Genomic Sequencing in Public Health Newborn Screening—Hopes and Challenges

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Disclosures

I have no financial interests to disclose.

The opinions presented are my own, and not the opinion of any other organization, entity or individual.

Why focus on newborn screening?

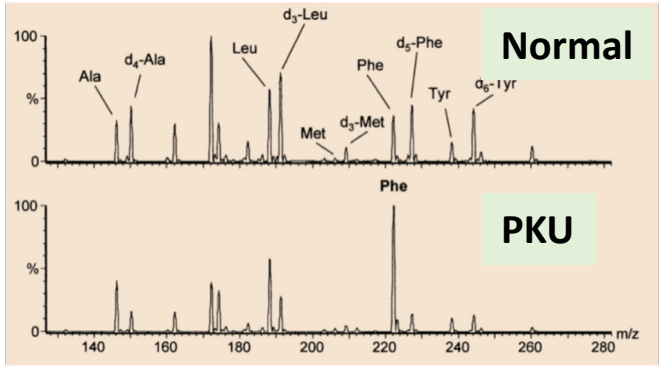
- Newborn screening is already the largest genetic screening program in the country.
- The newborn period can be an ideal interval to identify genetic disease and begin treatment before symptoms develop.

Why don’t we sequence all newborns, identify all treatable genetic diseases, and start treatment right away?

Current newborn screening for metabolic disorders is based on blood biochemical metabolites

