

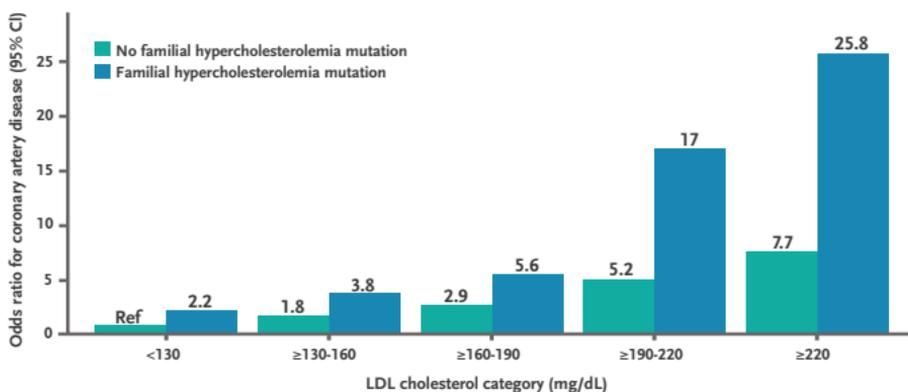
A better indicator of risk: Genetic testing for familial hypercholesterolemia



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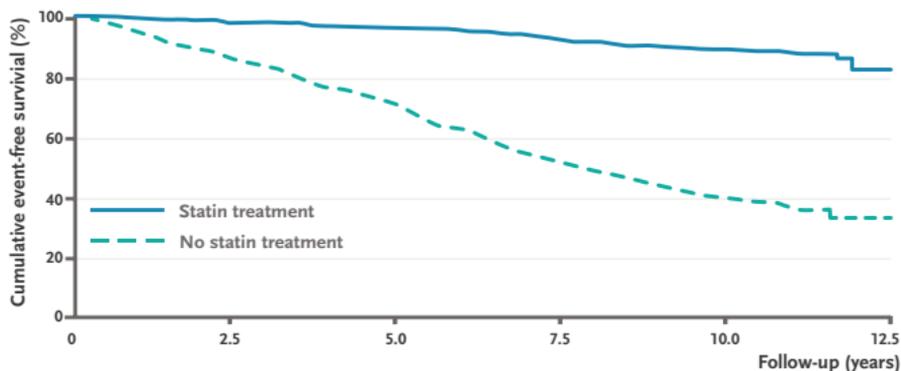
BENEFITS OF GENETIC TESTING

Genetic diagnosis of familial hypercholesterolemia (FH) indicates **substantially higher** risk of coronary artery disease than clinical diagnosis alone.



Impact of familial hypercholesterolemia mutation status on coronary artery disease according to LDL cholesterol level. Adapted from Khera AV et al. 2016.

If FH is identified early and treated aggressively, **morbidity and mortality are reduced by 80%**.



Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with FH according to statin treatment ($P < 0.001$ for difference). Adapted from Verschmissen J et al. 2008.

Genetic testing also enables **life-saving early interventions for at-risk family members**; even family members with normal cholesterol levels could be at increased risk. If a patient receives a genetic diagnosis of FH, the CDC recommends genetic testing of family members.

CONSIDERATIONS FOR TESTING

Familial hypercholesterolemia (FH) should be suspected when:

- LDL-C \geq 190 mg/dL in adults
- LDL-C \geq 160 mg/dL in patients <20 years old, and/or
- known FH-causing genetic variant present in family

The likelihood of FH increases when the following are present:

- Cholesterol deposits on the
 - skin (xanthlasma, tuberous xanthomas)
 - tendons (tendon xanthomas)
 - cornea (arcus corneae)
- First-degree relative with
 - LDL-C \geq 190 mg/dL
 - premature coronary artery disease (<55 years for males, <65 years for females)

Questions? Call Invitae Clinical Consult at 800-436-3037.
Learn more about Invitae's high-quality, affordable genetic testing at www.invitae.com/cardiology

References:

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2. Khara AV *et al.* Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol.* 2016;67(22):2578-89.
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4. Centers for Disease Control and Prevention. Public Health Genomics Database. <https://phgkb.cdc.gov/PHGKB/topicFinder.action?query=fh&Mysubmit=init>. Accessed February 2018.

