# Guidelines for Ordering Hemoglobin Gene Testing

| Suspected Condition | Recommended Tests to Order | Notes and Guidance |
|---|---|---|
| **Sickle Cell Disease**<br>SS, SC, Sβ-thalassemia<br>SE, SD, SO, S-HPFH, S-Other | 1 ***HBB*** (β-globin) gene sequencing<br>2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA)<br>3 ***HBA*** (α-globin) locus deletion/duplication analysis (MLPA) | Beta-globin sequencing and deletion mapping are recommended to differentiate homozygous (e.g. Hb SS) and compound heterozygous states (e.g. Hb SC, Sβ-thalassemia, S-HPFH). Alpha-globin copy number can modify phenotype of sickle cell disease. |
| **Thalassemia**<br>α, β, (δβ), (γδβ), (εγδβ)<br>α triplications/quadruplications<br>Hb E disorders<br>Hb Constant Spring, others | 1 ***HBB*** (β-globin) gene sequencing<br>2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA)<br>3 ***HBA*** (α-globin) genes sequencing<br>4 ***HBA*** (α-globin) locus deletion/duplication analysis (MLPA) | Comprehensive testing is highly recommended because of the complexity of the thalassemia syndromes, and the fact that the phenotype of thalassemia is modified by the genotypes of both the α-globin and β-globin loci. |
| **Common β-variants**<br>Hb C, D, O, others | 1 ***HBB*** (β-globin) gene sequencing<br>2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) | Both panels are recommended to differentiate homozygous (e.g. Hb CC) and compound heterozygous states (e.g. Hb Cβ-thalassemia, Hb C-HPFH). **For Hb E, use the guidance for thalassemia.** |
| **Common α-variants**<br>Hb G-Philadelphia, Hb I, others | 1 ***HBA*** (α-globin) gene sequencing<br>2 ***HBA*** (α-globin) locus deletion/duplication analysis (MLPA) | Both panels are recommended because sequence variants can occur on a chromosome with 1 or 2 α-globin genes, and α-globin gene copy number affects the proportion of the variant Hb. **For Hb Constant Spring (and related Hbs), use the guidance for thalassemia.** |
| **Other Hemoglobinopathy**<br>Unstable Hb, Altered Oxygen Affinity Hb, Methemoglobin (Hb M) | 1 ***HBB*** (β-globin) gene sequencing<br>2 ***HBA*** (α-globin) genes sequencing | These Hb disorders are sequence variants of either the α-globin or β-globin genes. |
| **Possible Hb Disorder or Complex Genotype** | 1 ***HBB*** (β-globin) gene sequencing<br>2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA)<br>3 ***HBA*** (α-globin) genes sequencing<br>4 ***HBA*** (α-globin) locus deletion/duplication analysis (MLPA) | Comprehensive testing is recommended. |

Key: ● minimum recommended testing ● suggested testing

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# Guidelines for Ordering Genetic Testing for Disorders of Fetal Hemoglobin (Hb F)

| Suspected Condition | Recommended Tests to Order | Notes and Guidance |
|---|---|---|
| **Neonatal (transient) thalassemia syndrome** | 1 ***HBG*** (γ-globin) gene sequence analysis<br>2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) | |
| **Hereditary persistence of fetal hemoglobin (HPFH)** | 1 ***HBG*** (γ-globin) gene sequence analysis<br>2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) | |
| **Abnormal phenotype ± abnormal Hb analysis** | 1 ***HBG*** (γ-globin) gene sequence analysis | Abnormal phenotypes may include hemolysis, cyanosis, anemia, polycythemia, and methemoglobinemia. |
| **Abnormal Hb analysis only** | 1 ***HBG*** (γ-globin) gene sequence analysis | No clinical phenotype. |

Key: ● minimum recommended testing ● suggested testing

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