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

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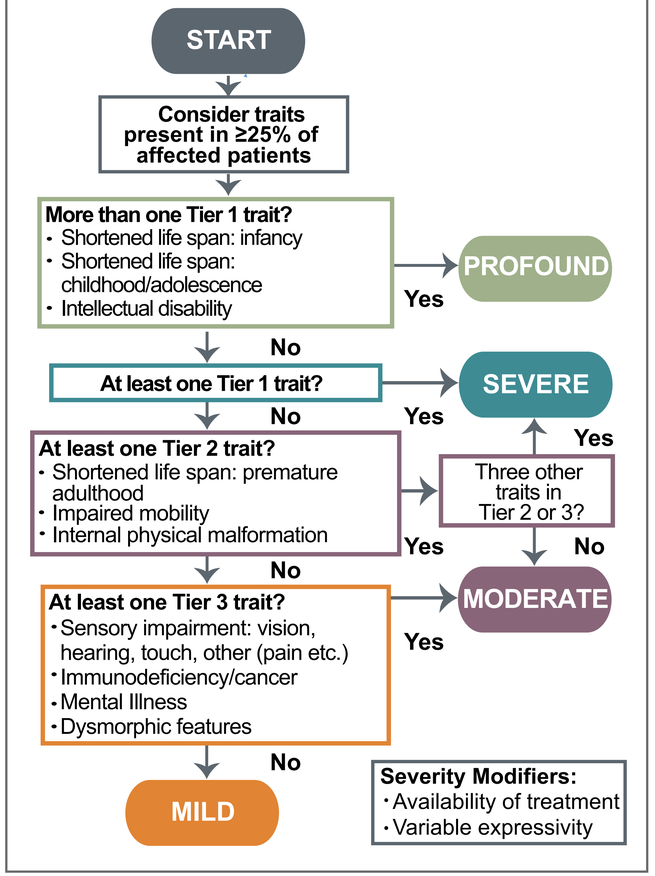
INTRODUCTION

- 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.[1,2]
- A 2014 study developed and validated a framework to objectively classify disease severity into four levels: mild, moderate, severe, or profound.[3]
- 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).[3]
- 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.

Figure 1. Decision Framework for Severity Classification.[3]



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*, *ABCC8*, *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.

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

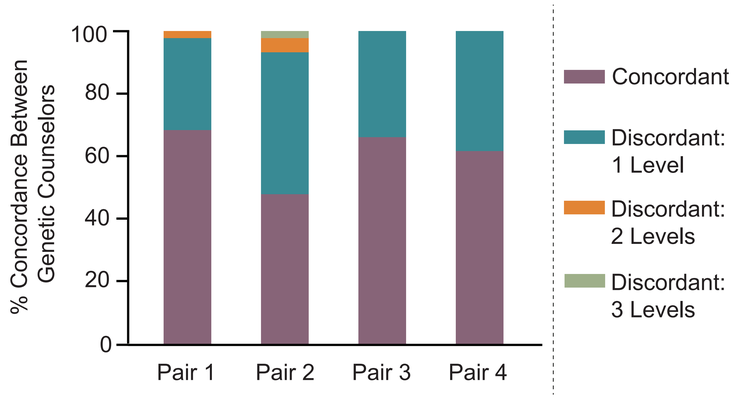
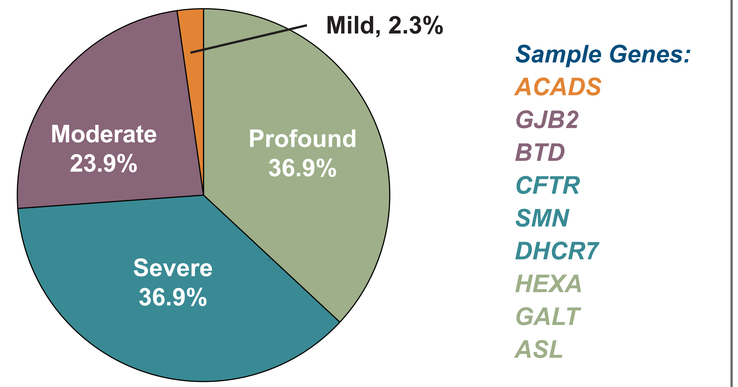


Figure 3. Final Severity Classifications.



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: **1.** Committee Opinion no. 690 Summary: Carrier Screening in the Age of Genomic Medicine. *Obstet Gynecol.* 2017 **2.** Committee Opinion no. 691 Summary: Carrier Screening for Genetic Conditions. *Obstet Gynecol.* 2017 **3.** Lazarin, et al. Systematic Classification of Disease Severity for Evaluation of Expanded Carrier Screening Panels. *PLoS ONE.* 2014

Presented at ACOG from October 30-31, 2020.