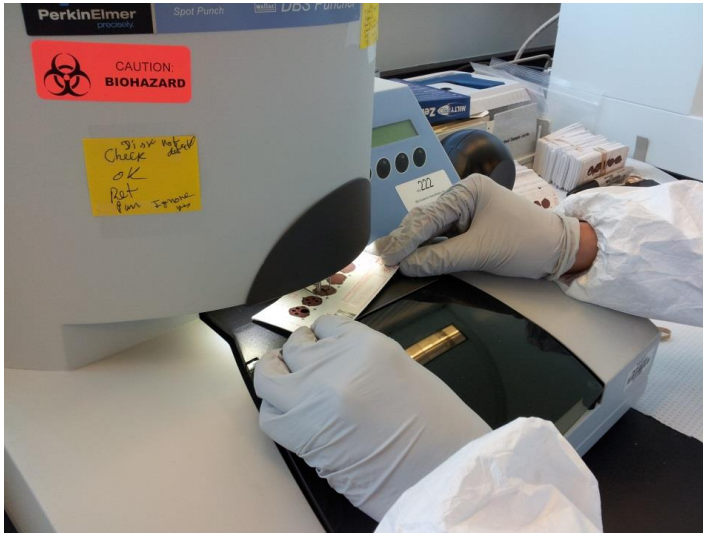


NSIGHT NBSeq



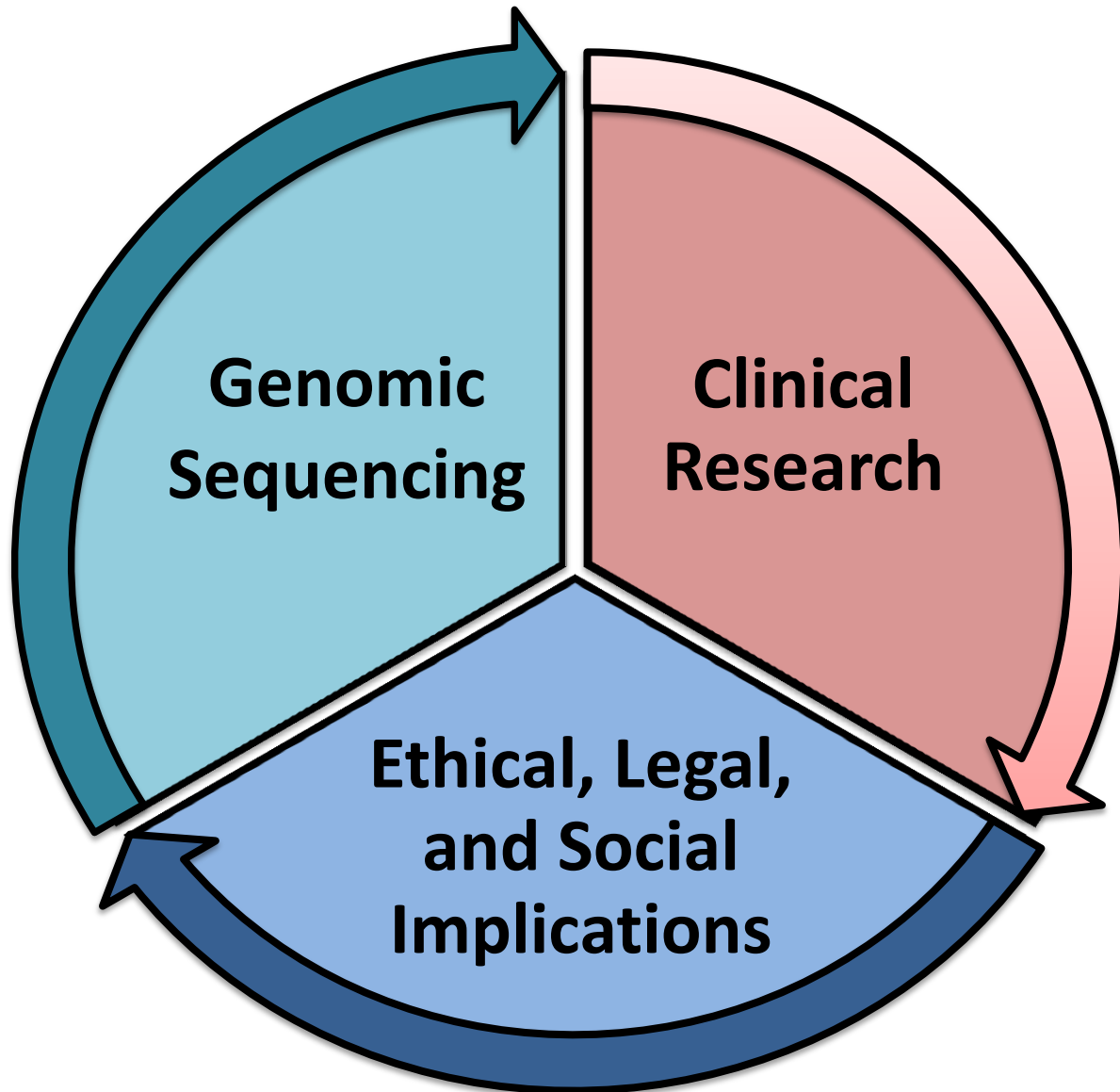
Barbara A. Koenig, PhD
Pui-Yan Kwok, MD PhD
Jennifer Puck, MD
University of California San Francisco

