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Genomic sequencing of newborns?

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

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The Promise

"I think it won't be too many years before parents will be able to go home from the hospital with their newborn babies with a genetic map in their hands that will tell them, here's what your child's future will be like."

Bill Clinton, *Tallahassee Democrat*, 10/11/1996, A12

The hope

- Sequencing will yield
  - A correct diagnosis
  - That hadn’t been already made
  - For a treatable disease
  - And treatment will lead to a better outcome.
- And will do this consistently and cost-effectively
- In broader and broader populations

Preliminary Conclusions from UCSF study of newborn bloodspots from the California Biobank.

Presented at ASHG 2017

WES not recommended as a STAND ALONE tool for primary public health NBS for IEMs

General Population → MS/MS Newborn Screening → MS/MS positive

Missed cases and high false positive rate render exome sequencing unsuitable for newborn screening of metabolic disorders in the general population

In several MS/MS screen positive cases, sequence data provided information that would help inform diagnosis

….But DNA may play key role as second-tier test

depending on the disorder, the gene(s), the variant(s)…

A Spectrum of Sequencing in NBS
Aaron Goldenberg

Unique Features of NBS

- Blood spot collection is “unconsented”
- Legal justification transformed
- Although this varies from state to state, samples are stored in the state of California “biobank” available for research

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Public Health Context

- Sequencing would identify numerous conditions that do not meet the legal and ethical justification for state mandated screening, and for which states cannot provide follow-up care
  - Preservation of screening programs is critical for public health and equality

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Public Health Context

- However, sequencing could be used as a secondary or adjunct tool for detecting conditions that meet traditional newborn screening criteria.
  - Additional consideration needed regarding:
    - Return of secondary results
    - Storage of data

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Concerns raised by state NBS programs

- Workforce and costs
- Education and communication
- Incidental findings
- Impact of private companies, potential to drive implementation
- Burden on parents
- Impact on original intent of public health NBS

Aaron Goldenberg, 2017 ELSI Congress

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General Conclusions

- Thus far, WES has only been shown to be useful in clinical populations where diagnostic uncertainty is a barrier to good care.
- There is not (yet?) evidence that sequencing every newborn would be sufficiently beneficial to children or families, to justify using it in routine care, public health, or as a DTC service.

General Conclusions: Remaining Questions

- Are our recommendations simply a result of lack of “data,” and thus time bound?
- Will accumulation of evidence “solve” the dilemmas of sequencing newborns?

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How is this test different from other tests?

Why is this test different?

- Uncertainty of findings
- Interpretation requires broad data sharing
- Return of secondary (unexpected) findings

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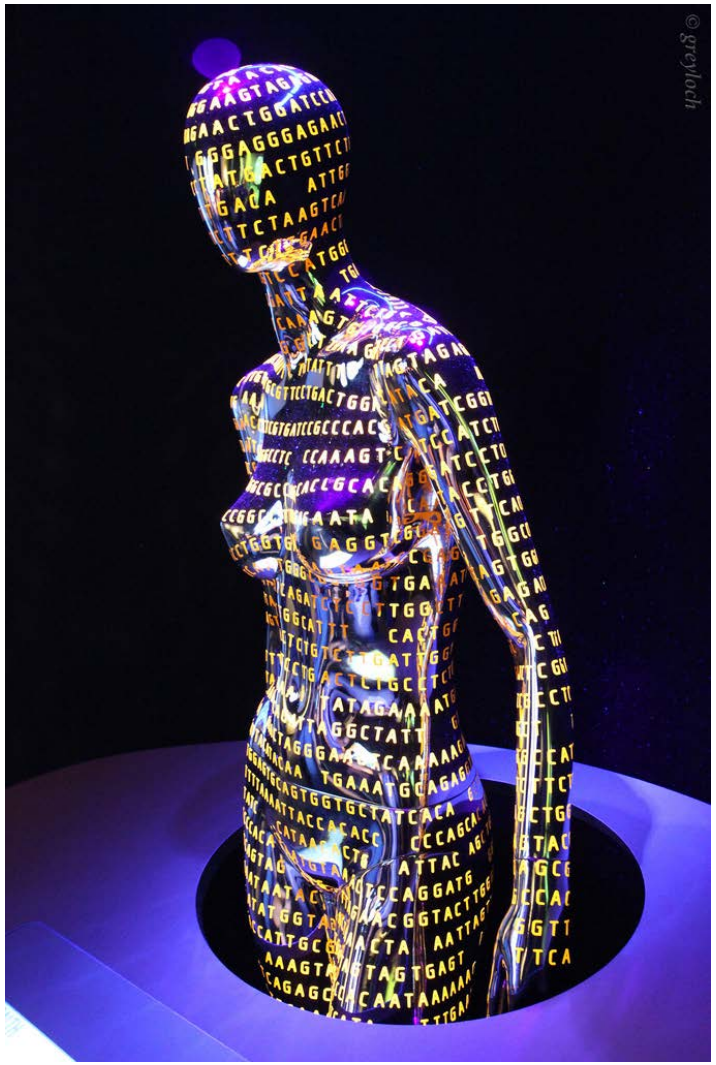
Why is this test different?
Data, Data, Everywhere



