisco General Hospital (SFGH) uses. (Dr Nussbaum misspoke here – it is the AmpliChip that is FDA approved and this is what we would propose to use for Cyp2D6 and Cyp2C19). For standard blood groups, we will use GeneDx to confirm gene variants. Finally, in labs doing whole gene exome, approximately 3-5% report finding deleterious mutations in the 56 ACMG genes. In 40-50 patients, we might find none, but if any are found, we will confirm them if the patient opts in.

[Slides 14, 15, Project 3 and Project 3, continued] Project 3 studies the ELSI implications of research related to DNA-based analysis associated with newborn screening. We intend to develop a consent form and procedures for extended information for the patients with primary immunodeficiencies. We will specifically aid in the implementation of Project 2. Focus groups of key stakeholders will determine the views, perspectives, and value preferences about the expansion of newborn screening programs. We will be collaborating with UC Hastings and plan to work with The Hastings Center in New York regarding newborn screening policy working groups.

[Slide 16] Project status as of 4/8/14 – we have successfully extracted DNA and sequenced exomes from 8 sample newborns from pre-1982 samples. Project 2 has successfully extracted DNA from the above samples, We knew nothing about the individuals whose spots were used to extract DNA and perform whole exome sequencing, and looked at quality and coverage. We looked at metabolic genes and the results look good, with the quality and coverage being high. Project 3 has begun developing the HRPP framework and gathering materials for the focus groups.

The presentation concluded at 12:26 PM, and the remaining time was spent on questions by the FDA.

Kelli Kelm: Any comments from UCSF?
Barbara Koenig: No.
Kelli Kelm: Thanks. Getting a chance to look at the preliminary material was helpful.
Robert Nussbaum: Yes.
Kelli Kelm: Are there any plans to put the information in the medical record?

Robert Nussbaum: No. There are no plans for the pharmacogenetic component, but we are discussing returning the information to patients, and if that happens, we could put it in. The D-Met chip is used in the clinical laboratories, so it would make no difference.
Kelli Kelm: The D-met chip?
Robert Nussbaum: Not the AmpliChip, but the D-Met chip.
Kelli Kelm: The D-Met chip is not approved yet.
Barbara Koenig: We will use the currently-approved chip.
Robert Nussbaum: I will check with Alan Wu at SFGH to see if he is using the FDA-approved chip.
Kelli Kelm: The D-met chip is broader. If you add others not covered by D-met, some tests will not be FDA-cleared.
Robert Nussbaum: We will go to GeneDx for those.
Kelli Kelm: Is there a procedure to confirm results related to specific conditions?
Robert Nussbaum: Anything that goes into the medical record or to the patients will be confirmed by Sanger sequencing. I'm not sure in 6 months or a year or two years what will happen. Right now, some labs are not confirming, but some are.
Kelli Kelm: I am interested in what you are doing now.
Robert Nussbaum: The plan is to confirm.
Kelli Kelm: With what? The D-Met chip is different than the AmpliChip.
Robert Nussbaum: The AmpliChip is used at SFGH. I misspoke.
Kelli Kelm: We need to confirm that.
Robert Nussbaum: We will confirm.
Kelli Kelm: Will the sequencing data go into the medical record?
Robert Nussbaum: No.
Barbara Koenig: Most centers' IRBs are new to these issues. We haven't worked this through yet with our IRB, but that will be accomplished in our Project. We will be putting material into the medical record.
Kelli Kelm: You aren't putting information into the record and then modifying later?
Barbara Koenig: Anything that can be confirmed in the lab will be placed into the medical record, like any other pharmacogenetic information.
Kelli Kelm: Will you put your sequence data in?
Robert Nussbaum: No.
Barbara Koenig: No.
Kelli Kelm: New information from GeneDx will provide follow-up. What method are you using?
Robert Nussbaum: They use PCR followed by Sanger sequencing. We will ask them to set up using PCR and Sanger.
Kelli Kelm: Will that be CLIA-validated?
Robert Nussbaum: Yes, it is a custom process, but completely clinically validated, costing probably $350 per site.
Kelli Kelm: Will this come from research?
Robert Nussbaum: No, it won't be from research.
Kelli Kelm: Please provide a reference for that. Do you have any more questions for us?
Robert Nussbaum: The action items are: 1) to confirm use of AmpliChip at SFGH; and 2) to provide more information on the out-of-the-usual service that GeneDx will provide.