NBSeq

Explore potential applications of whole exome sequencing (WES) to public health newborn screening (NBS).

Specifically, evaluate the feasibility of WES to replace or augment MS/MS for metabolic disorders.

Required 3 Components of NSIGHT



Project 1

- 1570 dried blood spots from the California Department of Public Health Biobank
 - 1357 true positive metabolic disorder cases
 - 203 false positive and false negative metabolic disorder cases
- Extract and sequence DNA (WES)
- Annotate variants in a set of ~90 primary metabolic genes and additional genes identified through pathway analysis
- Identify variants associated with metabolic disorders. Compare with variants found in false positive and false negatives

Project 2

- Build on success of newborn screening for early detection of severe combined immunodeficiency (SCID)
- Non-SCID immune disorders would also benefit from early diagnosis and treatment. There are >240 known and additional unknown primary immunodeficiency genes, but no screening biomarkers comparable to TRECs for non-SCID
- **Could WES identify actionable conditions prior to onset of severe infectious complications?**
- Project will enroll 50 individuals with poorly characterized immune defects who were born in CA in 1982 or later
- Stored NBS blood spots are retrieved for WES. Analysis is by VARANT pipeline of Brenner et al.

Project 3

How will next-generation sequencing enhance, challenge, or transform traditional state-mandated NBS? How “should” it?

- In collaboration with UCSF IRB, to develop a policy for return of incidental finding when conducting whole genome analysis in infants or children.
- To determine the views, perspectives, and value preferences of key stakeholders about the potential expansion of NBS programs with NGS.
- To identify, in collaboration with the UC Hastings College of Law, the constitutional issues raised by the potential incorporation of whole genome analysis into NBS.
- To create, in collaboration with other NSIGHT investigators and the Hastings Center, a national policy board that will develop (and disseminate) recommendations about the appropriate use of whole genome analysis in newborns.

