Whole Genome Sequencing in Newborn Screening

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Contention

- There is a fundamental mismatch between the technical approach (whole genome sequencing) and the screening context (mandatory state public health programs).

Screening Efficacy

- There are remarkably few effective population screening programs
  - PAP smears/ hypertension/ cholesterol
  - Mammography?
  - PSA?
- Effective programs for uncommon conditions rely on screening tests that have high clinical sensitivity and specificity

Shotgun testing

- We teach our students to avoid “shotgun” testing
  - Targeted testing in high-risk populations has much higher positive predictive value
  - “High risk” determined by a history and physical or subpopulation characteristics

Newborn Screening Programs

- Designed to detect carefully selected conditions through universal population screening using high throughput sample analysis within a system that efficiently delivers confirmatory testing and early clinical interventions.
- Newborn screening is a *system*: all elements must work together

Evidence-Based Process

- Secretary's Advisory Committee on Heritable Diseases in Newborns and Children
  - Chartered in 2003
  - Provided recommendations to the Secretary of DHHS about conditions to include on the Recommended Uniform Screening Panel (RUSP)
  - Each condition evaluated through a detailed evidence review process
    - Test characteristics
    - Clinical validity and utility
    - Preparedness of public health programs

The First Step: Evidence

- The first step is to demonstrate that WGS/WES has net benefits as a primary screening tool in asymptomatic individuals
  - Only then could the enormous undertaking of population screening be considered

Whole Genome/Exome Sequencing in NBS

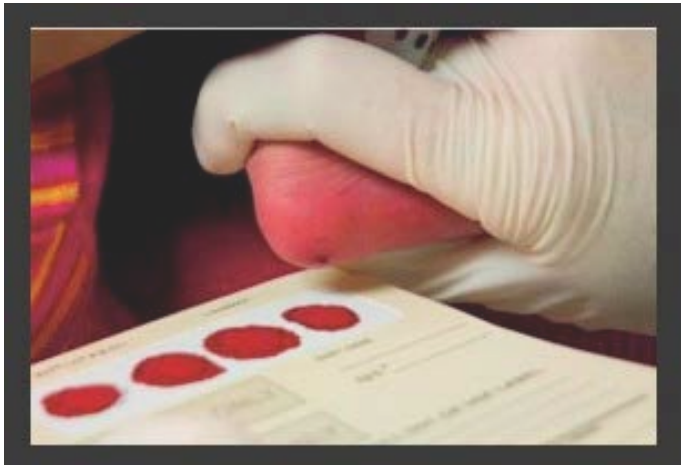
- What would the purpose(s) of WGS/WES in newborn care?
  - Primary screening tool for all newborns?
  - Primary screening tool as commercial supplement to state programs?
  - Second tier testing in initial positive or affected infants?
  - Identify new genetic variants that inform prognosis or treatment in selected populations of sick children?

Genome Scale Sequencing vs DNA-Based Platforms

- Almost all current NBS tests are **not** DNA based
- To date, other biomarkers have been more sensitive and specific
- As more about the genetic basis of targeted conditions in known, more tests may be DNA-based
- If so, by no means clear that genome scale sequencing will be necessary or appropriate compared to targeted testing

Basic Program Structure

- All states except Wyoming and the District of Columbia have “MANDATORY” newborn screening programs
- Most states (43) permit parents to opt-out for religious or philosophical reasons



WGS/WES using Dried Bloodspots

- Challenging but feasible
- High throughput is a challenge
  - New York state = 700 births/day
  - California = 1500 births/day

What is Our Obligation to Disclose Clinically Relevant Results?

- WGS/WES could entail a large expansion of conditions detected
  - A host of risk-conferring variants
  - Carrier states? (Current carrier screening using large panels detects carrier states in 20% of patients)
  - Variants associated with common conditions such as CVD, diabetes, mental health disorders?

