University of California
San Francisco

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

April 8, 2014

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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

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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

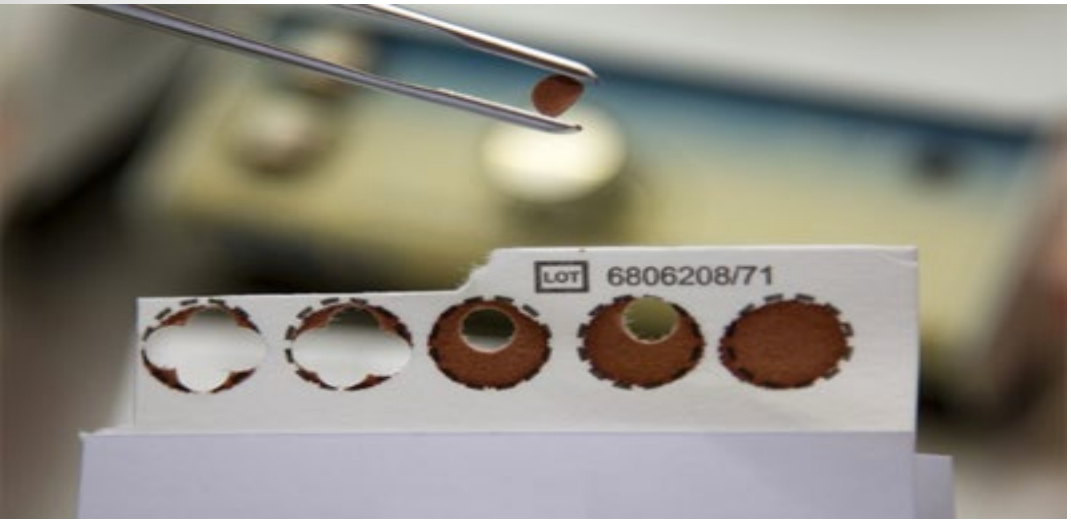
- Dr. Jonathan Gitlin, Science Policy Analyst
  Policy and Program Analysis Branch, National Human Genome Research Institute, NIH

National Human Genome Research Institute

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

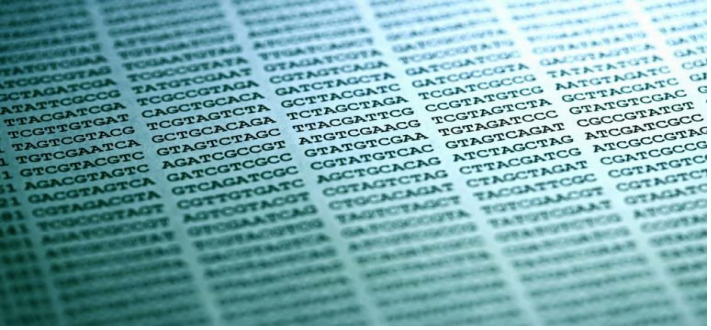
FDA Team on Teleconference

- 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

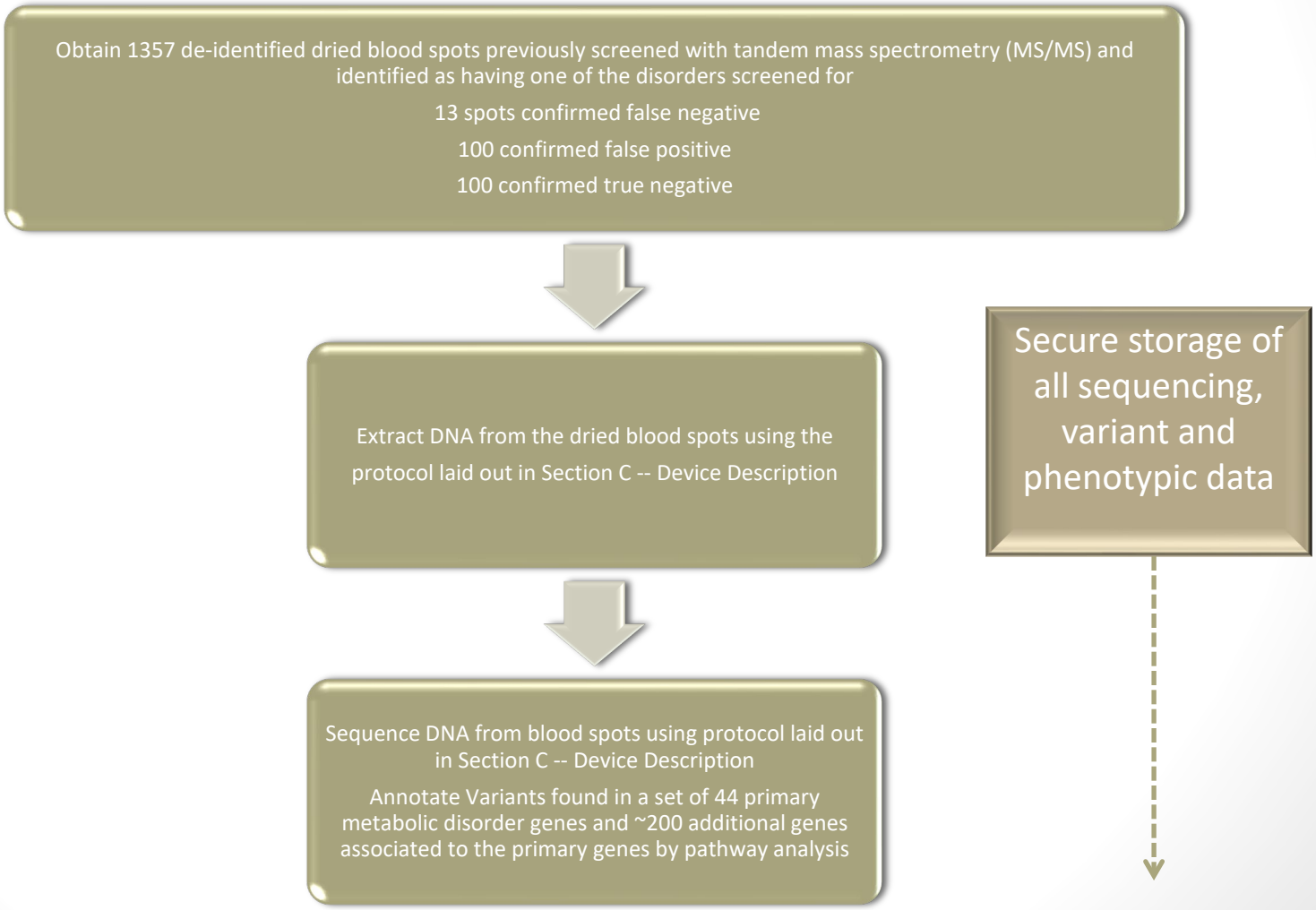
Whole Exome Sequencing and Analysis of Variants in Newborn Blood Spots Relevant to Metabolic Disorders and Primary Immunodeficiency

