Clinical validity of expanded carrier screening: High concordance of inter-lab variant classifications

Counsyl

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Introduction

In order for clinical genomic screens to properly guide patient health-management decisions, novel variants identified via sequencing must be properly classified. Consensus on the classifications of individual variants among submitters to databases such as ClinVar is often used to assess the clinical validity of a genetic test. The ACMG/AMP variant classification guidelines recommend requiring more evidence for pathogenic assertions in an unaffected population, e.g., in expanded carrier screening (**ECS**), where most patients are asymptomatic. We evaluated the clinical validity of ECS by analyzing variant-classification concordance between Counsyl's Foresight ECS and ClinVar submissions.

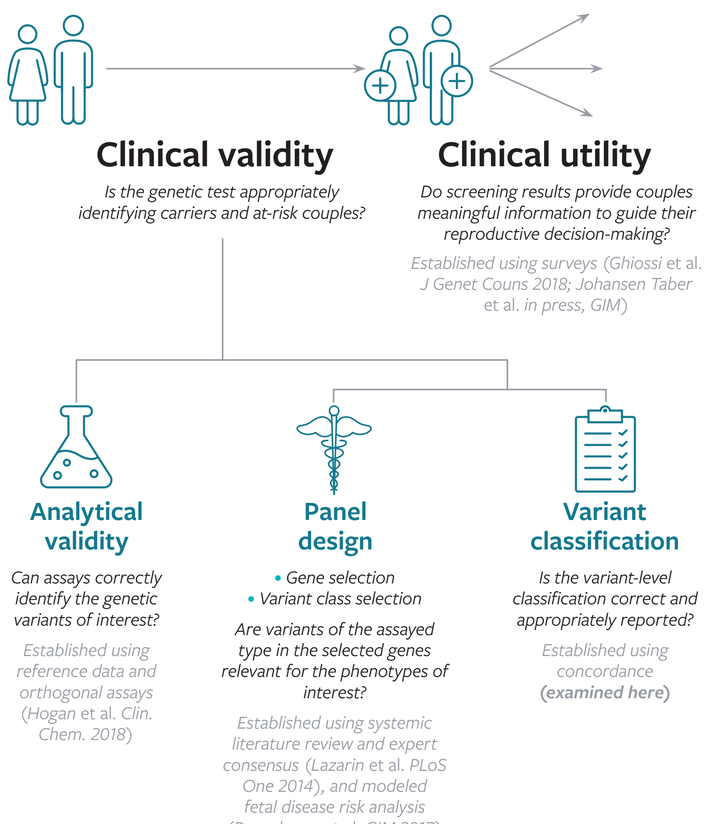


Figure 1. The clinical validity of a carrier screen. We have previously established portions of the clinical validity of our ECS and explore the validity of variant interpretation in this work.

Methods

Concordance (**Figures 2, 3**) was assessed between ClinVar entries (April 2018; ignoring old entries, submitters with few entries, and common variants) and Counsyl interpretations, and discordances were categorized by their underlying cause. To estimate the worst-case scenario for Foresight performance, disease-level metrics (e.g., positive predictive value, PPV) were calculated from carrier rates of different variant categories assuming ClinVar assertions are correct, e.g., "false positives" arose from variants considered pathogenic by Counsyl but not in ClinVar.

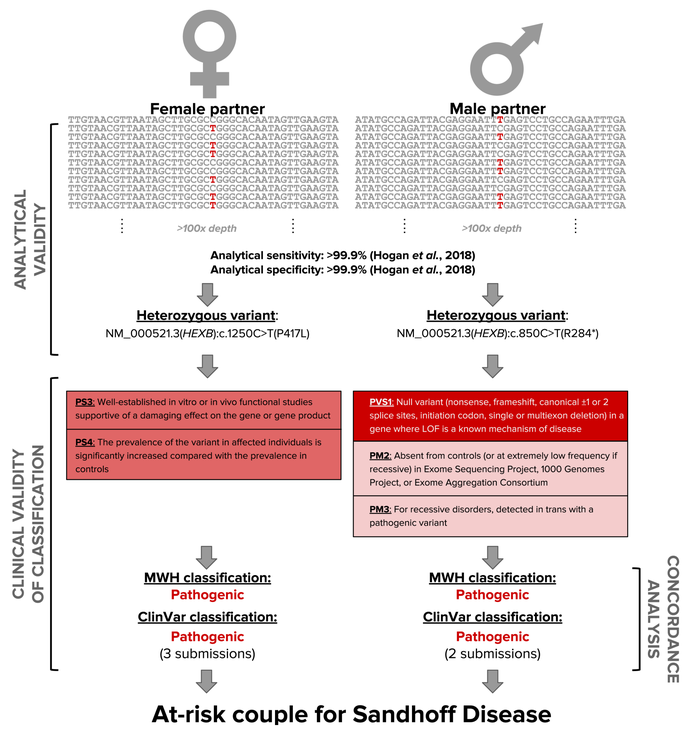


Figure 2. Expanded carrier screening detects at-risks couples. An example of detecting a couple at-risk for Sandhoff disease.

