A Data-Driven Approach for Determining the Optimal Content for Expanded Carrier Screening Panels

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RESULTS

Carrier rates vary widely by ethnicity (Figure 2): rare carriorn conditions such as cystic fibrosis do not meet the ACOG 1-in-100 carrier rate threshold in all ethnicities. Of the 176 conditions on the ECS panel, 172 met all six criteria, with the remaining four conditions not present in at least one ethnicity. Hexagons and Xs denote ethnicity-specific carrier rates above and below 1-in-100, respectively. We evaluated the impact of exclusion of conditions that did not meet various ACOG inclusion criteria on the exclusion of both individual carriers and at-risk couples. Postulating that ECS panels need to ensure high condition-specific clinical sensitivity, we introduce a statistical framework that estimates clinical sensitivity for carriers for rare diseases by modeling whether there are enough reported cases to interpret the pathogenicity of observed variants (Figure 1).

Figure 1: A month schematic showing how clinical sensitivity is estimated for a hypothetical condition. We assume this hypothetical condition has five pathogenic variants with variant frequencies shown and a carrier rate of 1-in-10,000, resulting in a prevalence of 1 in 400,000. (A) Assumed number of pathogenic variants, including both variants observed in the patient cohort and unobserved variants (green, variants denoted with O) and a minority of unobserved variants (green, variants denoted with U). (B) Simulations of the expected number of reported cases (assuming all cases will be reported). Estimated clinical sensitivity is defined as the sum of all reported cases weighted by the estimated total prevalence. (C) U.S.-weighted at-risk couple rate. (D) The number of observed at-risk couples that would be identified by the panel subset. Horizontal lines show respective numbers for the 176 Universal panel.

Figure 2: Impact of different 1-in-100 carrier rate threshold definitions on carrier rates and at-risk couple rates. Included conditions meet the 1-in-100 carrier frequency thresholds for (A) 13 genes and (B) 176 genes. Estimated clinical sensitivity are shown in Figure 4. Simulations suggest that the 1-in-100 threshold does not correspond to a drop in clinical sensitivity, which remains above 85% for conditions with carrier rates above 1-in-100.

Figure 3: Illustration of condition-specific clinical sensitivity. Dots show median estimated and lines show 95% confidence intervals.

CONCLUSION

The 1-in-100 criterion is a critical and binds at-risk couple detection without substantially raising the burden of testing partners of carriers, suggesting that this threshold should be reconsidered in favor of criteria that ensure high clinical sensitivity.

We retrospectively analyzed de-identified data from 56,281 patients who underwent ECS over a 17-month period using a 176-condition panel. We excluded patients with personal or family history of disease and all patients provided informed consent for testing and anonymized research. We evaluated the impact of exclusion of conditions that did not meet various ACOG inclusion criteria on the exclusion of both individual carriers and at-risk couples.

METHODS

We assume this hypothetical condition has five pathogenic variants with variant frequencies shown and a carrier rate of 1-in-10,000, resulting in a prevalence of 1 in 400,000. (A) Assumed number of pathogenic variants, including both variants observed in the patient cohort and unobserved variants (green, variants denoted with O) and a minority of unobserved variants (green, variants denoted with U). (B) Simulations of the expected number of reported cases (assuming all cases will be reported). Estimated clinical sensitivity is defined as the sum of all reported cases weighted by the estimated total prevalence. (C) U.S.-weighted at-risk couple rate. (D) The number of observed at-risk couples that would be identified by the panel subset. Horizontal lines show respective numbers for the 176 Universal panel.