Subspecialty Genetic Test Utilization Guidance Supports Diagnostic Certainty: A Case Series in Hemophilia A

Adapted from a poster by: Stefanie N. Dugan, MS, CGC, Jamie McCreery, MS, CGC, Kenneth D. Friedman, MD, Matthew W. Anderson, MD, PhD, Rupa Udani, PhD
BloodCenter of Wisconsin, Milwaukee, WI

Overview
Hemophilia A, an X-linked bleeding disorder caused by pathogenic F8 variants resulting in deficiency of coagulation factor VIII, is well-recognized in affected males, but diagnosis of female carriers, with implications for bleeding and reproductive risks, can be challenging without genetic analysis. The diversity of pathogenic variants in F8, including sequence variants, intronic inversions, large deletions/duplications, and structural rearrangements, complicates genetic diagnosis. Determining optimal genetic testing strategy requires working knowledge of hemophilia, including severity criteria, correlation between variant type and disease severity, and detection rate and limitations of testing methodologies. Genetic counselors within the hematology reference laboratory possess such knowledge and were deployed to provide test utilization guidance to ordering providers.

Approach
Cases of F8 analysis for diagnosis of hemophilia A carrier status were reviewed by a genetic counselor at the time of test submission, at the time of report generation, or upon pre-submission provider inquiry in order to obtain clinical history and to ensure that clinically appropriate testing and recommendations were provided. Clinical care providers or the referring institutions were contacted to obtain sufficient detail to guide test algorithms (Figure 1) and allow generation of appropriate post-test interpretation and recommendations. When genetic counselor review identified a modified testing strategy offering potential cost avoidance or increased diagnostic certainty, test utilization guidance was offered to the ordering clinician, with orders modified upon clinician approval.

Hemophilia A Diagnostic Testing Guide

Case Studies
In the three described cases (Figure 2), testing ordered on a pregnant female with family history of hemophilia A was altered following test utilization guidance (Table 1), directly impacting the diagnostic outcome. In case 1, F8 sequencing was changed to F8 reflex analysis, with inversion analysis performed before F8 sequencing: testing revealed a pathogenic F8 intron 22 inversion. In case 2, prior F8 inversion analysis was determined to be uninformative: targeted analysis for the familial missense variant yielded informative negative results. In case 3, F8 sequencing orders were modified to reflex to F8 inversion and then to F8 deletion/duplication analysis: a pathogenic F8 multi-exonic deletion was identified.