Gene Sequencing in Newborn Screening: Covering the Bases of Education and Follow-Up

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Outline

- Education
- Personnel
- Case Examples
- Considerations
EDUCATION: OUR BASELINE
Health Literacy – where are we?

• Only 12% of adults have proficient health literacy\(^1\)
  – Affects all races and ethnicities; though some more than others

• Almost 10% of the US population is considered Limited English Proficient\(^2\)

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\(^1\) National Assessment of Adult Literacy; \(^2\) Migration Policy Institute
Genetic Health Information

• Often derived from television
  – House, CSI, Gray’s Anatomy, etc.

• Misconceptions
  – Timeliness
  – Absoluteness
  – High expectations of capabilities
Current State of Newborn Screening Education

• ‘The PKU Test’ lives on...
• Low understanding of what screening is and is not
• Programs rely on providers as mouthpieces
  – Variable success pre- and post-analytically
EDUCATION: FUTURE STATE
Gene Sequencing: General Education

- Awareness of genetic exceptionalism
- Hesitancy around genetic testing
  - BabySeq experience
- “Knowledge is Power”...
  - But... “Ignorance is Bliss”
Gene Sequencing: Education of Providers before Starting

- Physicians indicate an overall lack of knowledge and confidence in discussing genetic risk.¹
- Newborn screening-specific needs:
  - Still requires 1st tier – false negatives still possible
  - Whether carrier status will be reported and how
  - Will notification be made on biochemical result while DNA pending

¹ Mikat-Stevens, et al., Genetics in Medicine (2015) 17, 169-176
Gene Sequencing:
Pre-Analytical Education

• Likely largely unchanged
  – Methodologies not typically discussed
• Need to discuss increased possibility of detecting carrier status/ambiguous results
  • Dependent upon reporting paradigm
• Prior awareness of NBS makes abnormal result reporting easier
Gene Sequencing: Post-Analytical Education

- What do we know about specific variants found
- Need to confirm molecular results clinically
  - Mixed thoughts on this
- Genotype does not always dictate phenotype
  - Will need other diagnostic testing as well
Gene Sequencing: Post-Analytical Education

- How to communicate to parents
  - Risk communication
  - Genetic information
- Difference between carrier and disease states
- Implications for other family members
PERSONNEL NEEDS
The Follow-Up Team

- Need for staff comfortable in discussing genetic information with providers (and parents)
  - Inheritance
  - Phasing
  - Deletions, duplications, conversions, points
  - Homozygosity, heterozygosity
The Follow-Up Team

• Importance of communication between lab, follow-up, and sub-specialists
  – Work together to determine and update variant interpretations
  – Responsibility to check databases?
  – Increased importance to participate in long-term registries to help characterize variants
Notification and Follow-Up Protocol

• Likely will need to change:
  – More important to talk directly with primary care provider (avoid telephone game)
  – Consider fax of information first

• Development of follow-up protocols for VUS’s

• Need standardization amongst programs
  – Unified genetic nomenclature
CASE EXAMPLES:
THE SIMPLE, COMPLEX, AND DOWNRIGHT CRAZY
“Simple” Case Example: Cystic Fibrosis

• Elevated IRT (281.1 ng/ml) followed by DNA
  – Shows homozygous ΔF508
• ΔF508
  – Known CF-causing allele with likely pancreatic insufficiency
• Enzymes should be started as soon as possible with sweat test confirmation < 4 wks of age
“Complex” Case Example: Cystic Fibrosis

• Elevated IRT (67 ng/ml) followed by DNA
  – Het for 2 variants: S1255X (ex. 19) and S1255X (ex. 20)
• CFTR2 indicates that S1255X (ex. 20) causes CF when found with another CF-causing variant
  – S1255X (ex. 19) not listed

• How should this result be handled?
“Complex” Case Example: Cystic Fibrosis

• Treat as ONE variant:
  – S1255X (ex. 19) and S1255X (ex. 20) act as a haplotype
• Enzymes don’t need to be started
• Sweat test results = 4 and 5 mmol/L
“Complex” Case Example: Cystic Fibrosis

• Elevated IRT (≥62 ng/ml) followed by DNA
  – Het for 2 variants: ΔF508 and L32M
  – Initial sweat test <60 mmol/L
  – CRMS designation

• Conversion can occur (both in sweat test and fecal elastase)
  – Repeat sweat test now >60mmol/L
  – Now meets Classic CF diagnostic criteria

• CF relies on much more than genotype for diagnosis
  – CRMS represents a diagnostic odyssey

1 Salinas, et al., PLOS ONE (2016) 11(5)
Case Example: CAH

• CAH has relatively high FPR and FNR – molecular testing appealing

• \textit{CYP21A2} gene in chromosomally complex region – 30kb deletion, gene conversion, pseudogene, etc.

• Phenotype is typically dictated by the less severe of the two variants
Case Example: CAH

• Due to complex region, multiple variants are common (~13% in MN population)

• CAH-0028: 8 variants found
  – Homozygous I727N; homozygous V281L, het I236N, het V238E, het M239K, het L307fs
Case Example: CAH

- Phasing exceedingly important to understand configuration of variants!
Case Example: CAH

• What is the phenotype?
• Patient actually has SW CAH due to NC variants being in cis with other variants
X-ALD: A Discussion

- X-linked disorder affecting primarily males
  - Most females will show symptoms later in life
- Between 4.1% and 19% de novo rate\(^1\)
- No relevant genotype-phenotype correlation
  - Addison’s disease only
  - Adrenomyeloneuropathy
  - Celebral X-ALD

X-ALD: A Discussion

• >700 known variants; increasing likelihood of detecting VUS
• Genotype does not affect treatment or management
• May help distinguish X-ALD from other peroxisomal disorders
FUTURE CONSIDERATIONS
Gene Sequencing Education and Follow-Up: Challenges

• Ever increasing need to educate providers
  – Understanding of sequencing technology
  – Understanding of genetic terms and implications

• Expanded role of primary care in ongoing monitoring for ambiguous/late-onset results
Gene Sequencing Education and Follow-Up: Challenges

• Need to ensure prepared follow-up workforce
• Ensuring variant information reaches providers
• In states with few clinical Genetic Counselors, will programs need to take this on?
• Ambiguity and extended follow-up – when is a diagnosis complete?
Gene Sequencing Follow-Up and Education: Opportunities

Newborn Screening-specific:

• Potential for earlier diagnosis

• Potential for more appropriate treatment
  - ... or avoidance of inappropriate treatments

• Potential for lower FPR and FNR
Gene Sequencing Follow-Up and Education: Opportunities

• Contribute to knowledge and understanding
• Addressing health equity and access
  – Don’t need pre-authorizations
  – Provides potentially needed information to families who might otherwise not be able to afford it
• How does the addition of gene sequencing contribute to the mission of NBS?

• What is the impact to the SYSTEM of adding gene sequencing
  – To affected
  – To unaffected
  – To unknown
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