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The bigger picture: Genetic testing for inherited arrhythmias and cardiomyopathies



Arrhythmias and cardiomyopathies may have a genetic cause that affects prognosis and management. Testing can:

- Confirm a clinical diagnosis and differentiate from other causes
- Predict response to pharmacotherapies
- Inform avoidance of arrhythmia triggers, including swimming, startling, sleeping, and certain medications
- Aid in the decision to place an ICD or pacemaker

Testing also enables life-saving interventions for asymptomatic or pre-symptomatic family members. Family cascade genetic testing is universally recommended across all heritable arrhythmias and cardiomyopathies by ACC, AHA, HRS, HFSA, and PACES.

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References:

1. Al-Khatib SM *et al.* 2017 AHA/ACC/HRS guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society.
2. Hershberger RE *et al.* Genetic evaluation of cardiomyopathy - a Heart Failure Society of America practice guideline. *J Card Fail.* 2009;15(2)83-97.
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2017 ACC/AHA/HRS GUIDELINE RECOMMENDATIONS

	Condition	Patient with established or suspected diagnosis	Family members
Arrhythmia	LQTS	Recommended: Class I	Recommended: Class I
	CPVT	Reasonable: Class IIa	Recommended: Class I
	Brugada syndrome	May be useful: Class IIb	Recommended: Class I
	SQTS	May be useful: Class IIb	Recommended: Class I
Cardiomyopathy	ARVC	Reasonable: Class IIa	Recommended: Class I
	HCM	Reasonable: Class IIa	Recommended: Class I
	NICM w/CCD	Reasonable: Class IIa	Recommended: Class I
SCA or SCD	Postmortem	Reasonable: Class IIa	Recommended: Class I
	SCA/D <40 years old	Further clinical evaluation for targeted genetic testing	Recommended: Class I

ARVC = arrhythmogenic right ventricular cardiomyopathy

CCD = cardiac conduction disease

CPVT = catecholaminergic polymorphic ventricular tachycardia

HCM = hypertrophic cardiomyopathy

LQTS = long QT syndrome

NICM = non-ischemic cardiomyopathy

SCA = sudden cardiac arrest

SCD = sudden cardiac death

SQTS = short QT syndrome

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Thoracic aortic disease is typically asymptomatic until a life-threatening event occurs. Arm yourself and your patient with the knowledge to prevent aortic dissection.

Clinical diagnosis is not always straightforward. Genetic diagnosis clarifies when an aorta warrants surgical repair.

Genetic variants	Associated disease	Surgical repair generally recommended ¹
<i>FBN1</i>	Marfan syndrome	When external diameter reaches 5.0 cm
<i>TGFBR1, TGFBR2, TGFB2, SMAD3</i>	Loeys-Dietz syndrome	External diameter less than 5.0 cm
<i>COL3A1</i>	Vascular Ehlers-Danlos syndrome	Role of non-life-threatening aortic repair is unclear due to tissue fragility, tendency to hemorrhage, and poor healing
<i>ACTA2, MYH11, among others</i>	Heritable thoracic aortic disease	Aortic dilation, which may or may not progress to dissection
Multiple genes	Other syndromes	Aortic dilation, which may or may not progress to dissection

Bicuspid aortic valve (BAV) often occurs together with thoracic aortic aneurysm/dissection (TAAD).²

Familial cascade genetic testing is also recommended once the causative variant is identified in the affected patient.¹

CONSIDER GENETIC TESTING FOR PATIENTS WITH:

- TAAD or BAV

and

- Family history of either TAAD or BAV (present in 20% of individuals with TAAD³)

or

- Features of Marfan, Loews-Dietz, or vascular Ehlers-Danlos syndrome
 - Features of Marfan syndrome:⁴
Ectopia lentis, long limbs, long fingers, pectus deformity, hindfoot deformity, pneumothorax, scoliosis, reduced elbow extension, skin striae, myopia
 - Features of Loews-Dietz syndrome:⁵
Pectus deformity, scoliosis, joint laxity, long fingers, widely spaced eyes, bifid uvula/cleft palate, craniosynostosis, translucent skin, easy bruising, dystrophic scars
 - Features of vascular Ehlers-Danlos syndrome:⁶
Intestinal rupture, uterine rupture during pregnancy, thin translucent skin, easy bruising, thin lips, small jaw, narrow nose, prominent eyes

Questions about which patients to test? Talk to an Invitae genetic counselor by calling 800-436-3037.

Learn more about Invitae's high-quality, affordable genetic testing at www.invitae.com/cardiology.

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2. Prakash SK *et al.* *J Am Coll Cardiol*. 2014;64(8):832-9.
3. Biddinger A *et al.* *J Vasc Surg*. 1997;25(3):506-11.
4. Loews BL *et al.* *J Med Genet*. 2010;47:476-85.
5. Loews BL *et al.* *Nat Genet*. 2005;37:275-81.
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