Gene Characterization: A Scientific Approach To Multi-gene Panel Testing Design

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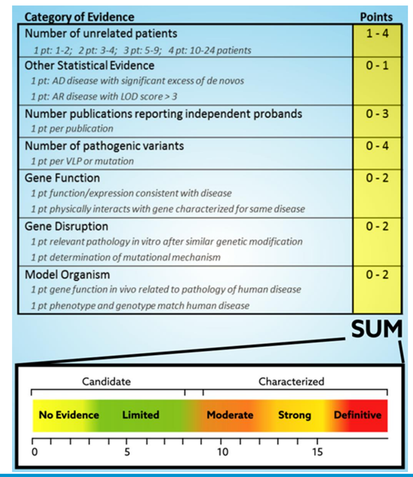
BACKGROUND

- Multi-gene panel tests (MGPT) have grown in use with advances in sequencing technology.
- Higher gene content on MGPTs can increase the rate of variants of uncertain significance (VUS).
- Inclusion of genes of uncertain significance (GUS) on MGPTs can lead to uninformative clinical impact for patients and complicate results disclosures for clinicians[1,2,3]
- Proper clinical validity aims to assess relevant information to identify genes with clinically significant gene-disease relationships.
  - ➢ May maximize clinical impact for patients
  - ➢ May minimize the VUS rate

METHODS

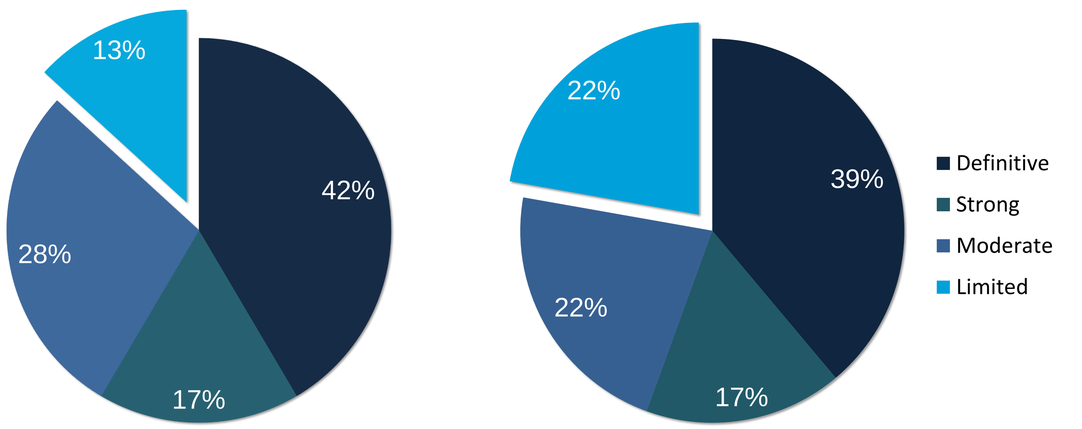
- Retrospective analysis of the data from 3,524 cases tested for as many as 106 genes from cardiovascular MGPTs, and 245 cases tested for either 11 Diamond-Blackfan anemia (DBA) genes or 7 dyskeratosis congenita (DKC) genes.
- Clinical validity scoring was performed on all genes using a system based on a recently published paper by Smith et al., 2017[4]
  - ➢ Point-based clinical validity scoring assessing Mendelian gene-disease relationships.
- Data was assessed to determine how many mutations/VLPs and VUSs were identified per gene per clinical validity category.

Fig 1. Clinical Validity Scoresheet[4]



RESULTS

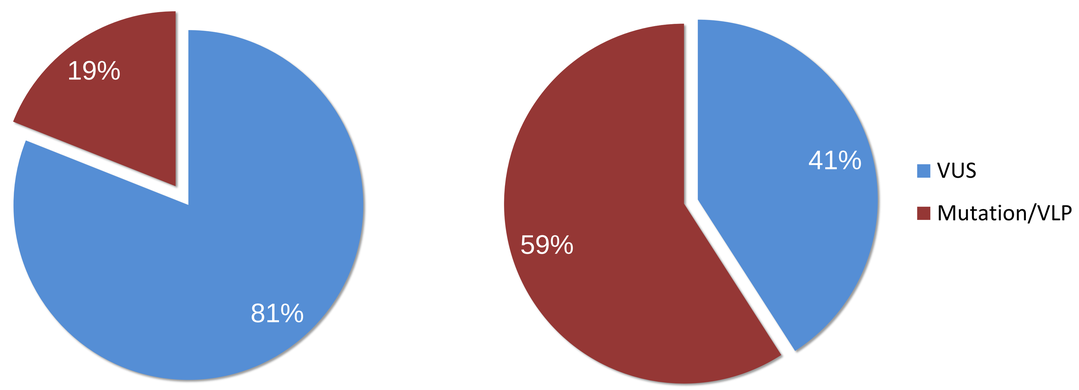
Fig 2. Distribution of Clinical Validity Scores for Multi-Gene Testing Panels