Kelli Kelm: We need specific information on exact genes. Have your memo provide single findings information. Any other genes you might be reporting? How do you define confirmed and not confirmed?
Robert Nussbaum: In each field, it depends where the field goes, and then it's back to you and the IRB. But all will be confirmed at the start.
Tiina Urv: Kelli, a lot of people from the FDA are not on this call – are they participating?
Kelli Kelm: We have a review team. For instance, David, even though he is not here, will be a part of the team. Make sure all your decisions are consistent and make sense. I will be sure to contact you if questions from others not present come up.
Robert Nussbaum: Any more comments from UCSF?
Cristina Kapustij: No, that's okay.
Robert Nussbaum: The meeting is adjourned. (12:43 PM)

University of California
San Francisco

UCSF/FDA IDE Pre Submission Teleconference Regarding an NIH U19 Funded Research Study on Newborn Screening

April 8, 2014

University of California
San Francisco

UCSF Team on Teleconference

- Dr. Robert Nussbaum, PI, "**Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening"**
  Chief, Division of Genomic Medicine, UCSF

- Dr. Barbara Koenig, PI, Project 3, UCSF U19 NBS Grant
  Professor of Medical Anthropology & Bioethics, Departments of Social & Behavioral Sciences & Anthropology, History, & Social Medicine

- Dr. Robert Currier, Collaborator, UCSF U19 NBS Grant
  Acting Chief Program & Policy Branch, Genetic Disease Screening Program, California Department of Public Health

- Dr. Steven Brenner, Co-Investigator, UCSF U19 NBS Grant
  Professor, Department of Plant & Microbial Biology, UC Berkeley
  Adjunct Professor, Department of Bioengineering & Therapeutic Sciences, UCSF

University of California
San Francisco

UCSF Team on Teleconference

- Cristina Kapustij, Program Manager, UCSF U19 NBS Grant

- Dr. Tiina Urv, NIH Program Director, U19 NBS Grants
  Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH

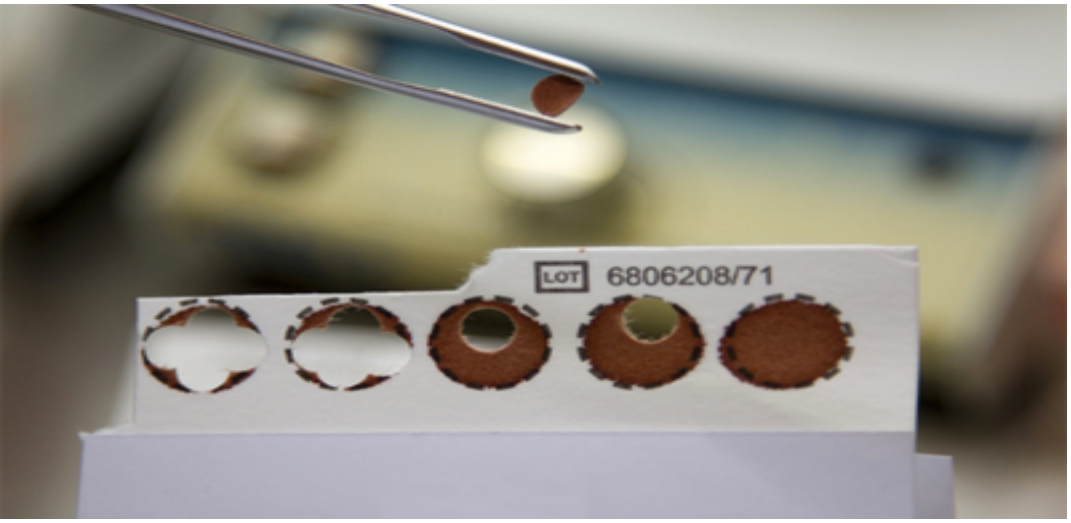
- Dr. Jonathan Gitlin, Science Policy Analyst
  Policy and Program Analysis Branch, National Human Genome Research Institute, NIH