Most parents don't remember NBS

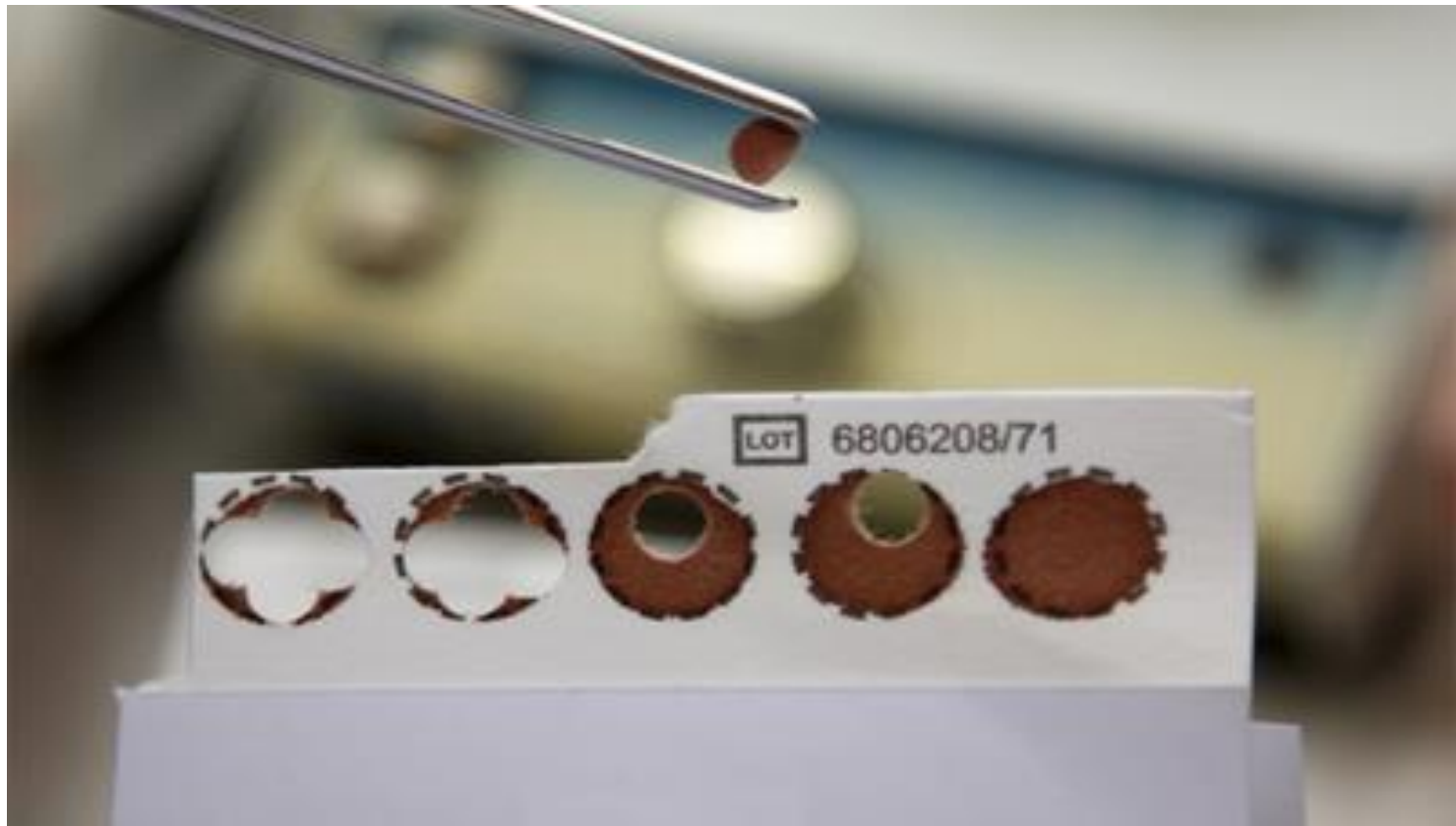
“I don't really remember [NBS]. My son was a preemie, I had a C-section...There was a lot of crazy stuff going on, so I have no memory, honestly.”

Perspectives from those with experience of immunodeficiency disorders

- “Had somebody asked me after all the trauma of giving birth, ‘do I want an additional test on my child,’ I may have said no....I would’ve regretted that decision...So I think everyone should do it because there is no risk.”

The Starting Question

What is the appropriate balance between parental consent and public governance in NBS?



Deliberative Community Engagement

The CONSIDER Project

PI: Julie Harris-Wai, PhD, MPH

AHRQ: R21 HS023547

Purpose

To generate informed, deliberative , community-based recommendations to inform critical and time urgent policy decisions.

