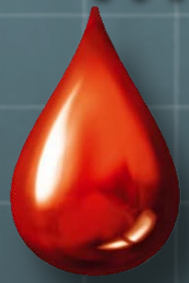
Whole Genome Sequencing in Newborn Screening:
What are we testing for?



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THE UNIVERSITY OF UTAH

The Human Genome

February, 2001

Relevant Questions

- Given the power of genomic technology to conduct WGS/WES…
- How can this technology be best used to benefit children?
- Might this technology have an application in newborn screening?

If WGS is the new hammer…

Does newborn screening look like a nail?

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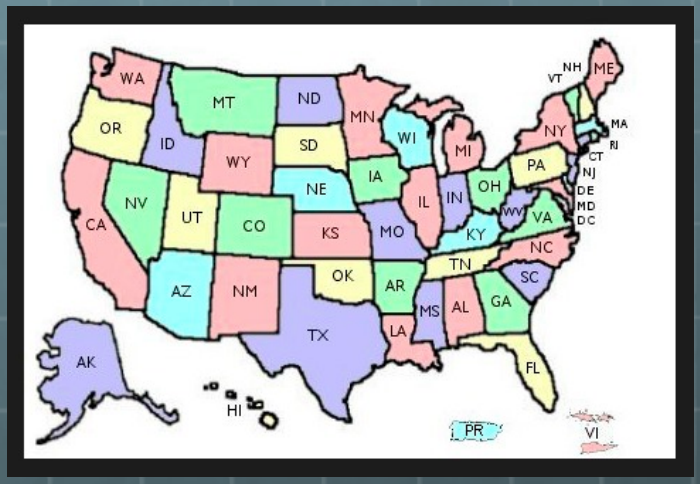
United States



- 4 million newborns screened per year in all states, districts, and protectorates
- Single largest application of genetic testing
- 50th anniversary of NBS programs in US!
- 12,500 infants per year diagnosed with a condition through newborn screening

Newborn Screening

- One of the great public health achievements of the modern era
- Early identification of infants with genetic, metabolic, endocrine, and infectious disorders
- Rapid expansion of conditions targeted
  - 2003: all but 4 states screening for only 6 conditions
  - 2013: all states screening for more than 30

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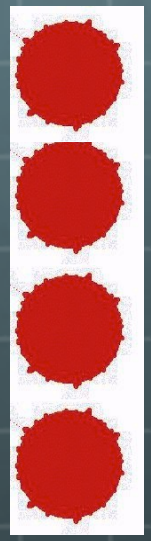
Basic Program Structure



- Blood collected from heelstick in newborns
  - Preferably after 12 hours of age
  - Before 6 days of age
  - Before a transfusion
- Sent to state lab for analysis
- Results returned to hospital and physician of record for the baby
  - Results within 2 weeks
- 98 - 99% of newborns are screened in each state
- Cost about $80 - $110, charged to families as part of delivery in most states

Basic Program Structure

- All states except Wyoming and the District of Columbia have MANDATORY newborn screening programs
  - Parental permission not necessary for screening
  - Justification is the benefit of screening to the infant
- Most states (43) permit parents to opt-out for religious or philosophical reasons
  - Ability to opt-out not effectively communicated to parents

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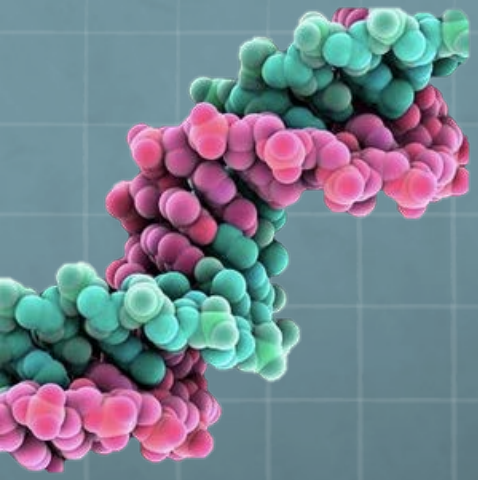

Whole Genome/Exome Sequencing in NBS

- What would the purpose of WGS/WES in this context?
  - Primary screening tool for all newborns?
  - Primary screening tool as commercial supplement to state programs?
    - Newborn screening vs screening of newborns
  - Secondary testing of affected infants
    - Identify genetic variants that impact treatment or prognosis in affected children

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WGS/WES using Dried Bloodspots

- Challenging but technically feasible
- High throughput would be a challenge as a primary screening tool
  - New York state = 700 births/day
  - California = 1500 births/day

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Challenges

- Multiplex platforms foster rapid expansion of programs beyond the evidence base supporting efficacy
  - ACMG report in 2006 advocating a uniform national panel
    - Tandem Mass Spectroscopy is a multiplex platform
    - Extra "points" to conditions on multiplex platform
    - Advocated 29 conditions and 25 secondary conditions
    - Very limited data on many conditions
    - Assumed an ethical obligation to disclose findings
  - Conditions adopted that would not be adopted with a condition-specific review

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Challenges

- Research on rare conditions faces serious obstacles
  - Uniform protocols and data pooling from multiple centers
  - Need for long-term follow-up to assess efficacy of interventions

Challenges

- Newborn screening (NBS) are state based programs that ensure equal access
  - Economic limits to expansion
- NBS is mandatory in most states
  - Requires clear evidence of benefit to the child

Ethical and Policy Challenges

- **The scope of conditions to be targeted by NBS**
  - **Duane Alexander and Peter Van Dyke (Pediatrics 2006)**
  - ***"The technology could be expanded to screen for additional disorders as mutational analysis or other multiplex technology becomes available, with decisions being based more on what not to screen for (perhaps Huntington disease) than on what to include."***