National Human Genome Research Institute

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

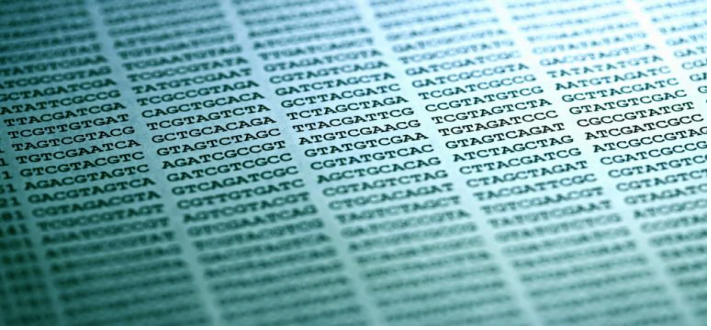
FDA Team on Teleconference

- Courtney Lias, Division Director, Division of Chemistry and Toxicology Devices
- Yung Chan, Branch Chief, Clinical Chemistry Devices Branch
- Elizabeth Mansfield, Director of Personalized Medicine Staff
- David Litwack, Personalized Medicine Staff
- Sunita Shukla, Scientific reviewer, Division of Chemistry and Toxicology Devices
- Kellie Kelm, Lead Scientific reviewer, Division of Chemistry and Toxicology Devices



Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening

- Notice of Award: September 3, 2013
- Project Start Date: September 5, 2013



Overall Aim of Project

- Compare whole exome sequencing to tandem mass spectroscopy, the test currently in use for newborn screening for biochemical disorders
- Test the use of whole exome sequencing for primary immunodeficiency diseases not detected in the TREC assay currently used in newborn screening but for which newborn screening might be appropriate
- Explore parent attitudes towards receiving genetic information beyond what is ordinarily returned through newborn screening, focusing on pharmacogenetic and blood group variants but also, if they arise, incidental findings in the 56 ACMG genes
- Develop appropriate legal and ethical frameworks to make sure NBS by WGA can be done to the benefit of all stakeholders.

Project 1

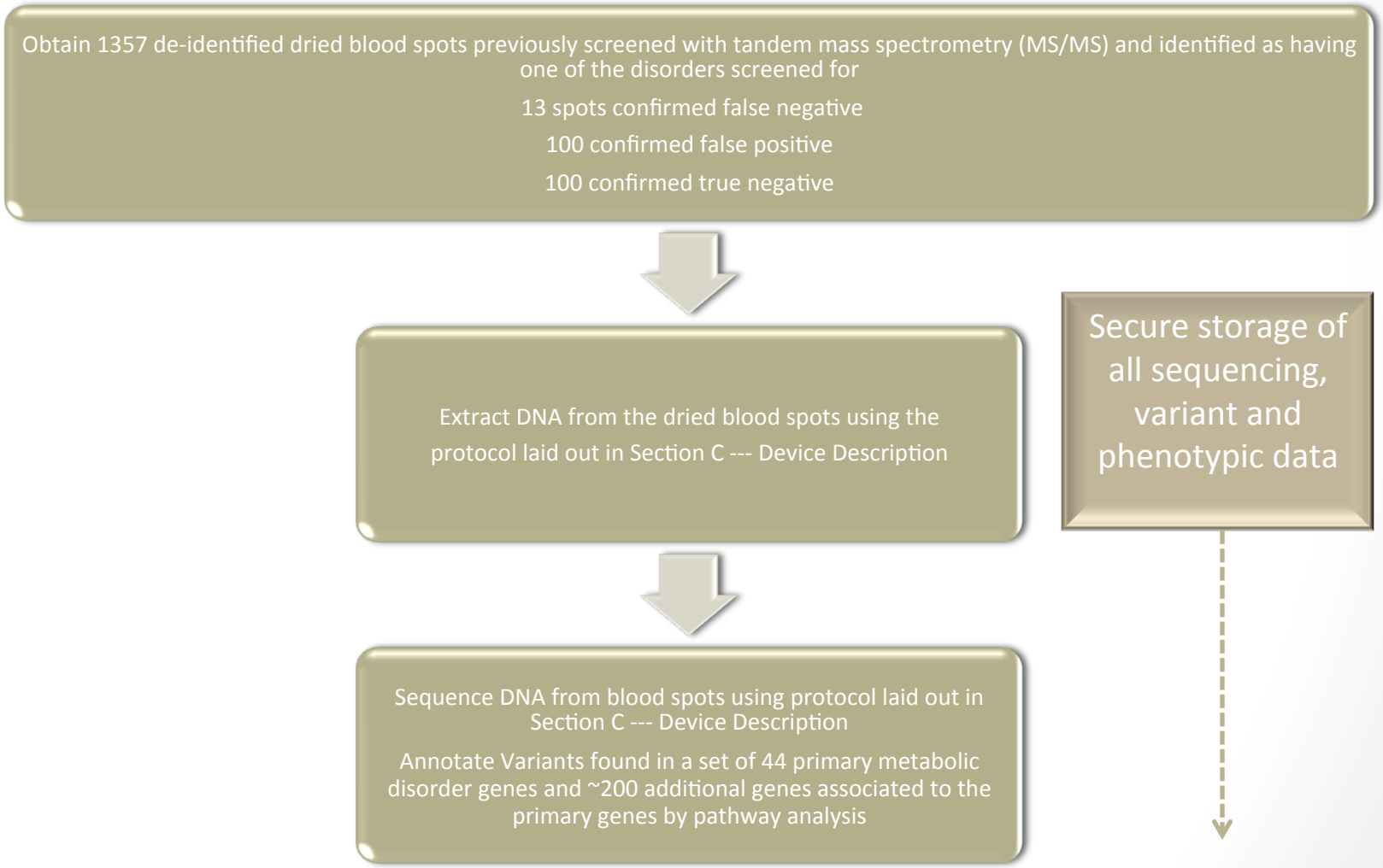
Whole Exome Sequencing and Analysis of Variants in Newborn Blood Spots Relevant to Metabolic Disorders and Primary Immunodeficiency

