WFH
WORLD FEDERATION OF HEMOPHILIA
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FEDERACIÓN MUNDIAL DE HEMOFILIA

Chapter 4
GENETIC ASSESSMENT

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GENOTYPE ANALYSIS SHOULD BE OFFERED TO ALL PEOPLE WITH HEMOPHILIA AND THEIR "AT-RISK" FEMALE FAMILY MEMBERS.

When is genetic testing indicated?

To define specific genetic mutation

To establish diagnosis in difficult cases

To predict risk of inhibitor development

To identify female carriers

To provide prenatal diagnosis

Referring for genetic testing

4.1.1 **Suspected or established hemophilia**
Test to identify the specific genetic variant

4.1.2 **Obligate carriers and "at-risk" females**
Test for previously identified familial genetic variant in the *F8* or *F9* gene

Prior to REFERRAL for genetic testing:

4.1.5 **Phenotypic screening for:**
FVIII or FIX levels, VWF antigen, and VWF activity testing

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4.1.6 **Genetic Counselling (pre and post testing, by genetic counsellor if available) for:**
Limits of molecular results; possibility of incidental findings; consent; education

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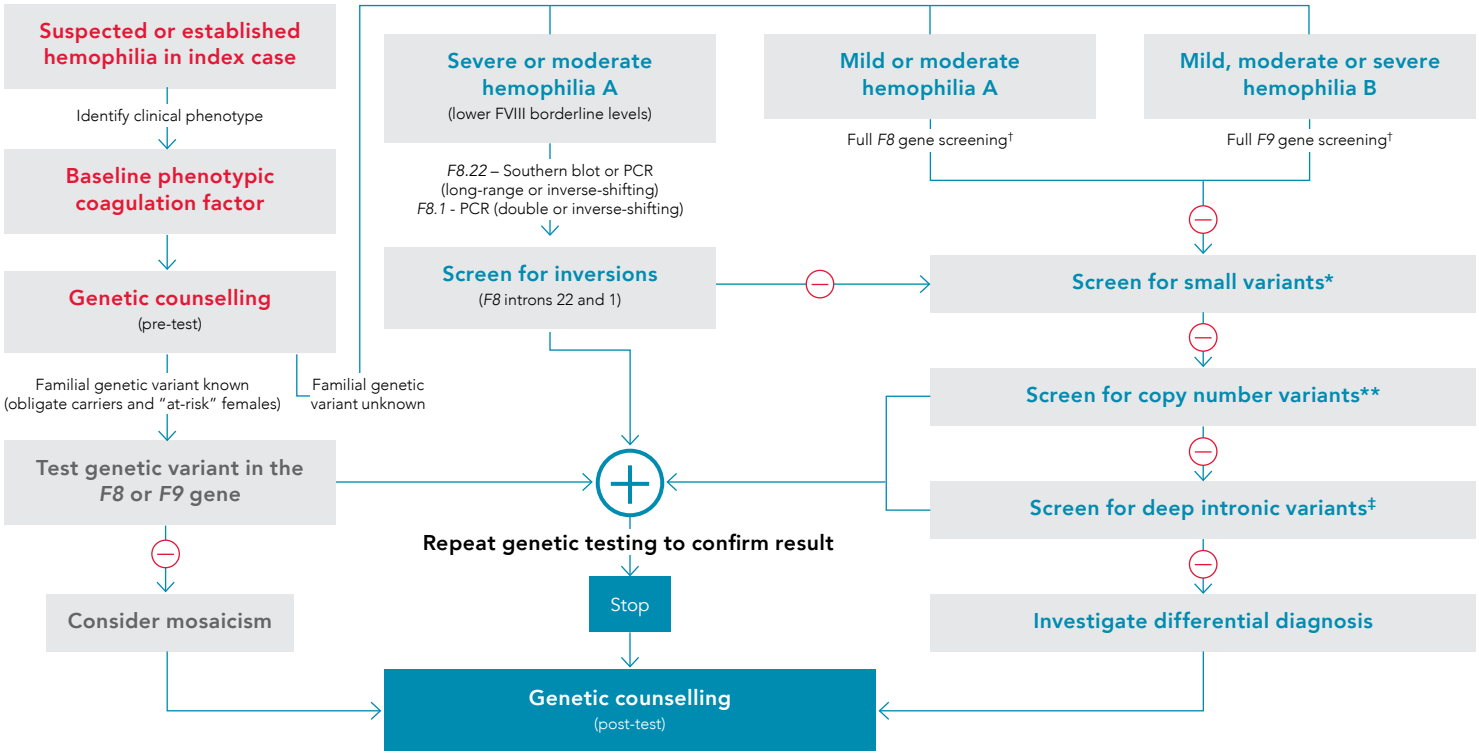
Approach for genetic testing for hemophilia



†Depending on availability, full *F8* or *F9* gene screening is performed by PCR and Sanger sequencing or NGS for the detection of missense, nonsense, splice-site, small and large deletions, duplications, and insertions; where resources are limited, laboratories may choose a cost-effective screening approach prior to Sanger sequencing. *Small variants includes: SNVs and small insertions, duplications, or deletions covering the essential regions of *F8* for hemophilia A (including the 26 exons) or *F9* for hemophilia B (including the 8 exons), exon/intron boundaries, promotor and 5' and 3' untranslated regions. **Copy number variants include large *F8* (hemophilia A) or *F9* (hemophilia B) deletions, duplications, or complex rearrangements. ‡NGS and WGS techniques may be used, but only after it is established that structural variants can be detected by the technique. Based on Recommendation 4.2.
NGS, next-generation sequencing; PCR, polymerase chain reaction; SNV, single nucleotide variants; VWD, von Willebrand disease; WGS, whole genome sequencing.

- ✓ Genotype analysis should be offered to all people with hemophilia and their "at-risk" female family members
- ✓ Genetic counselling for people with hemophilia and their families is an essential requirement prior to genetic testing
- ✓ Genetic diagnostic laboratories should adhere to strict protocols and procedures and undergo periodic accreditation
- ✓ The interpretation of the results of genetic testing should be performed by scientists who have knowledge and expertise in hemophilia genetics
- ✓ The ordering clinician and reporting scientist should be available to discuss the potential phenotypic consequences of the reported genotype

This educational material was made possible through the support of the Hemophilia Alliance
For more information on the WFH Guidelines for the Management of Hemophilia, visit www.WFH.org/TGResourceHub