Cardio Panel (N=106 genes)

DBA/DKC Panels (N=18 genes)

Fig 3. Mutation/VLP and VUS Rates Per Panel

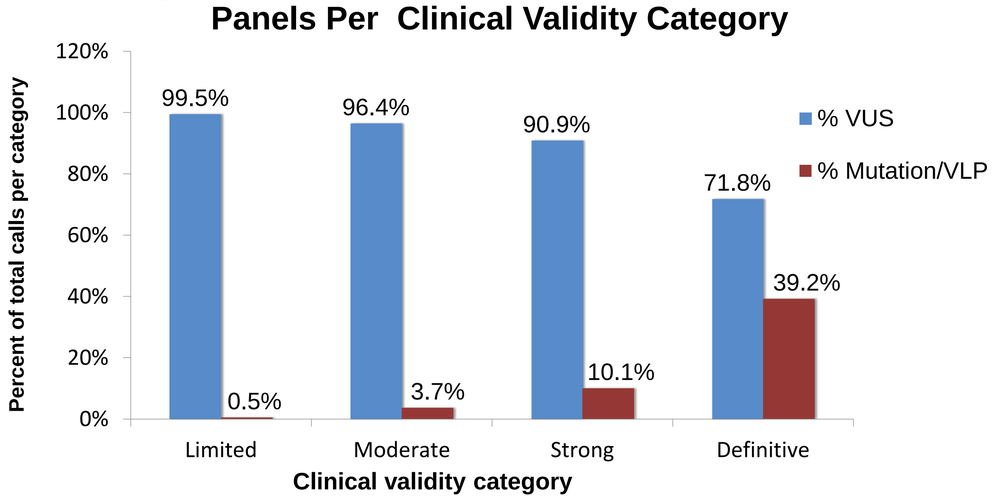


Cardio Panel (N=106 genes)

DBA/DKC Panels (N=18 genes)

RESULTS

Fig 4: Mutation/VLP and VUS rates of Combined Panels Per Clinical Validity Category



Two of the largest known human genes (TTN and DMD) are included in the Definitive category. Analysis did not account for gene size.

Clinical Validity	Type	DKC/DBA	Cardio
Limited	Genes (N)	4	14
	VUS (N)	2	191
	Mutation (N)	0	1
Moderate	Genes (N)	4	30
	VUS (N)	5	510
	Mutation (N)	4	15
Strong	Genes (N)	3	18
	VUS (N)	0	348
	Mutation (N)	4	31
Definitive	Genes (N)	7	44
	VUS (N)	20	1405
	Mutation (N)	31	528

Table 1: Distribution of Genes, VUS, Mutations/VLPs per clinical validity category

TAKE-HOME POINTS

- When designing MGPTs, a proper clinical validity process may improve detection rates.
- Genes in all clinical validity categories contribute to VUS rates therefore, VUS rates of MGPTs are likely to increase as their gene content increases.
- Rates of clinically significant findings tend to increase with inclusion of genes with higher clinical validity scores but are not impacted by inclusion of genes with limited clinical validity.
  - ➢ Mutations and VLP made up nearly 40% of the total calls for genes in the Definitive clinical validity category.
  - ➢ Only 1 VLP was identified among genes with limited clinical validity
- The data herein highlight the importance of clinical validity assessment to molecular laboratories.

REFERENCES

1. Richter, S et al. *Ann Oncol.* 2013; 24 Suppl 8:viii69-viii74.
2. Eccles, BK et al. *BMC Cancer.* 2015; 15:396.
3. Turbitt, E et al. *Clin Genet.* 2015; 87(1): 21-29.
4. Smith, ED et al. *Hum Mutat.* 2017; 38(5): 600-608.

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