Mutation panel vs sequencing data: pros and cons

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Gene Sequencing in Public Health Newborn Screening
Atlanta, GA
Feb 16, 2017
Star TREK the Next Generation
Case 1

Term infant
DOL 3 NBS specimen received
NICU infant
Elevated IRT
None of 39 CFTR mutations
Case 1

At about 3 years of age

Multiple GI issues

Sweat Test result: Abnormal

Reviewed NBS results

Sequencing requisitioned
Case 2

Term infant

DOL 2 NBS specimen received

NICU infant with likely bowel obstruction and sib of Case 1

Elevated IRT

None of 39 CFTR mutations
Might this have been different?

- Failsafe IRT
- IRT ALONE
- IRT/IRT
- IRT/DNA
- IRT/DNA/EGA
- IRT/EGA
Might this have been different?

- Failsafe IRT
- All single mutation observations go to sequencing
- All IRT elevations go to sequencing for targeted pathogenic mutations
Might this have been different?

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- All single mutation observations go to sequencing
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- All IRT elevations go to sequencing
Current Purposes of DNA in NBS
(data generated prior to full diagnostic evaluation)

1. Enhance capacity of screening for conditions not otherwise included...
   TREC assay for SCID: molecular in **FIRST TIER**

2. Enhance specificity of 1st tier test....
   CFTR mutation assay after IRT: DNA test is in **SECOND TIER**

3. Supplemental just-in-time
   Increase available information to aid diagnostic evaluation...
   GALT mutation assay: molecular in **SECOND TIER**
Current Purposes of DNA in NBS
(data generated prior to full diagnostic evaluation)

1. Enhance capacity of screening for conditions not otherwise included…
   TREC assay for SCID: molecular in FIRST TIER

2. Enhance specificity of 1st tier test….
   CFTR mutation assay after IRT: DNA test is in SECOND TIER

3. Supplemental just-in-time
   Increase available information to aid diagnostic evaluation…
   GALT mutation assay: molecular in SECOND TIER
Genotype Distribution Among 450 New England CF infants relative to common allele

- DF508/DF508
- DF508/other
- no DF508
Proportion of New England CF Infants shown to carry one or two mutations by newborn screening
Genotype Distribution Among 300 Massachusetts CF infants relative to common allele

- DF508/DF508
- DF508/other
- no DF508
Carriers confirmed after diagnostic testing
- identified in order to find CF

~5% will have two carrier parents
Case 1 and Case 2: Might this have been different?

- Failsafe IRT
- All single mutation observations go to sequencing
- All IRT elevations go to sequencing for targeted pathogenic mutations
- All IRT elevations go to sequencing
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Anticipating future applications of genomic technology in NBS

- Expand the list of treatable conditions that can be screened
- Strengthen interpretations of current screening results
- Provide that single black box?
- Generate a knowledge base from which we develop other (non-genomic) screening assays
To be determined:

Analytic validity
- Promising – known issues with large deletions, rearrangements, copy number variants

Analytic validity in high throughput
- Promising – Scan or target...

Clinical validity
- Ongoing learning...complex traits...
Challenges: the Report

Technical Report
- CLSI demographics
- Reason for testing
- Disease locus tested
- Result is In Range or Out of Range

Out of Range:
Number of DNA sequence variants detected by the screen
Report Content

- **Names** of DNA sequence variants *detected* by the screen (colloquial and (?) HGVS)
- **Names** of DNA sequence variants *TESTED*.

nomenclature
- colloquial: Delta F508
- HGVS: c.1521_1523delCTT

Human Genome Variation Society
http://www.hgvs.org/
Newborn Screening is …

a public health program that provides an opportunity for early identification and early treatment of infants with conditions that otherwise would go unrecognized prior to irreversible clinical damage.