Dried blood spots

Tandem Mass Spectrometry (MS/MS) biochemical profile



Positive screens lead to follow-up and diagnosis in metabolic centers

~500,000

babies per year born and screened in California

48

types of metabolic disorders are screened by MS/MS

sensitivity > 99%

specificity > 99%

~150

newborns per year are diagnosed with some metabolic disorder

State responsibilities for Newborn Screening

General Public Health Considerations

- Good stewardship
- Public Interest
- Universality
- Equity
- Trustworthiness

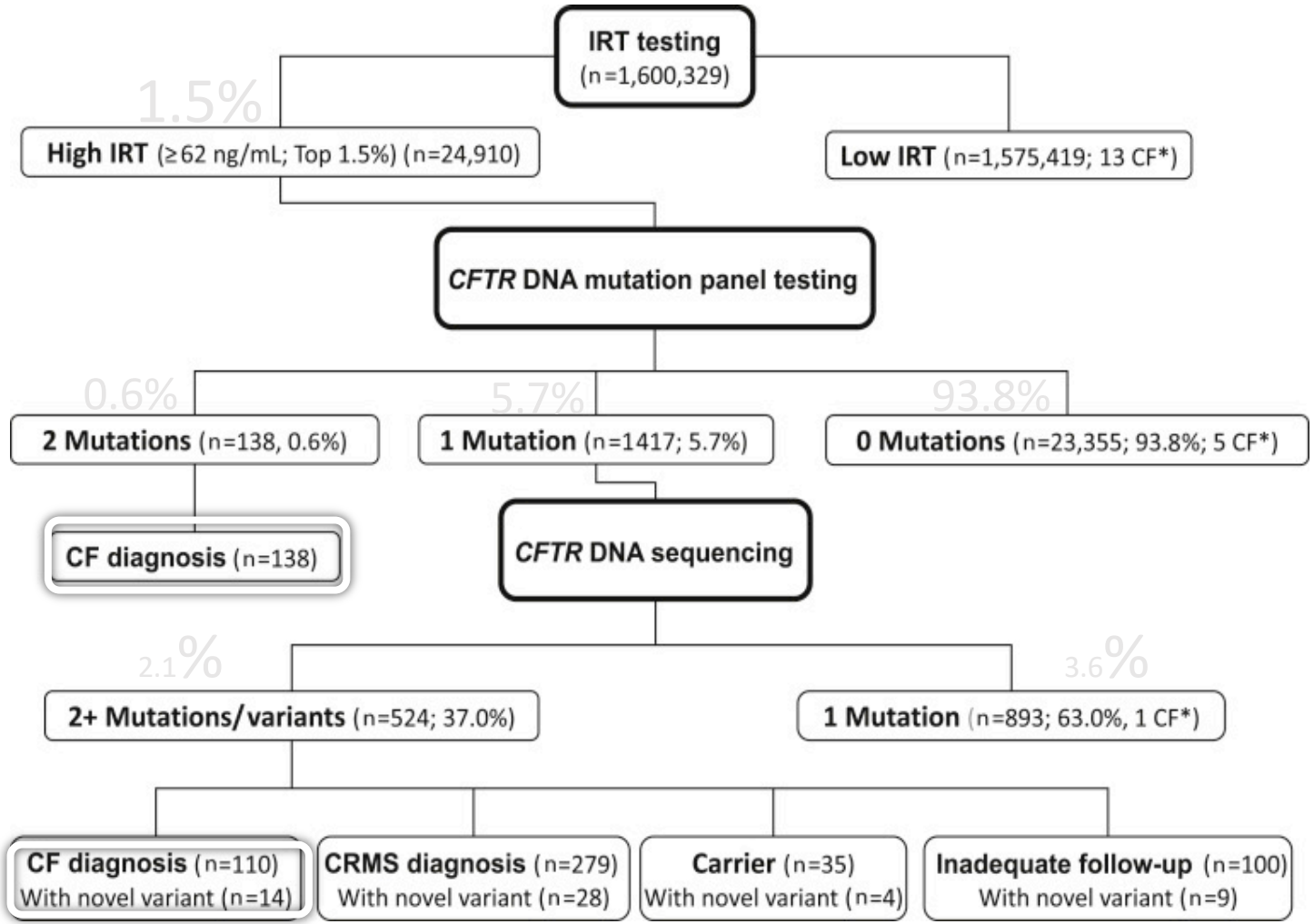
Specific NBS Considerations

- Target disorders
  - Serious
  - Urgent
  - Treatable
- Screening performance
  - Detection rate
  - False positive rate
  - Turn-around-time
  - Through-put

Gene sequencing is in wide use in newborn screening— after an initial positive biochemical test

- To reduce the false positive rate
  (for example, screening for cystic fibrosis)
- To aid in differential diagnosis
  (for example, X-linked adrenoleukodystrophy)

Secondary Use: Sequencing to Reduce False-Positive Rates with Cystic Fibrosis as a Model



Prach et al. J Mol Diagn. 2013 Sep; 15(5): 710–722.)

Secondary Use: Sequencing to Narrow Differential Diagnosis: Adrenoleukodystrophy

- In screening for adrenoleukodystrophy (ALD), there are two tiers of biochemical assays. Every baby who is positive for both is referred for follow-up. There are multiple possible genetic causes of the biochemical elevations.
- Sequencing of *ABCD1* provides informative results for the follow-up, to begin to distinguish between ALD and other possible causes of the biochemical elevations (primarily other peroxisomal disorders).

Genetic sequencing for primary population screening

Sequencing as Primary Population Screening when there is no other test

- There are many genetic disorders that have the characteristics of newborn screening disorders, except there is no test other than sequencing
- "Binning" by the UNC NEXUS group have identified 822 gene-disease pairs of which ~466 meet NBS criteria for screening by sequencing. These disorders include current NBS conditions, as well as other disorders with onset in infancy or in childhood that have treatment, monitoring, and/or medical management that can potentially improve clinical outcomes

Roman et al. AJHG Volume 107, Issue 4, 1 October 2020, Pages 596-611

The genetic screening dichotomy

When there IS a diagnostic test

- High sensitivity (do not miss any cases).
- Consider referring cases with 1 pathogenic variant + 1 VUS
- Additional evidence for VUS classification

When there is NO diagnostic test

- High specificity (do not refer any case with any degree of uncertainty).
- Refer only cases homozygous for a known pathogenic variant.

Sequencing for Primary Population Screening--Challenges

- Performance (Sensitivity and Specificity).
  - Analytic Validity of Results: Large scale deletions can be a significant source of disease in some disorders (e.g. Krabbe disease) and the pipeline must be able to detect CNVs
  - Clinical Validity of Results: Sensitivity and specificity depend on establishing comprehensive gene-disease relationships and being able to classify more VUSs as pathogenic variants.
  - Racial/Ethnic disparities in variant classification