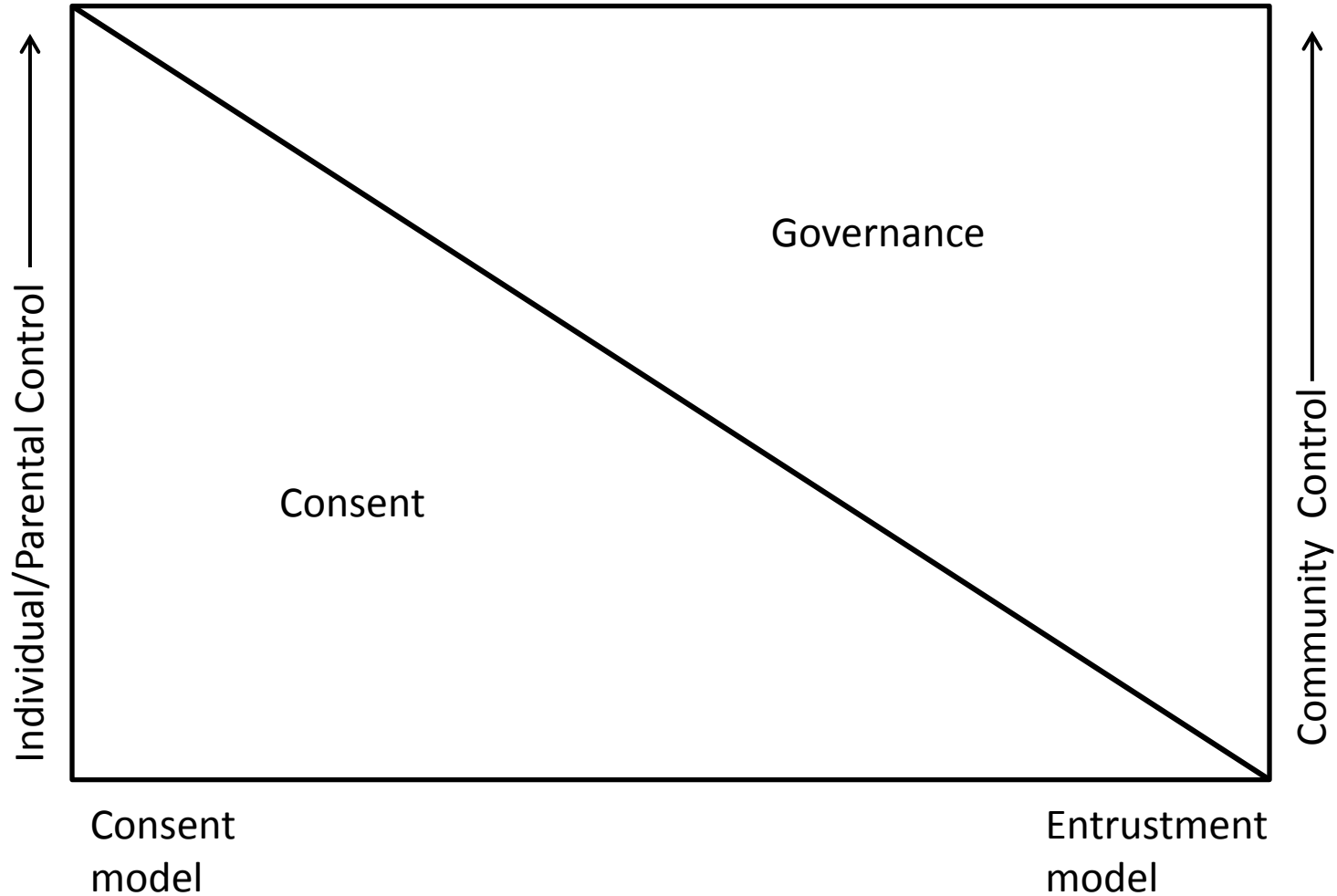
Co-Investigator

Bob Currier, PhD

(California Department of Public Health)

This presentation does not reflect the views of CDPH

Balancing Consent and Governance



Promise of Deliberative Community Engagement

- Move past the limits of individual informed consent/choice as the sole strategy for implementation
- Debate/discuss tradeoffs
- Set meaningful “defaults” in the policy arena
- Consider impact of “false positive” results
- Address broad public concerns such as eugenics, privacy vs research benefit

Arguments in favor of governance

- The “capture” of the policy process by special interest groups (advocates) reflects a “democratic deficit.”



Kristin L. Carman , Coretta Mallery , Maureen Maurer , Grace Wang , Steve Garfinkel , Manshu Yang , Dierdre Gilmo...

Effectiveness of public deliberation methods for gathering input on issues in healthcare: Results from a randomized trial

Social Science & Medicine, Volume 133, 2015, 11 - 20

Summary:

Deliberative Community Engagement

- Key conditions for meaningful deliberation
 - Time
 - Information
 - Atmosphere of Mutual Respect

Demographics

- 33 Participants selected to represent the full diversity of the California population
- Simultaneous interpretation allowed the participation of mono-lingual Spanish speakers

Provide Information and Answer Questions

- Received “briefing book” ahead of event.