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Data, Data, Everywhere

- What should be returned?
- What is “actionable?”
- Managing “variants of uncertain significance”

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Genetics in Medicine
Official Journal of the American College of Medical Genetics

GENETICS IN MEDICINE | CORRIGENDUM

CORRIGENDUM: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Genetics in Medicine (2017) **19**, 484 | doi:10.1038/gim.2017.17

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Why is this test different? Family

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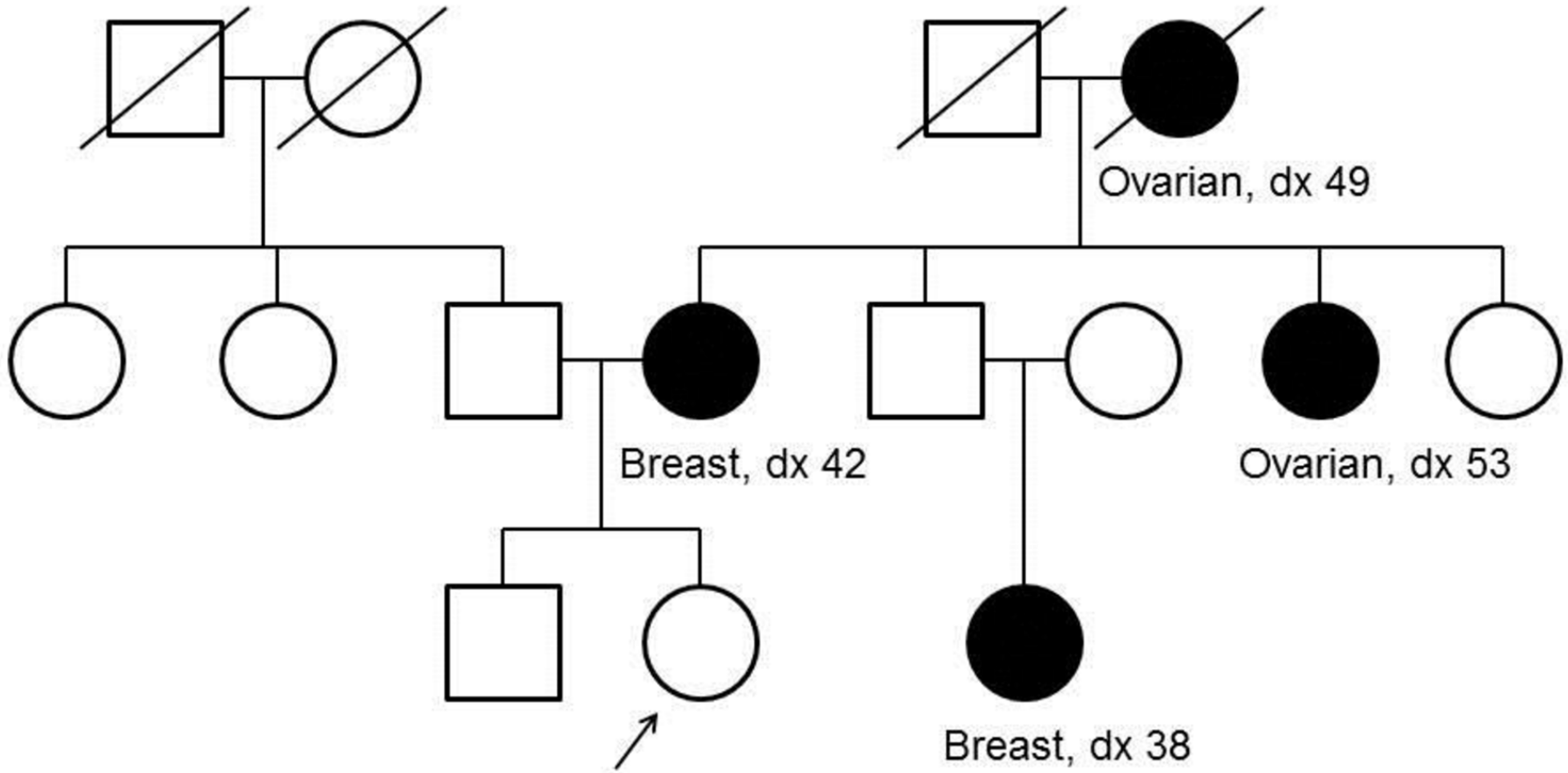
Classic *BRCA1* Pedigree



