Guidelines for Ordering Hemoglobin Gene Testing

Suspected Condition	Recommended Tests to Order	Notes and Guidance
Sickle Cell Disease SS, SC, Sβ-thalassemia SE, SD, SO, S-HPFH, S-Other	1 ***HBB*** (β-globin) gene sequencing 2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) 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 α, β, (δβ), (γδβ), (εγδβ) α triplications/quadruplications Hb E disorders Hb Constant Spring, others	1 ***HBB*** (β-globin) gene sequencing 2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) 3 ***HBA*** (α-globin) genes sequencing 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 Hb C, D, O, others	1 ***HBB*** (β-globin) gene sequencing 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 Hb G-Philadelphia, Hb I, others	1 ***HBA*** (α-globin) gene sequencing 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 Unstable Hb, Altered Oxygen Affinity Hb, Methemoglobin (Hb M)	1 ***HBB*** (β-globin) gene sequencing 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 2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) 3 ***HBA*** (α-globin) genes sequencing 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 2 ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA)	
Hereditary persistence of fetal hemoglobin (HPFH)	1 **HPFH** gene analysis	Includes: ***HBG*** (γ-globin) gene sequence analysis, ***HBB*** (β-globin) locus deletion/duplication analysis (MLPA) and **HPFH** SNP analysis
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: 1 minimum recommended testing 2 suggested testing

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