Genomic Testing (Secondary Findings) ACT Sheet

APOB, LDLR, PCSK9 Pathogenic Variants (Familial Hypercholesterolemia)

Pathogenic or likely pathogenic variants (mutations) in the *APOB, LDLR, or PCSK9* gene predispose to familial hypercholesterolemia, a condition in which elevated levels of low-density lipoprotein cholesterol (LDL-C) increase the risk of premature atherosclerotic cardiovascular disease (CVD) and tendon xanthomas. Most are heterozygotes (He-FH). Homozygotes (Ho-FH) experience a more aggressive course.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Inform the individual (or parent/guardian) of the genomic screening result and that there is a high lifetime risk of developing disease.
- Obtain family and medical history and evaluate the patient.
- Measure blood pressure, blood glucose, and lipid levels.
- Refer for genetic consultation and counseling.

Clinical Considerations: While the American Academy of Pediatrics recommends routine lipid screening in childhood and adolescence, this is rarely performed leading to missed opportunities to identify children with lipid disorders such as familial hypercholesterolemia and initiate effective therapies to reduce the risk for premature cardiovascular disease. Males with FH have a 50% risk of CVD by age 50 years, while women have a 30% risk of CVD by age 60 years. Evaluation includes monitoring blood pressure, blood glucose, and lipid levels. Most individuals are heterozygotes (He-FH). If untreated, elevated LDL-C levels that may already be present in childhood predispose to coronary heart disease and stroke. Homozygotes (Hom-FH) experience a more aggressive course. Patients with FH and elevated LDL-C are candidates for lifelong, high-intensity statin therapy beginning in children at age 8 or older and should consider daily aspirin if not contraindicated. Management may also include smoking cessation and encouraging physical activity, avoiding obesity and diets high in saturated fats and cholesterol, as well as limiting alcohol intake. Elevated blood pressure and diabetes are additional risk factors for CVD and should be treated aggressively. Most patients who are homozygous or compound heterozygous for pathogenic or likely pathogenic variants experience severe CVD by their mid-20s or earlier without aggressive treatment.

Mode of Inheritance: FH is inherited in an autosomal dominant manner. Individuals with either He-FH due to a pathogenic *APOB, LDLR,* or *PCSK9* variant develop FH with variable expressivity. Penetrance is high but incomplete.

Additional Information:

- GeneReviews
- Medline Plus
- AHA
- ClinGen Actionability Report

Referral (local, state, regional, and national):

- Testing
- Find Genetic Services

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LOCAL RESOURCES: Insert local website links

State Resource site *(insert website information)*

Name	
URL	
Comments	

Local Resource Site *(insert local and regional website information)*

Name	
URL	
Comments	

APPENDIX: Resources with Full URL Addresses

Additional Information:

Gene Reviews
https://www.ncbi.nlm.nih.gov/books/NBK174884/

Medline Plus
https://medlineplus.gov/genetics/gene/apob/

American Heart Association
http://www.heart.org/en/health-topics/cholesterol/causes-of-high-cholesterol/familial-hypercholesterolemia-fh

ClinGen Actionability Report
https://actionability.clinicalgenome.org/ac/Adult/ui/stg2SummaryRpt?doc=AC065

Referral (local, state, regional and national):

Testing
https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=APOB

Find Genetic Services
https://clinics.acmg.net

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