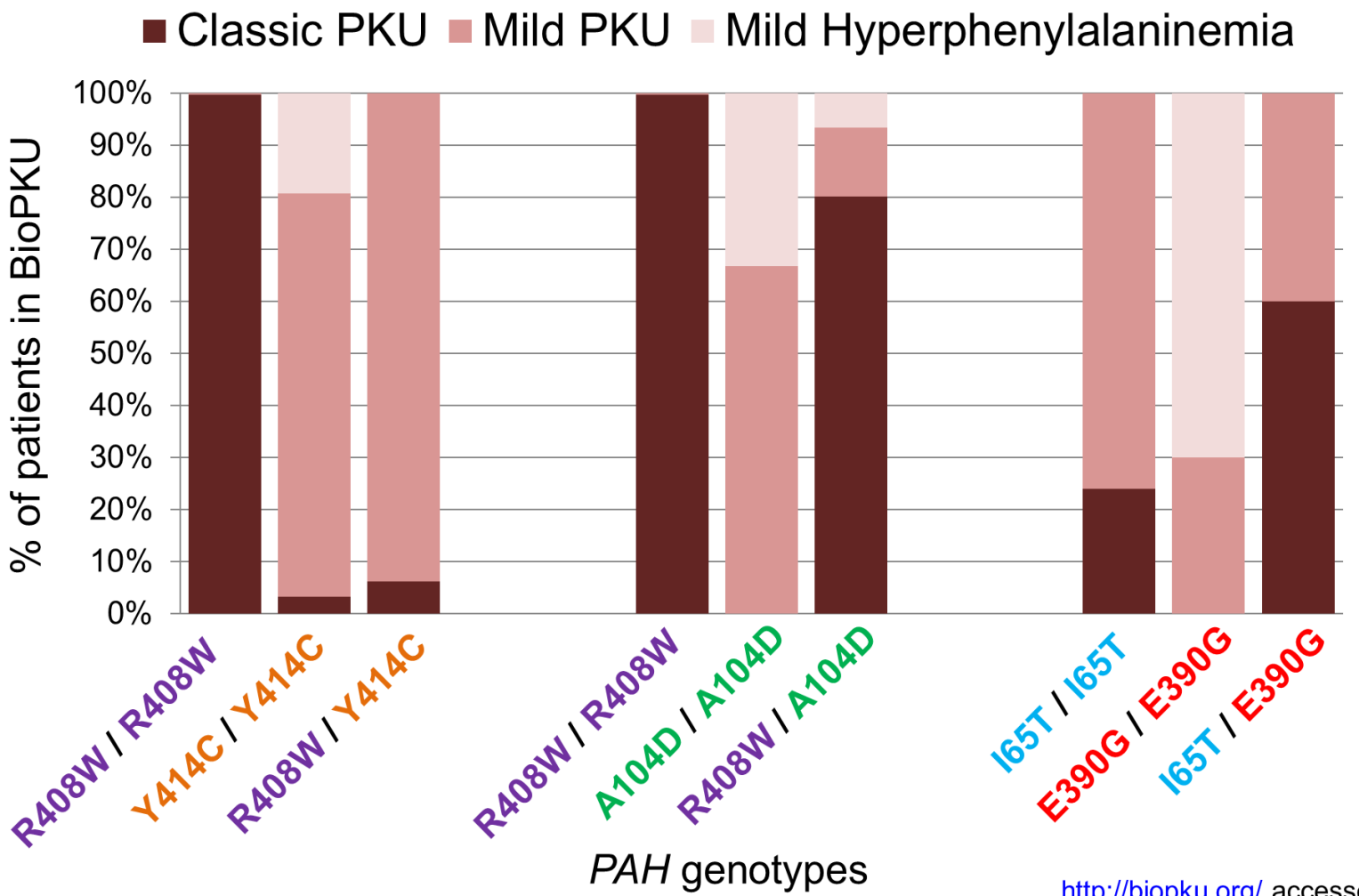
Racial and ethnic disparities in diagnostic efficacy of comprehensive genetic testing for sensorineural hearing loss

- 240 pediatric patients with sensorineural hearing loss of unknown etiology who underwent genetic testing
- 3.8 ± 2.1 variants detected per patient; not different between White/Asian and Hispanic/Black cohorts.
- Variants identified in Hispanic and Black children were less likely to be classified as pathogenic/likely pathogenic than in White/Asian subjects (15% vs. 24%, $p < 0.001$)
- Hispanic and Black children were less likely to have a definite genetic diagnosis that were White and Asian subjects (10% vs. 37%, $p < 0.001$)
- (Similar data exist for Hereditary Cancer Syndrome Genes)

Florentine et al. Hum Genet. 2022 Apr;141(3-4):495-504.

Genotypic complexity

The disease severity for compound heterozygotes not always obvious from individual allele severities



http://biopku.org/ accessed Apr 2016

Summary

- **Compared to current NBS, sequencing used as primary screening modality costs much more per patient than NBS and suffers from reduced analytical sensitivity and reduced clinical sensitivity due to VUSs, which exacerbates racial/ethnic disparities by reducing screening sensitivity**
- **Secondary sequencing is a powerful method for resolving False Positive NBS results and for defining the diagnosis when NBS implicates multiple disorders**
- **Primary sequencing holds much promise for NBS for disorders without a biomarker available – however, without definitive follow-up diagnostic testing available, false positives would need to be minimized, at the expense of sensitivity.**

Action Items

- Screening tests that distinguish early-onset from late-onset forms of disease.
- Diagnostic tests that can be applied after screening (*i.e*. pre-symptomatically).
- Sharing of variant data from patients identified through screening, rather than clinically
- Interpretation of compound heterozygotes.
- Pre-symptomatic clinical management of genetic disease.
- Disease characteristics in diverse populations.

Thank you for your attention