Diagnostic Yield of Metabolic Analyte-based Testing Panels

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BACKGROUND

- Newborn screening (NBS) is important for early detection of many inherited metabolic disorders (IMD).
- Due to the nature of NBS, presumptive positive results require further testing and confirmation.
- Early diagnosis and management of affected individuals can effectively prevent the morbidity and mortality associated with IMD.
- The metabolic analyte-based genetic testing panels provide a unique option for clinicians to achieve a diagnostic confirmation for the majority of metabolic diseases on the US Recommended Uniform Screening Panel as well as identify individuals with suspected IMD.
- In this study, we present data to substantiate the clinical utility of metabolic analyte-based panels.

METHODS

- This study cohort included 240 individuals suspected of having an IMD either from NBS or clinical assessment. There were 100 females and 140 males with the following age distributions: 2 years or younger (n = 187); 2–18 years old (n = 26); and 18 years or older (n = 27).
- A total of 24 differential diagnosis panels (Table 1) were offered based on the analyte(s), which were abnormal on biochemical or newborn screening tests.
- Genomic DNA samples were analyzed by next-generation sequencing to identify potentially clinically relevant genetic variants: pathogenic (P), likely pathogenic (LP), and variant of uncertain significance (VUS).
- Variant interpretation followed a five-tier classification system, which is compliant with the ACMG guidelines (PMID: 28492532).
- Depending on mode of inheritance of a patient's condition, identification of monoallelic (dominant) or bi-allelic (recessive) pathogenic or likely pathogenic variant(s) in a gene responsible for the observed biochemical or clinical phenotype was considered a "positive" diagnosis.

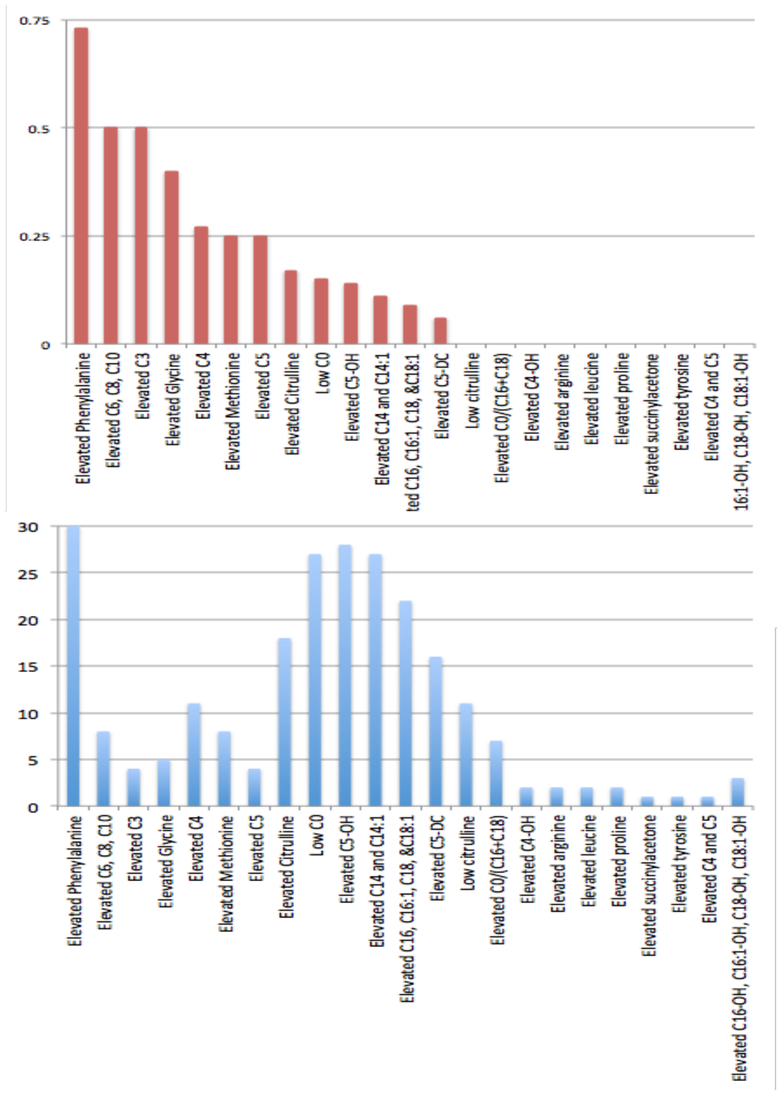
Table 1. List of analyte-based testing panels.