Request de-identified newborn blood spots from the California Department of Public Health (CDPH) for clinical validation

Follow appropriate CDPH protocols, including institution and state IRB approval, for obtaining blood spots for clinical validation

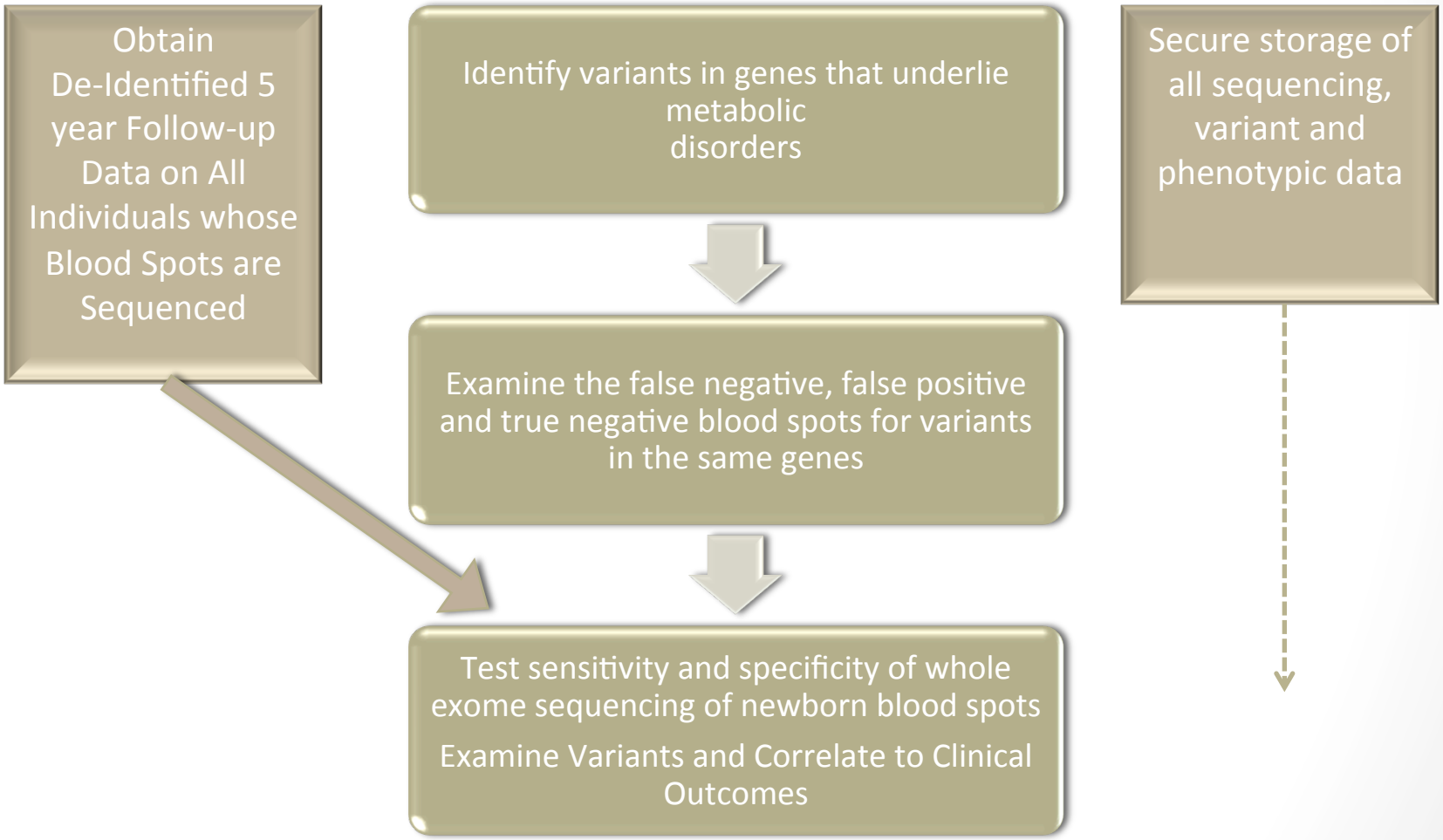
Project 1 (cont.)