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

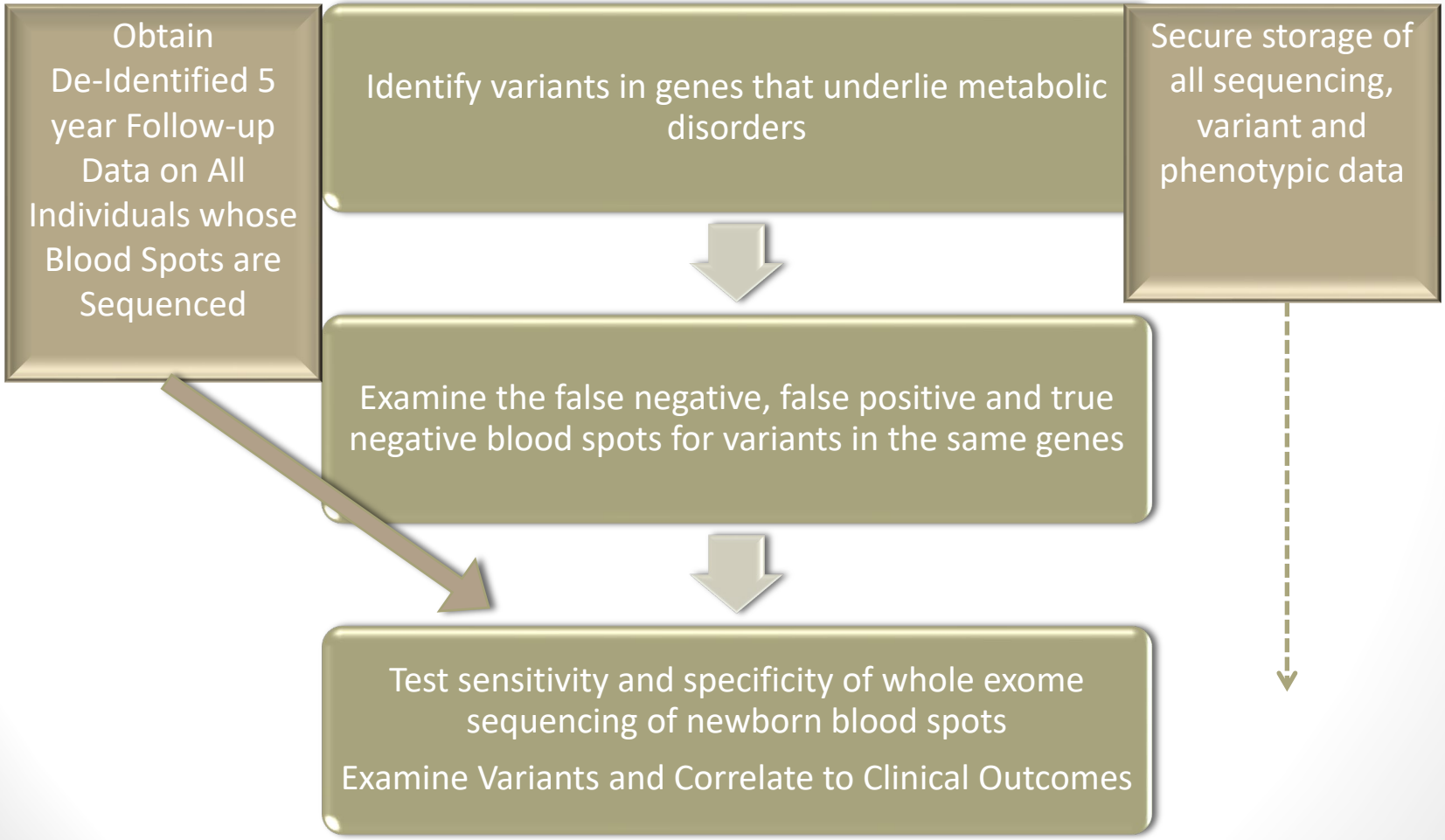
Project 1 (cont.)

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?