https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#section/all

An ethical dilemma

- A newborn in the NICU with undiagnosed anomalies is sequenced
- A “known pathogenic” variant in BRCA1 is identified, Sanger confirmation reveals maternal inheritance
- What should the team do?
  - Research?
  - Clinical?

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An ethical dilemma (adult onset conditions)

- Don’t return
  - Respect autonomy of child
  - Right to an open future
  - Protect child from psychosocial harm
- Return
  - Obligation to benefit affected relative (mother)
  - Professional integrity
  - Health & life of parent is in child’s best interest

Thanks to Ingrid Holm, Boston Children’s

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What if this same variant were identified in the context of state-mandated or expanded newborn screening?

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Why is this test different? Data Sharing

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Data Sharing

- Variants can only be understood when compared with “reference” data bases, which can only work if data are broadly shared
- Uncertainty in interpretation (particularly for ancestrally diverse populations)
- Transformation in the demarcation between research vs. clinical care

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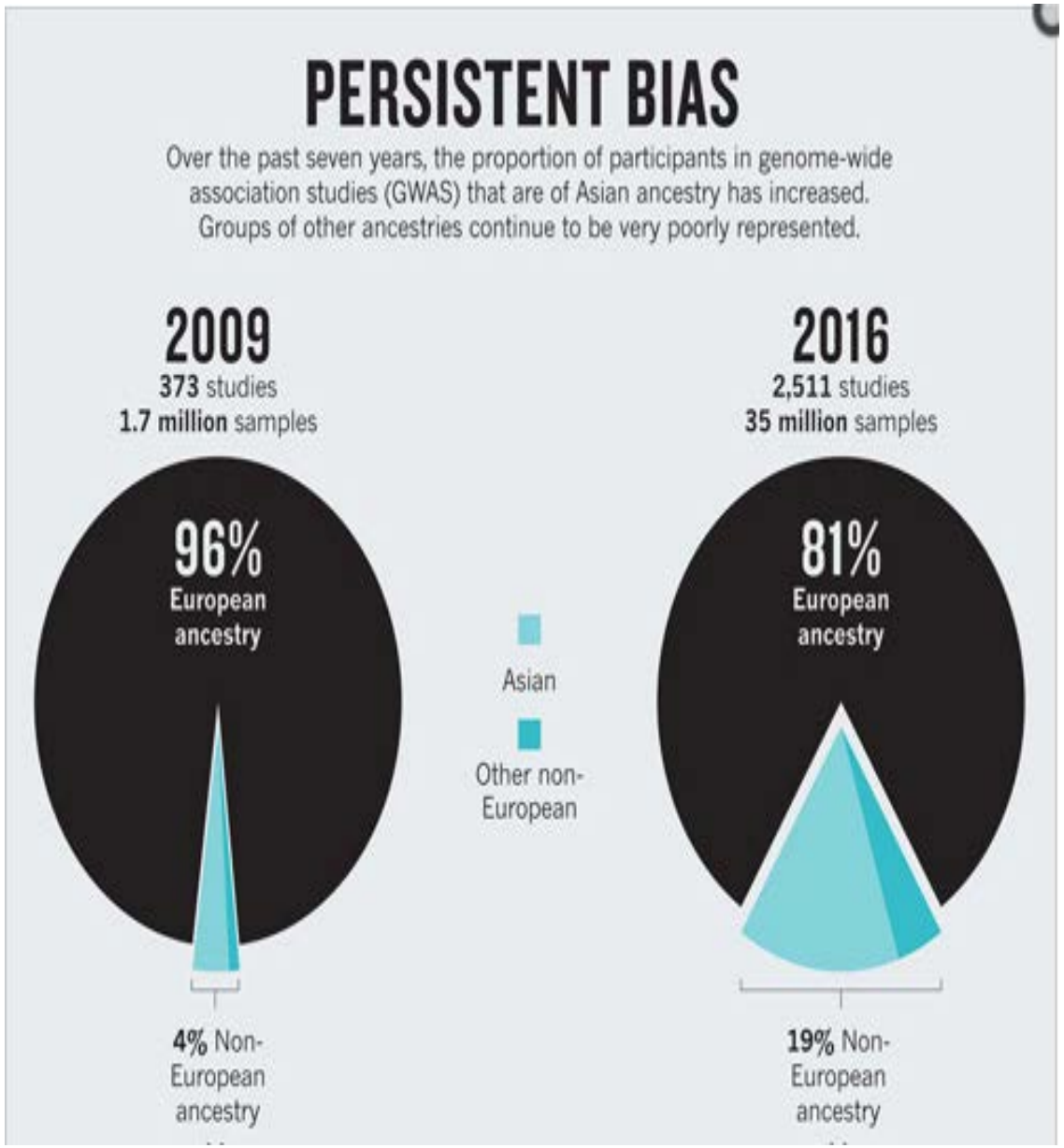

Popejoy, Alice B., and Stephanie M. Fullerton. "Genomics Is Failing on Diversity." *Nature* 538, no. 7624 (October 12, 2016): 161–64

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Critical Need for Robust Community Engagement!