Developing a Screening Method for SCID

Jennifer Puck, MD

Jennifer.Puck@ucsf.edu

Department of Pediatrics
University of California San Francisco
and Benioff Children's Hospital
San Francisco, California

UCSF

JENNIFER PUCK

MONICA SMITH

BOB CURRIER

UCSF

Large and Small Group Discussion

- Over four full days (two weekends)
- Professional facilitation



PROGRAMA DE CARRERA

EXPERIENCIAS

PREOCUPACIONES

- 1- PENSAR INDIVIDUALMENTE Y ALCANZAR 3-2 MAS IMPORTANTES
- 2- COLOCAR EN ORDEN
- 3- IDENTIFICAR
 - ACUERDOS SOBRE ESTEREOTIPOS
 - ACUERDOS SOBRE PREOCUPACIONES
 - DESACUERDOS
- 4- INFORME
- 5- PERSONA

MARYNIEVES DIAZ-MENDEZ

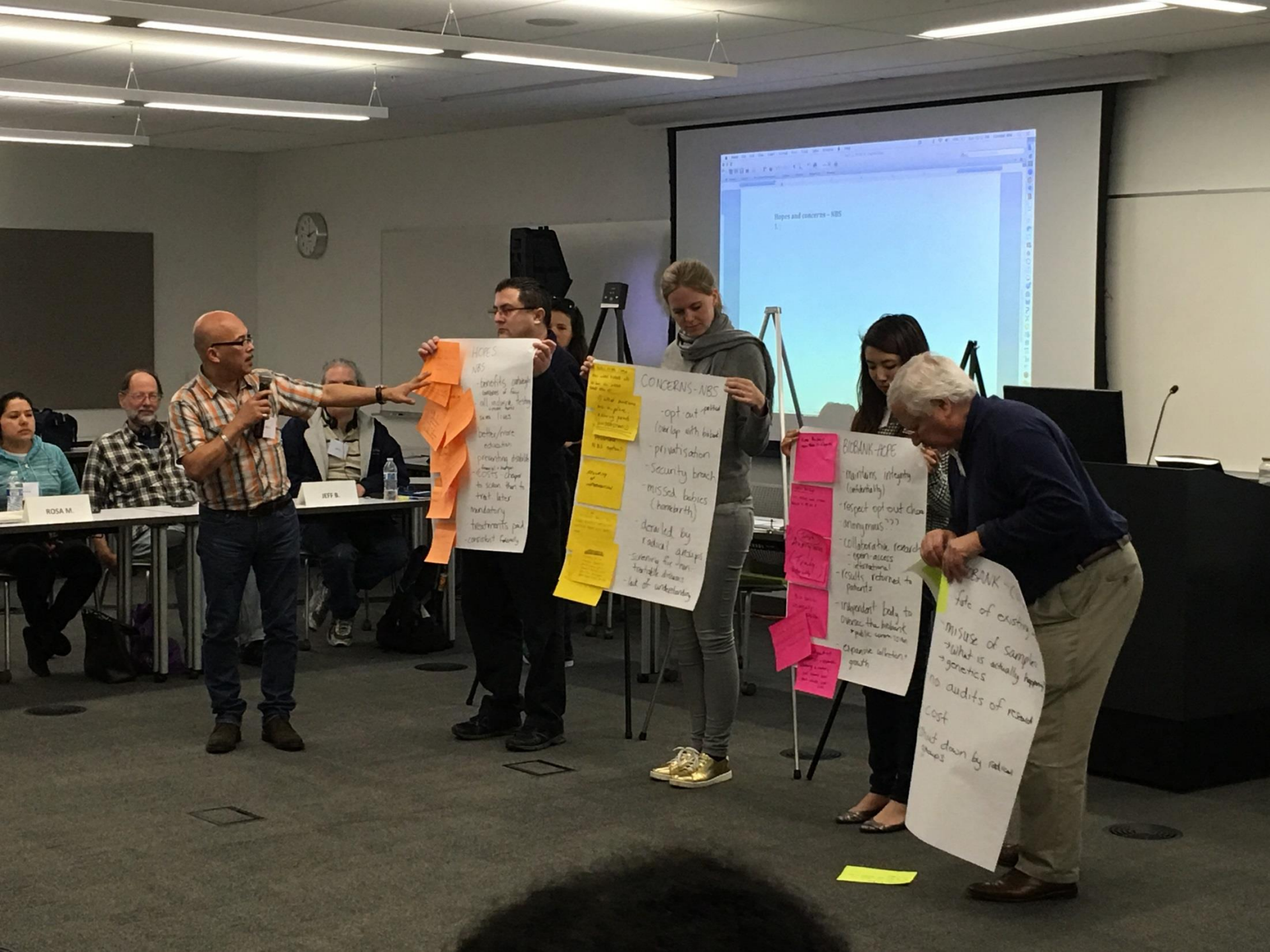
EXPERIENCIAS

PREOCUPACIONES

ACUERDOS SOBRE ESTEREOTIPOS

ACUERDOS SOBRE PREOCUPACIONES

DESACUERDOS



ROSA M

JEFF B

HOPE'S
 NBS
 - benefits outweigh
 - all, not just for
 - better/fine
 - education
 - prioritising babies
 - parents' choice
 - to know their
 - that later
 - mandatory
 - test results paid
 - consent family

Other points
 - all parents
 - all parents
 - all parents
 - all parents
 - all parents

CONCERNS-NBS
 - opt out path
 - work up with bid
 - privatisation
 - security breach
 - missed babies
 (homebirth)
 - derailed by
 - radical dissent
 - screening for non-
 - forable diseases
 - lot of uncertainty

BIGBANK-HEPE
 - maintain integrity
 (anonymity)
 - respect opt out choice
 - anonymous
 - collaborative research
