Stage I: Rule-Out Dashboard

Secondary Findings in Adults

GENE/GENE PANEL: *LDLR, APOB, PCSK9*	**DISORDER:** Heterozygous Familial Hypercholesterolemia
HGNC ID: 6547, 603, 20001	**OMIM ID:** 143890, 144010, 603776

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	**Patient Management**
☒	☐	**Surveillance or Screening**
☒	☐	**Family Management**
☒	☐	**Circumstances to Avoid**

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☒ **YES** ☐ **NO**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Summary Report

Secondary Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: *LDLR, APOB, PCSK9*		**DISORDER:** Heterozygous Familial Hypercholesterolemia	
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		The prevalence of heterozygous familial hypercholesterolemia (HeFH) is estimated as 1/200 to 1/300.	(1-3)
Signif/Burden of Condition	**Clinical Features** (Signs/symptoms)	HeFH is characterized by elevated levels of plasma low-density lipoprotein cholesterol (LDL-C), increased risk of premature cardiovascular disease (CVD), and tendon xanthomas. Untreated, LDL-C concentrations are typically in the range of 190-350 mg/dL. CVD includes both coronary heart disease (CHD) and stroke, though CHD is the more common CVD while stroke occurs rarely. Presentation of CHD may include angina pectoris, myocardial infarction, and peripheral vascular disease. Corneal arcus is also common.	(1-6)
	Natural History (Important subgroups & survival/recovery)	In HeFH, a raised LDL-C concentration is present during childhood and may lead to early development of atherosclerosis and CHD, even in the absence of other risk factors for coronary disease. Untreated males have a 50% risk of CHD by age 50 with onset typically in their 30s and 40s while untreated women have at least a 30% risk by the age of 60 with onset typically in their 40s and 50s. HeFH patients with tendon xanthomas have higher risk of CVD compared to FH patients without xanthomas.	(1-6)
2. How effective are interventions for preventing the harm? **Information on the effectiveness of the recommendations below was not provided unless otherwise stated.**			
Patient Management		Patients should consider lifelong, high-intensity statin therapy beginning in children aged 8 or older, although it may be administered to younger patients in special cases. **(Tier 1)** These recommendations have been confirmed in more recent guidelines which base recommendations on elevated cholesterol levels without regard to specific etiology such as FH. **(Tier 5)** In a study of 2146 patients with FH, patients taking statins were shown to reduce their risk of coronary heart disease by 76% compared to untreated patients. **(Tier 5)** Patients should consider taking daily aspirin or other proven similarly effective drug if aspirin is contraindicated. Among patients with a history of atherosclerotic disease, aspirin has been shown to reduce all-cause mortality by 18%, number of strokes by 20%, myocardial infarctions by 30%, and other vascular events by 30%. Among patients without a history of atherosclerotic disease, aspirin has been shown to reduce the risk of myocardial infarction by 30%. However, evidence of effectiveness of aspirin in patients with FH was not provided. **(Tier 1)** High blood pressure and diabetes are additional risk factors for CHD and should be treated aggressively. **(Tier 2)**	(2;4) (7) (8) (4) (1;9)
Surveillance		A baseline electrocardiogram should be considered. **(Tier 2)** Lipid levels should be measured every 12 months. **(Tier 2)** Blood pressure should be monitored every 6 to 12 weeks. **(Tier 2)**	(2) (9) (9)
Family Management		Cascade testing using a combination of genetic testing and LDL-C concentration measurement within families of patients with HeFH is recommended to identify relatives with a clinical diagnosis /or genetic diagnosis of HeFH and HoFH . **(Tier 1)**	(2)
Circumstances to Avoid		Patients should avoid additional risk factors for CHD, including smoking, physical inactivity, diets high in saturated fats and cholesterol, unhealthy body weight, and excessive alcohol consumption. **(Tier 2)**	(1;2)

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Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

GENE/GENE PANEL: *LDLR, APOB, PCSK9*	**DISORDER:** Heterozygous Familial Hypercholesterolemia	
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	Autosomal codominant	
Prevalence of Genetic Mutations	Genetic mutations associated with HeFH have been estimated in Dutch population as 1/137-1/244. **(Tier 5)**	(10;11)
Penetrance OR Relative Risk (include high risk racial or ethnic subgroups)	Males have a 50% risk of CHD by age 50 while women have a 30% risk by the age of 60. **(Tier 3)**	(3)
	Locus and allele specific penetrance varies for elevated LDL-C levels. High penetrance, up to 90%, has been noted for patients heterozygous with mutations in LDLR and incomplete penetrance for patients heterozygous for mutations in APOB. The penetrance associated with most mutations in PCSK9 is unclear, though patients heterozygous for the Ser127Arg variant have 90% penetrance and patients heterozygous for the Asp374Tyr variant have high penetrance. **(Tier 3)**	(3)
	Information on relative risk associated with HeFH was unavailable.	
Expressivity	Expression is variable, with some individuals with HeFH having no detectable signs of disease. **(Tier 4)**	(3)
4. What is the nature of the intervention?		
Nature of Intervention	The identified action items for this disorder include surveillance (echocardiogram), clinical monitoring (blood pressure and lipid levels) and medication use (statins and aspirin), which are likely associated with mild to moderate risk and burden.	
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	HeFH is associated with early onset elevated cholesterol levels and CHD **(Tier 3)**, which are not typically screened for in younger adult populations, thus this disorder would likely escape clinical detection given typical clinical care.	(3)

Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
LDLR *APOB* *PCSK9*	High cholesterol/Statins	2	3C	3A	3	11CA

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/

Stage II: Summary Report

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Date of Search (MM.DD.YYYY): 06.30.2014 (updated 04.14.2015)

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