Whole exome sequencing and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiency



Project 1 (cont.)

Whole exome sequencing and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiency diseases



Project 1 (cont.)

Whole exome sequencing and analysis of variants in newborn blood spots relevant to metabolic disorders and primary immunodeficiency diseases

No Return of Results as this was clinical validation of de-identified blood spots

Project 2

Examination of variants in selected immunodeficiency, pharmacogenetic genes and other "ACMG Incidental Findings Genes" (should they arise) obtained by Whole Exome Sequencing of newborn blood spots from patients who are suspected of having primary immunodeficiencies not identified by TREC newborn screening. To be done in conjunction with Project 3

Obtain approval of UCSF Committee on Human Research prior to recruitment

Identify patients attending Immunodeficiency Clinic at UCSF and request consent to obtain the original newborn blood spot

Explain to parents/patients we are looking to see if by analyzing DNA in the blood spot we could have identified their primary immunodeficiency

Project 2 (cont.)

Obtain consent from parents for exome sequencing and analysis

Provide Opt-Out for pharmacogenetic and other genes relevant to their disease, and

Provide Opt-Out for other "Incidental Findings" not directly relevant to the immunodeficiency disease but of medical/clinical significance to the patient or parents

All DNA Sequencing will be Performed in the Institute of Human Genetics Sequencing Lab on HiSeq 2500 machines. The lab and analytic pipeline are slated to be CLIA Certified July 1, 2014

Return results for which consent was obtained

Project 2 (cont.)

In Conjunction with Project 3

Categories of Return	Verification Method (If Necessary)
Immunodeficiency Gene Results	Mutation Confirmation at GeneDx (Including Genes not routinely offered by GeneDx)
Known Pharmacogenetic Genes as Established by Published Guidelines	Affymetrix AmpliChip
Standard Blood Groups	Mutation Confirmation at GeneDx (Including Genes not routinely offered by GeneDx)
Gene Variants Relevant to your Child or Family as Established by ACMG Guidelines and the other U19 Groups	Mutation Confirmation at GeneDx (Including Genes not routinely offered by GeneDx)

Project 3

ELSI Implications of Research Related to DNA Based Analysis Associated with Newborn Screening - Generally Developing an Overall Approach and Specifically Aiding in Implementation of Project 2

- **HRPP Framework**: develop a participant protection framework for conducting whole genome/whole exome sequencing during the neonatal period, as an adjunct to the standard NBS blood spot. Families experiencing severe primary immunodeficiency who are offered WGA of their child's NBS blood spots (Project 2, Aim 2c) will serve as the exemplar for discussion.

- **Focus Groups**: Using PGx variants that predict response to drugs commonly used in childhood as a case example, we will determine the views, perspectives, and value preferences of key stakeholders about the potential expansion of newborn screening programs with the advent of WGA.

Project 3 (cont.)

ELSI Implications of Research Related to DNA Based Analysis Associated with Newborn Screening Using - Generally Developing an Overall Approach and Specifically Aiding in Implementation of Project 2

- **Legal Landscape**: In collaboration with the UCSF/UC Hastings Consortium on Law, Science and Health Policy, identify the legal and constitutional issues for using WGA.

- **Policy Recommendations**: Informed by Aims 1-3, and in collaboration with a "Policy Advisory Board" convened by The Hastings Center (New York), develop and disseminate policy recommendations for expanded NBS programs based on WGA.

Project Status as of 4/8/14

Project 1: Has successfully extracted DNA and sequenced exomes from 8 sample newborn bloodspots from a pre-1982 “burn bag” of blood spots with no associated information the California Department of Public Health supplied UCSF

Project 2: Has successfully extracted DNA from the above mentioned blood spots

Project 3: Has begun developing an HRPP framework together with the UCSF HRPP program.

Has begun gathering materials for the proposed focus groups.

Has begun scheduling meetings for the policy analysis board.

Further Questions?