 - open access
 - international
 - results returned to
 patients
 - independent body to
 oversee the bank
 - public consultation
 - expensive whether
 - youth

BIGBANK
 - fate of existing
 - misuse of samples
 - what is actually happening
 - genetics
 - no audits of research
 - cost
 - shut down by review
 - changes

Hopes and concerns - NBS
 1.

Recommendations

Not Forced Consensus

- Arrive at recommendations with broad support
- Highlight areas of persistent disagreement

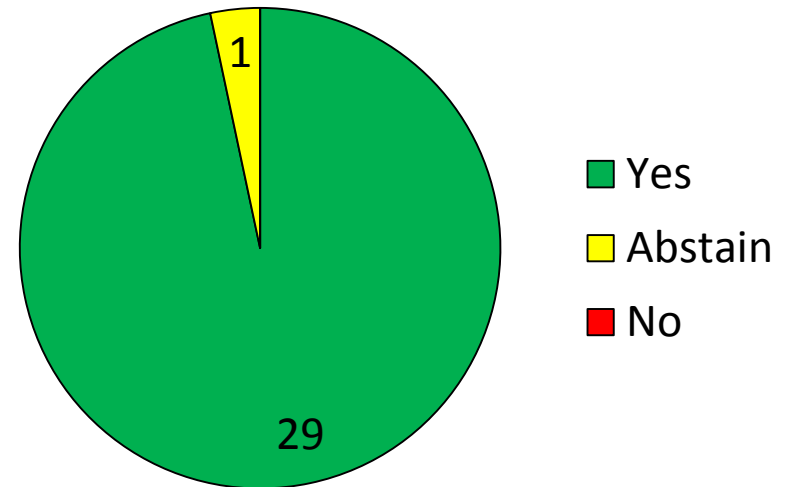
Recommendations

Topic 2: How to ask for permission without damaging the public health goals of the newborn screening program

- 2A. The NBS program should remain mandatory.
- 2B. Clearly separate the activities of i) the NBS Program and, ii) asking permission for the biobank program.

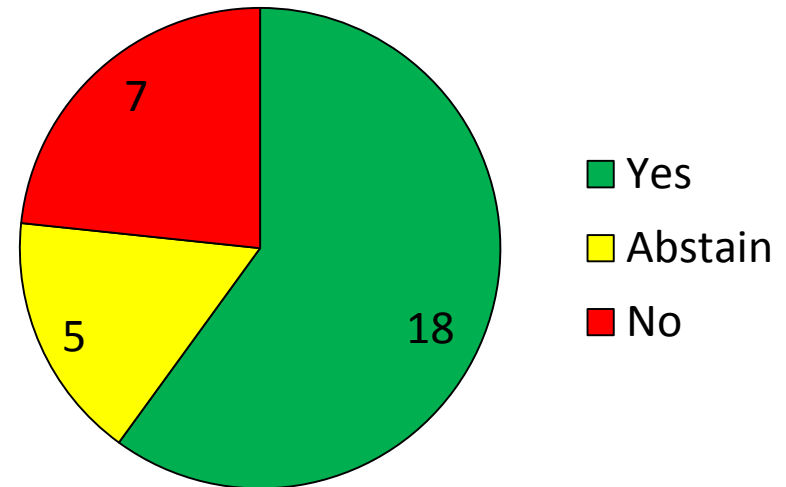
Nearly universal agreement on many topics

Clearly separate the process of collecting blood for newborn screening from asking permission for the biobank program



But some issues were significantly divided

The CDPH should have a policy allowing return of results for biobanking research



Recommendations

Topic 3 Appropriate use of existing biobank samples

- 3A. Samples that were collected without permission prior to the new 2015 law should:
 - Not be destroyed.
 - Not require contact and permission.
 - Be the subject of public education to raise awareness.

