NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #273
(Replaces Document #248)

MASAC RECOMMENDATIONS ON GENOTYPING FOR PERSONS WITH HEMOPHILIA

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on March 11, 2022, and endorsed by the NHF Board of Directors on July 6, 2022.

Since the genes for factors VIII and IX were identified and sequenced in the 1980s, numerous gene changes have been identified in persons with hemophilia A and B. This information has led to increased understanding of the molecular biology of these genes and has established new correlations between a person's genotype and phenotype. High through-put technology and strategies for more efficient genotyping have reduced the costs of doing genotyping significantly.

In 1998, MASAC recommended that NHF identify public and private funding sources that could facilitate widespread genotyping efforts in the hemophilia community. In 2003, this concept was endorsed but not funded by Congress. Another event that made a community-wide genotyping project feasible was the passage by Congress in 2008 of the Genetic Information Nondiscrimination Act (GINA). This act guarantees that genetic information cannot be used to discriminate against an individual. A multi-sector partnership formed between NHF, the American Thrombosis and Hemostasis Network, and Bloodworks to meet unmet needs for genotyping in the community through the *My Life, Our Future* (MLOF) program. MLOF provided free hemophilia A and B genotyping for patients with a diagnosis of hemophilia and at-risk female relatives in the U.S. from 2013-2017. After the completion of MLOF, individuals have had to have testing performed as part of standard clinical practice. Barriers to testing include access and financial considerations. Free genotyping services, such as the 8Check Gene Mutation Testing Service for patients with hemophilia A, can be a testing resource for patients and their at-risk relatives, when eligible.

Genotyping is high yield, with >98% of individuals with hemophilia A or B having an identifiable DNA change in their factor gene. Occasionally, individuals may have more than one DNA change that can cause hemophilia. More than one genotype can also be detected in different affected members of the same family. In females, genotype is the most reliable method for diagnosis, as factor levels correlate less well with bleeding in females than in males, and factor levels may even be normal in a symptomatic (bleeding) carrier. Thus, individual genotype information is needed for each patient.

Genotype information allows individuals and healthcare providers to make or refine the diagnosis of hemophilia, predict hemophilia severity, determine inhibitor risk, identify female genetic carriers, help with reproductive counseling and birth planning, and lead towards

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improved, individualized treatments. Also, with the emergence of experimental gene therapies, genotyping is important in predicting those individuals who might be potential candidates and in selecting the most appropriate form of gene therapy for each individual.

An important aspect of genotyping is genetic counseling. Counseling should be provided to individuals and families pre- and post-genotype testing to ensure that they understand the implications of the test results.

Therefore, MASAC makes the following recommendations:

1. MASAC recommends that individuals with hemophilia A or B undergo genotyping
2. MASAC recommends that affected male relatives (or other individuals with a single X chromosome) undergo genotyping
3. MASAC recommends that females (or other individuals with more than one X chromosome) at-risk to have inherited a hemophilia-causing genetic change undergo hemophilia genotyping, regardless of factor VIII or factor IX level
4. MASAC recommends genotyping should be performed in a laboratory experienced in hemophilia genetics and results interpretation

References:

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2. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, Carcao M, Mahlangu J, Ragni MV, Windyga J, Llinás A, Goddard NJ, Mohan R, Poonnoose PM, Feldman BM, Lewis SZ, van den Berg HM, Pierce GF; WFH Guidelines for the Management of Hemophilia panelists and co-authors. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020 Aug;26 Suppl 6:1-158. doi: 10.1111/hae.14046. Epub 2020 Aug 3. Erratum in: Haemophilia. 2021 Jul;27(4):699. PMID: 32744769.