Application of a Severity Framework to 176 Conditions on an Expanded Carrier Screening Panel

Aishwarya Arjunan, MS, CGC, MPH; Holly Bellerose, MS, CGC; Katherine Johansen Taber, PhD; Gabriel A. Lazarin, MS, CGC

All authors are current or former employees of Myriad Genetics, Inc. and/or Myriad Women’s Health

INTRODUCTION

- Expanded carrier screening (ECS) identifies couples at risk of conceiving a pregnancy affected by dozens to hundreds of potential diseases.
- Disease severity is a key consideration for inclusion in an ECS panel, yet severity is a subjective measurement based on individual evaluation of phenotypic characteristics.
- A 2014 study developed and validated a framework to objectively classify disease severity into four levels: mild, moderate, severe, or profound.
- Here we apply the framework to the genes underlying 176 Mendelian conditions screened on a clinically available ECS panel.

METHODS

- Four pairs of genetic counselors from pediatric clinical settings applied the prescribed framework to classify four random subsets of the 176 conditions into four severity levels (Figure 1).
- Each pair of genetic counselors was notified of discordant classifications and reviewed the initial severity classifications for a final classification.
- Factors contributing to discordant classifications were collected and reviewed.
- The time required for severity classification was tracked to measure the feasibility of assessing severity of other Mendelian conditions.

RESULTS

- Upon initial review, 107 of the 176 disease-associated genes (61%) had concordant classifications by the genetic counselors using the published framework (Figure 2).
- With the exception of four genes (NR0B1, ABCG8, KCNJ11, CYP21A2), all discordant classifications were within one level of severity classification.
- Discordances were mainly due to incomplete penetrance and variable expressivity.
- After final review of discordances and consensus on final classifications, four genes were categorized as mild, 42 as moderate, 65 as severe, and 65 as profound (Figure 3).
- Each genetic counselor classified 22 genes in 30 days, and each pair reconciled discordances within 20 days on average.

CONCLUSIONS

- A systematic approach to severity classification can be accomplished efficiently to inform inclusion of conditions on an ECS panel.
- The level of discordance after initial review underscores the importance of collaboration with multiple clinicians during the classification process.
- Severity is often used as a proxy for the clinical validity of a disease. Policies stipulating severity as an important criterion for ECS panel assessment may use these data to improve clinical validity.

REFERENCES:

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<td>23.9%</td>
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Figure 1. Decision Framework for Severity Classification.

Figure 2. Concordance Between Genetic Counselors After Initial Gene Severity Classification.

Figure 3. Final Severity Classifications.