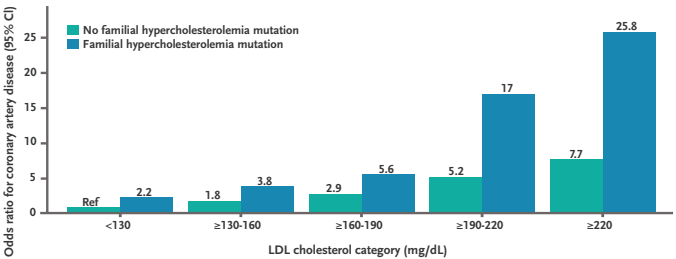
# A better indicator of risk: Genetic testing for familial hypercholesterolemia

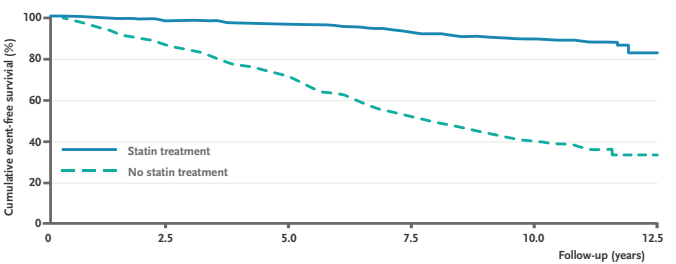
Familial hypercholesterolemia (FH) affects approximately 1 in 220 people, and more than a million people in the US have FH and are undiagnosed.

An established genetic diagnosis of FH indicates a **substantially higher** risk of coronary artery disease (CAD) 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 Versmissen J* et al. *2008.*

Genetic testing also enables **life-saving early interventions for at-risk family members**. Family members could be at increased risk even if their cholesterol levels are normal. Cascade genetic testing of family members is recommended by JACC scientific expert panel and the CDC after a patient receives a genetic diagnosis of FH.

## WHO TO TEST

**JACC scientific expert panel and CDC recommendations:**

Genetic testing for FH **should be offered** when there is:

- No apparent secondary cause of hypercholesterolemia and persistent levels are
  - LDL-C ≥190 mg/dL in adults
  - LDL-C ≥160 mg/dL in children
- Known FH-causing genetic variant present in family

Genetic testing **enables life-saving early interventions for at-risk family members;** even family members with normal cholesterol levels could be at increased risk.

The likelihood of FH increases when the following are present:

- Cholesterol deposits on the
  - skin (xanthalasma, tuberous xanthomas)
  - tendons (tendon xanthomas)
  - cornea (arcus corneae)
- First-degree relative with
  - LDL-C ≥190 mg/dL
  - premature CAD (<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:**

1. Sturm AC *et al.* Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol.* 2018;72(6):662-680.
2. Goldberg A, *et al.* Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J Clin Lipidol.* 2011;5(3 Suppl):S1-8.
3. Khera 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.
4. Versmissen J *et al.* Efficacy of statins in familial hypercholesterolemia: a long term cohort study. *BMJ.* 2008;337:a2423.
5. Centers for Disease Control and Prevention. Public Health Genomics Database. https://phgkb.cdc.gov/PHGKB/topicFinder.action. Accessed December 2017.



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P/N F213-2

# 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.
3. Ackerman MJ *et al*. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm*. 2011;8:1308-39.

## 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

**HEADQUARTERS & LABORATORY** | 1400 16th Street, San Francisco, CA 94103 | www.invitae.com
**IN THE US** | clientservices@invitae.com | p: 800-436-3037 | f: 415-276-4164
**OUTSIDE THE US** | globalsupport@invitae.com or visit www.invitae.com/contact
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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] |
|---|---|---|
| *FBN1* | Marfan syndrome | When external diameter reaches 5.0 cm |
| *TGFBR1, TGFBR2, TGFB2, SMAD3* | Loeys-Dietz syndrome | External diameter less than 5.0 cm |
| *COL3A1* | Vascular Ehlers-Danlos syndrome | Role of non-life-threatening aortic repair is unclear due to tissue fragility, tendency to hemorrhage, and poor healing |
| *ACTA2, MYH11,* among others | 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 TAAD[3])

***or***

- Features of Marfan, Loeys-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 Loeys-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.**


**References:**

1. Hiratzka LF *et al. Circulation.* 2010;121:e266-369.
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. Loeys BL *et al. J Med Genet.* 2010;47:476-85.
5. Loeys BL *et al. Nat Genet.* 2005;37:275-81.
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