Results

Out of 12,834 variants evaluated, 98.2% were concordant (**Figure 3**). Most discordances (76.8%) were due to pathogenic assertions in ClinVar that we considered not to be reportable (VUS or benign). Many discordances had a clear explanation: 25.7% were due to unclear submitter classifications, 14.8% were variants with no published cases, 3.4% were variants with homozygotes observed in the population, and 4.6% were due to categories where reporting of variants in a carrier-screening setting might not be appropriate compared to a diagnostic setting. The remaining 51.5% of discordances could not be clearly categorized. Overall, 31.7% of Foresight patients are carriers for concordant alleles, and only 0.9% carry uncategorized discordant alleles (0.7% carry variants that do not meet our ECS threshold for pathogenicity, while 0.2% carry variants that do; **Figure 3**). Importantly, our concordance data suggest a level of clinical validity for ECS diseases that yields high estimated clinical sensitivity and PPV (**Figure 4**). For example, the estimated clinical sensitivity for cystic fibrosis was 99.90% (PPV: 99.92%), comparable to levels reported for BRCA1/2 (Lincoln et al., JCO Precis Oncol 2017).

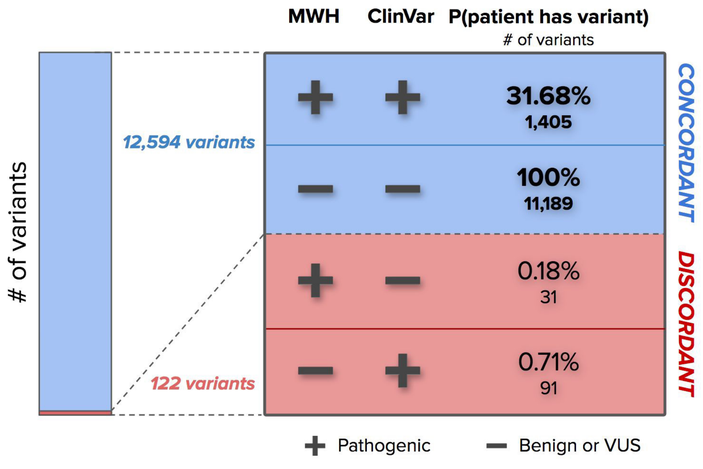
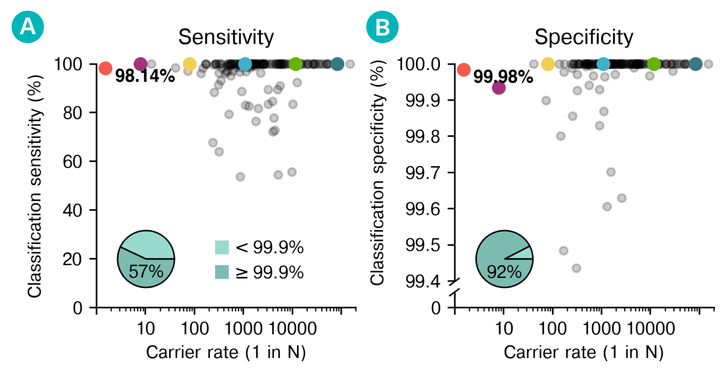
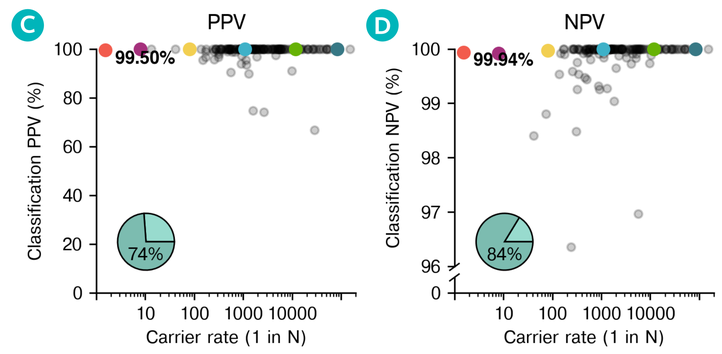


Figure 3. Summary of variant classification concordance data after expert review. Variants in each row were weighted by their allele frequency and combined to give the probability that a patient receives such a variant on a report.





E

Concordance-Based Variant Classification

Gene	Sensitivity	Specificity	PPV	NPV	Carrier rate
CFTR	99.89%	99.93%	99.91%	99.92%	1 in 8
DHCR7	99.86%	100.00%	100.00%	99.97%	1 in 81
GRHPR	100.00%	100.00%	100.00%	100.00%	1 in 1100
TTPA	100.00%	100.00%	100.00%	100.00%	1 in 12000
LAMA3	100.00%	100.00%	100.00%	100.00%	1 in 84000
Combined ECS	**98.14%**	**99.98%**	**99.50%**	**99.94%**	**1 in 1.5**

Figure 4. Clinical performance of expanded carrier screening. Values were calculated based on variant interpretation concordance on the assumption that ClinVar was the truth set. There would be an upward force on Foresight clinical performance values where ClinVar is wrong and Foresight is right; alternatively, there would be downward pressure on the values where both ClinVar and Foresight have the wrong classification. Notably, rare conditions do not suffer from poor clinical performance.

Conclusions

With a proper variant-interpretation workflow, ECS has high clinical validity. Residual discordances relative to ClinVar may be unavoidable because submitters sample from different patient populations (e.g., affected vs. unaffected).

Disclosure

All authors are employees of Myriad Women's Health (MWH), formerly Counsyl.

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