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Social Justice: Insurance Coverage

ARTICLE | Genetics inMedicine

Private payer coverage policies for exome sequencing (ES) in pediatric patients: trends over time and analysis of evidence cited

Michael P. Douglas, MS[1], Stephanie L. Parker[2], Julia R. Trosman, PhD[3], Anne M. Slavotinek, MD[4] and Kathryn A. Phillips, PhD[5]

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Social Justice & Access

- Study is the first in-depth review of private payer coverage policies for pediatric patients with neurodevelopmental disorders.
- In 2015, no payer (of 5) covered WES, but by 2017, three payers from the original registry payers did. And in 2017, 8 of the 15 payers covered WES.

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Further Considerations

- Will identification of rare disorders not currently screened for by state NBS programs advance our understanding of conditions currently not recommended on the RUSP?
  - A difficult question!
  - Yes, but.

Further Considerations

- Eugenics Redux (sidebar by Diane Paul)

- Implications of adding “reproductive benefit” as a rationale for NBS
  - Moves beyond the best interest of the child
  - Will this be considered “state-sanctioned eugenics?”

Guiding Questions

- ❑ Which contextual forces shape our discussion of the utility of sequencing in newborns?
- ❑ Under what circumstances should newborns be sequenced?
- ❑ How should state-mandated newborn screening programs use sequencing?
- ❑ What role should parents play in determining how sequencing information about their infant is used and stored?
- ❑ Should sequencing be part of routine pediatric practice?