Recommendations

Topic 3 Appropriate use of existing biobank samples

- 3C. It is appropriate for existing samples to be used for external research to benefit health and wellness.

Recommendations

Topic 5: Trustworthy biobank oversight

- 5A. Information that enables full transparency makes the biobank trustworthy.

Recommendations

Topic 5: Trustworthy biobank oversight

- 5G. A community advisory board should collaborate with the CDPH on decisions about how to return results from biobank research to individuals and families.

Accomplishments

- Successful extraction of DNA from dried bloodspots (DBS)
- High quality WES data from >600 DBS
- Development of state-of-the-art analysis pipeline for metabolic and immune disorders
- Project 3 focus groups completed
- 2 ELSI papers published (special issue of *Pediatrics*)
 - Parental Views on Expanded NBS with WGS
 - Constitutional Boundaries of State NBS with WGS
- Special issue of *Hastings Center Report* (in process)
- With AHRQ support, held Deliberative Community Engagement (March 2016)

Thanks to NBSeq Collaborators and Funders

UCSF

Barbara Koenig

Pui-Yan Kwok

Jennifer Puck

Laia Bars

Flavia Chen

Carol Fraser-Browne

George Freedman

Julie Harris-Wai

Galen Joseph

Mark Kvale

Richard Lao

Alan Nguyen

Neil Risch

Joseph Shieh

Diya Vaka

Eunice Wan

CDPH

Bob Currier



University of California
San Francisco

UC Berkeley

Steven Brenner

Aashish Adhikari

Yaqiong Wang

Yangyun Zou

UW

Sean Mooney

Binghuang Cai

UC Hastings Law

Jamie King

Monica Smith

Hastings Center

Josie Johnston

Erik Parens

Rachel Zacharias



Raj Srinivasin

Uma Sunderam

Sadhna Rana

Kunal Kundu

ACMG, NBSTRN

Amy Brower

NIH

Joy Boyer

Melissa Parisi

Anastasia Wise



National Human
Genome Research
Institute



UW Medicine

UW SCHOOL
OF MEDICINE

BIOMEDICAL INFORMATICS
AND MEDICAL EDUCATION



TATA CONSULTANCY SERVICES



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

CONSIDER (deliberation) Project

UCSF

Julie Harris-Wai, Ph.D., M.P.H.
CONSIDER Principal Investigator
Assistant Professor, Department of
Social and Behavioral Sciences

Barbara A. Koenig, Ph.D.
CONSIDER Project Co-Investigator
Professor of Medical Anthropology &
Bioethics

Roberta Ryan
Project Coordinator

Beatriz Anguiano
Bilingual Research Assistant

Flavia Chen, MPH
Project Manager, NBSeq

Lindsay Forbes
Project Manager, UCSF

Bob Currier, Ph.D.
Program and Policy, Acting Chief
Genetic Disease Screening Program

Additional Team Members

Holly Longstaff, Ph.D.
Event Moderator
Engage Associates Consulting Group
Vancouver, British Columbia

Liz Wilcox, MS, Ph.D.c.
Small Group Facilitator
Engage Associates Consulting Group
Vancouver, British Columbia

Galen Joseph, Ph.D.
Small Group Facilitator
Associate Professor in the
Department of Anthropology, History,
and Social Medicine
University of California, San Francisco

MaryNieves Diaz-Mendez, M.D.
Small Group Facilitator

Deborah Gordon
Small Group Notetaker
Assistant Professor, Department of
Anthropology, History, and Social
Medicine

Jay Sullivan
Audio Visual Lead
Philip R. Lee Institute for Health
Policy Studies
University of California, San Francisco

Rocio Pacheco
Simultaneous Interpreter

Gabriela Moya
Simultaneous Interpreter

CDPH