Wilson and Jungner

- ***"The central idea of early disease detection and treatment is essentially simple. However the path to its successful achievement ... is far from simple although sometimes it may appear deceptively easy."***

Synthesis of emerging screening criteria proposed over last 40 years

- Program should respond to a recognized need
- Objectives should be defined at the outset
- Defined target population
- Scientific evidence of program effectiveness
- Integrate education, testing, clinical services and management
- Quality assurance to minimize risks
- Ensure informed choice, confidentiality
- Promote equity and access for entire target population
- Evaluation should be planned from the outset
- Overall benefits should outweigh the harms

Andermann A, Bull WHO 2008;86:317

Institute of Medicine Report 1994

- ***"The committee recommends that newborn screening should not be undertaken unless there is a clear, immediate benefit to the particular infant being screened."***

Ethical and Policy Challenges

- Evidence-based decision-making
  - Historically, wide variation from state to state
  - Since 2006, Secretary's Advisory Committee for Heritable Diseases in Newborns and Children
    - Much more rigorous process for condition-specific decisions on inclusion in the Recommended Uniform Screening Panel (RUSP)

Secretary's Advisory Committee on Heritable Diseases in Newborns and Children

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.	Feasibility	HIGH or MODERATE
		HIGH	**A4** There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.				----
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.				----
NEG Benefit	Certainty	MOD/HIGH	**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.				----
⋮	Certainty	LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.				----

Population Screening for Children

- **USPSTF Recommendations**
  - PKU, CH, SSD: Grade A
  - Newborn hearing screening: Grade B
  - Iron deficiency: Grade I (insufficient evidence)
  - Lead: Grade D for average risk children
  - Testicular cancer: Grade D
  - Newborn hip dysplasia: Grade I

Population Screening in Adults

- USPSTF Recommendations
  - Colon cancer: Grade A for age >50
  - PAP smears: Grade A, women 21-65
  - Hypertension screening: Grade A
  - Tobacco use screening: Grade A
- Marginal Efficacy
  - Mammography: Grade B (biennial age 50-74)
  - PSA screening: Grade D
  - Osteoporosis: Grade B for women >65
  - Behavioral counseling for CVD: Grade C

Challenges

- What are we screening for?
  - For established conditions on NBS panels
    - Not clear that genetic data is more sensitive or specific than current test modalities
    - Cystic fibrosis – IRT is primary target despite knowledge of genetics
  - New conditions under some consideration may use DNA-based testing
    - SMA, Fragile X
    - Would be done as targeted test, not WGS/WES

Challenges

- What are we screening for?
  - WGS/WES would enable large expansion of conditions targeted
    - A host of uncommon conditions (ACMG list of 57 genes/ 24 conditions)
    - Carrier states
    - Cancer syndromes (adult and pediatric)
    - Variants associated with common conditions such as CVD, diabetes, mental health disorders

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Burdens of True Positives

- ACMG list of 57 genes/24 conditions
  - Estimates that 1% 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
    - Much larger if carrier states, etc. are reported
  - No infrastructure to manage disclosure and counseling at this volume

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Burdens of True Positives

- WGS/WES would generate information on adult onset conditions
  - ACMG 2013 recommends reporting these to parents for parental benefit
- Represents a major change in the philosophy of NBS programs
  - Traditional emphasis on immediate benefits for the child
  - Avoidance of genetic testing for adult onset conditions in children
    - Respect for future autonomy of the child
    - Uncertain psychological impacts for children and families

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Burdens of False Positives

- The most important adverse consequence of population screening
  - Patient anxiety
  - Cost of follow-up testing
- Positive predictive value of current tests = 1% to 40%
- Substantial portion of parents (10 – 20%) have residual anxiety about health of the child following false positive result

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Burdens of Ambiguous Results

- **WGS/WES would generate substantial number of variants of unknown clinical importance**
  - **Burden to parents and care providers if disclosed**
  - **Burden to laboratory and clinicians to ascertain clinical validity of numerous variants**

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
- System is cost-neutral for the state but enables uniform screening of newborns regardless of the ability to pay

Burdens of Cost

- WGS/WES for NBS
  - Assume $1000 per newborn for sequencing
  - Additional costs for data analysis…
  - Additional cost for family notification and follow-up…
  - Additional cost for confirmatory testing…

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

$4 billion dollars

per year for sequencing

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Conclusions

- Current NBS system is highly effective for some conditions, but struggles with funding, uncertain benefits for other conditions, lack of adequate research
- Population screening is notoriously complex and relatively few instances of highly effective population screening programs

Conclusions

- WGS/WES for NBS as a primary screening tool would:
  - Fundamentally change the philosophy of the programs
  - Drastically increase cost
  - Drastically increase burdens of false and ambiguous information to parents and clinicians
  - Confer uncertain benefits without a much more robust system to conduct research and longer-term follow-up

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Conclusions

- Given the additional burdens and uncertain benefits, WGS/WES in NBS could not be justified under a state mandate
- Implementation of an informed consent process necessary
  - Could be conducted as commercial supplement with consent
  - Could be conducted prenatally for adequate time and counseling

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Lewis Thomas, M.D.

(1913-1993)

- The Technologies of Medicine
  - Non-technologies
  - Decisive technologies or high technologies
  - Halfway technologies

WGS/WES in NBS

- Makes little sense as a primary screening tool under state mandated programs
- Makes *enormous* sense as a research tool to better understand the genetics of a host of important, complex, uncommon conditions
- We need better research *systems* to ascertain short and long term benefits of screening technologies

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Thank You!