Panel	Gene count	Panel	Gene count
Elevated C0/(C16+C18)	1	Elevated C6, C8 and C10	1
Elevated C14 and C14:1	1	Low C0	1
Elevated C3	up to 16	Low Citrulline	3
Elevated C3-DC	1	Elevated Arginine	1
Elevated C4 and C5	7	Elevated Citrulline	up to 5
Elevated C4	3	Elevated Glycine	up to 62
Elevated C4-OH	5	Elevated Leucine	5
Elevated C5	2	Elevated Methionine	up to 6
Elevated C5-DC	1	Elevated Phenylalanine	6
Elevated C5-OH	13	Elevated Proline	2
Elevated C16-OH, C16:1-OH, C18-OH and C18:1-OH	2	Elevated Succinylacetone	1
Elevated C16, C16:1, C18, and C18:1	2	Elevated Tyrosine	3

RESULTS

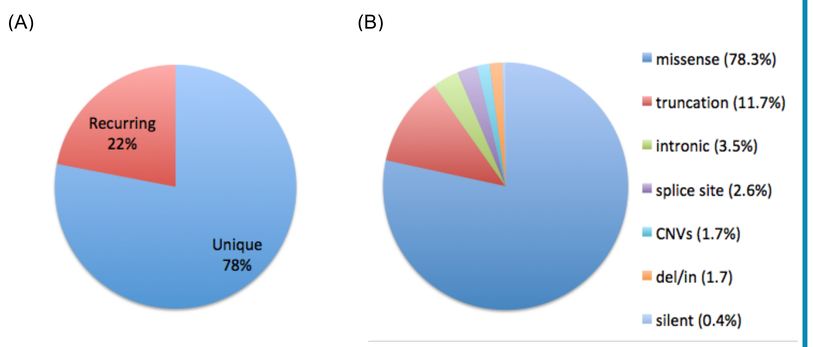
The combined diagnostic yield of all analyte-based testing panels was 23% (54/240).

Figure 1. Top: diagnostic yield; bottom: number of individuals with LP/P finding by panel.



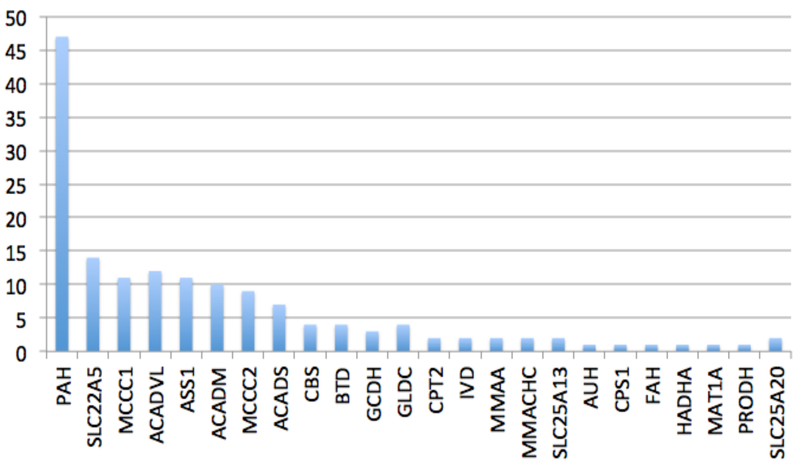
Panels with the highest diagnostic yields were: elevated phenylalanine (73%), elevated C6, C8, C10 (50%), elevated C3 (50%), and elevated glycine (40%). The bottom panel presents the number of individuals with at least one pathogenic variant identified.

Figure 2. Spectrum and proportional distribution of potentially clinically relevant variants identified in this study cohort by (A) novelty and (B) mutation type.



Overall, 240 potentially clinical relevant variants with classifications of VUS, LP, and P were detected.
(A) The majority of the variants are unique to our database.
(B) Missense and truncating variants dominate the mutation spectrum.

Figure 3. Frequency of LP/P variants detected in each gene.



CONCLUSIONS

- Metabolic analyte-based gene panels allow clinicians to quickly assess the entire spectrum of relevant diseases to confirm a diagnosis and avoid sequential testing, ultimately shortening the time to diagnosis and improving outcomes for patients.
- The combined diagnostic yield of metabolic analyte-based testing panels is 23% in this study cohort.
- Elevated Phenylalanine, Elevated C6, C8, C10, and Elevated C3 testing panels produced relatively high diagnostic yield. However, there is a significant portion of individuals in this study cohort who carry pathogenic variants without contributing to positive diagnostic yield. Further collection of testing data by increasing sample size and enhanced VUS resolution by collaborating with clinicians to collect detailed clinical phenotype information should improve the estimated diagnostic yield for these panels.

Disclosures: All authors are stockholders and employees of Invitae.