Burdens of True Positives

- ACMG list of 56 genes/24 conditions
  - Estimates that 1% - 4% of WGS/WES will have positive findings
  - 4 million infants born per year in US
  - 1% of 4 million = 40,000 infants with positive results
    - 3x - 4X the current rate of true positive results in current NBS programs
    - Much larger if carrier states, etc. are reported
  - No infrastructure to manage disclosure and counseling at this volume

Burdens of False Positives

- WGS/WES would generate substantial number of false positives and variants of unknown clinical importance
  - Burden to laboratory and clinicians to ascertain clinical validity of numerous variants
    - Making a call on a single unfamiliar variant may take hours of time by highly trained personnel
  - Burden to parents and care providers if disclosed

Solomon et al. Molecular Syndromology 2012;3:59-67

Burdens of Cost

- "Kit fees" for NBS are about $100 per newborn (varies by state)
  - State charges the birth facility
  - Birth facility charges the patient or patient's third party payer
  - Fee bundled in delivery charges
- Incremental charges for new tests are often in the $2 - $5 range per newborn (increases often require legislative approval)
- System is cost-neutral for the state but enables uniform screening of newborns regardless of the ability to pay

Burdens of Cost

- If the total cost = $1000 per infant =>

$4 billion dollars

per year for sequencing

- Additional costs for
  - Data analysis
  - Contact and follow-up of initial positive results
  - Confirmatory testing

Parental Permission

- Given the additional burdens and uncertain benefits, WGS/WES in NBS could not be justified under a state mandate
- An informed consent process would be necessary
  - Who would do this?
  - How would this be done?

American Society of Human Genetics Statement

- *"At the present time, genome-scale sequencing is not indicated for screening in healthy children. Accordingly, genome-scale sequencing is not indicated for the purposes of clinical newborn screening at this time. In the research setting, genome-scale sequencing in newborns for screening purposes can be justified as part of carefully developed protocols for better understanding the potential benefits and risks of this technology in this context."*

Botkin JR, Belmont JW, Berg JS, Berkman BE, Bombard Y, Holm IA, Levy HP, Ormond KE, Saal HM, Spinner NB, Wilfond BS, McInerney JD. ASHG Statement: Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Journal of Human Genetics 2015 Jul 2;97(1):6-21.

Federal Policy Change

- *Newborn Screening Saves Lives Reauthorization Act of 2014* (Public Law No: 113-240)
  - **TEXT OF SEC. 12. INFORMED CONSENT FOR NEWBORN SCREENING RESEARCH.**
  - *(a) IN GENERAL.—Research on newborn dried blood spots shall be considered research carried out on human subjects meeting the definition of section 46.102(f)(2) of title 45, Code of Federal Regulations, for purposes of Federally funded research conducted pursuant to the Public Health Service Act until such time as updates to the Federal Policy for the Protection of Human Subjects (the Common Rule) are promulgated pursuant to subsection (c). For purposes of this subsection, sections 46.116(c) and 46.116(d) of title 45, Code of Federal Regulations, shall not apply.*

Newborn Screening Saves Lives Reauthorization Act

- Interpretation
  - Research with newborn screening dried bloodspots is humans subjects research whether or not they are de-identified
  - Waiver of parental consent for research use is not permissible
  - This law will be superseded by anticipated changes in the Common Rule

NBS Saves Lives Act

- New consent provisions difficult to implement because no consent for NBS
- Post partum period is short, hectic, and with many clinical priorities
- Consent process likely to result in a substantial decrease in available DBS for research

NBS Saves Lives Act

- Selective intrusion of Congress into the domain of human subjects protections without broad dialogue
- Focused on one domain (NBS) but potentially applicable to a broad range of secondary research with biospecimens
- Suggests disagreement with current regulatory approach

Federal Notice of Proposed Rulemaking (NPRM) for Human Subjects Regulations

- NPRM proposed to extend the definition of "human subject" to biospecimens whether or not they are identifiable
- Broad consent from individuals would be necessary before biospecimens could be used for research
  - Criteria for waiver of consent would be limited

Conclusions

- WGS/WES for NBS as a primary screening tool would:
  - Fundamentally change the structure and philosophy of these effective programs
  - Dramatically increase cost
  - Dramatically increase burdens of false and ambiguous information to parents and clinicians
  - Confer uncertain benefits until robust systems in place to conduct research and longer-term follow-up

Conclusions

- Population screening is notoriously complex and relatively few instances of highly effective population screening programs
- Current NBS system is highly effective for selected conditions, but struggles with funding, coordination between system components, and lack of adequate research

WGS/WES in NBS

- Makes *good* sense as a research tool to better understand complex, uncommon conditions in infants and children

- Makes no sense now, nor likely in the future, as a primary screening tool under state mandated programs

WGS/WES in NBS

- Parental permission will be required for sequencing
- A permission process will be complex and time consuming
- A permission process raises the probability that a substantial subset of parents will decline testing, reducing the efficacy of these important public health programs


Thank You!