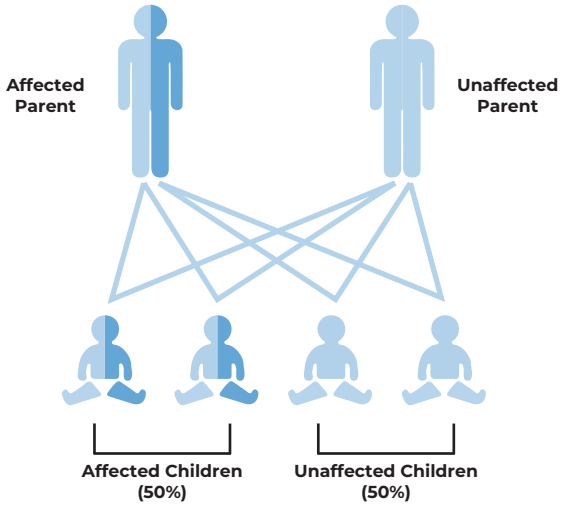
Innovative Gx Health

Genetic Testing Recommendations for Inherited Cardiovascular Diseases

When a patient is diagnosed with a cardiovascular disease, it affects not only the patient but also their family. Genetic testing can confirm a patient's clinical diagnosis, and in some cases, have direct implications for their prognosis and treatment options. Genetic testing can also identify family members who are at risk of developing the disease. For some inherited cardiovascular diseases, life-saving early interventions are an option available for asymptomatic relatives.

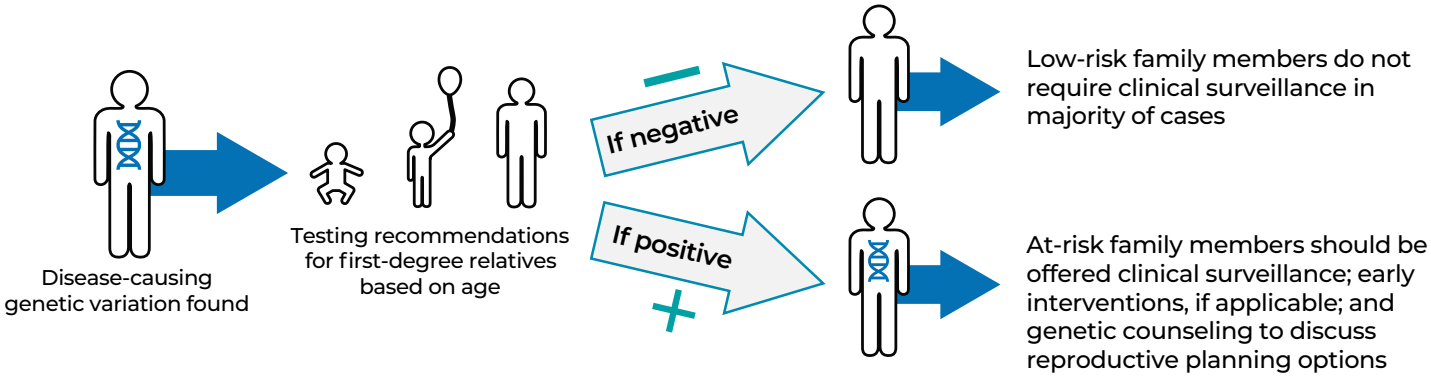
Inherited cardiovascular diseases are caused by changes in genes critical for heart function that can be passed down from generation to generation in a family. The majority of inherited cardiovascular diseases are inherited in an autosomal dominant pattern, which means first-degree relatives have a 50% chance of inheriting the same disease-causing genetic variation and being at increased risk of developing the disease. Family members who do not inherit the genetic variation are believed to have the same risk as the general population and do not need to undergo clinical surveillance.

Autosomal Dominant Inheritance



Professional societies - including the Heart Failure Society of America, Heart Rhythm Society, and European Society of Cardiology - offer guidelines outlining best practices for offering genetic testing to patients with potential inherited cardiovascular diseases. These genetic testing recommendations are constantly evolving as new genes are discovered and more research is conducted. At Innovative Gx Laboratories, we offer comprehensive testing for all guideline-recommended inherited cardiovascular disease genes, in addition to syndromic and emerging genes.

If a disease-causing genetic variation is found in a patient, targeted testing is recommended for their first-degree family members, regardless of whether they are showing symptoms or not. This approach is known as "cascade testing." The majority of inherited cardiovascular diseases are inherited in an autosomal dominant pattern, meaning first-degree relatives have an up to 50% chance of inheriting the same disease-causing genetic variation. Family members who decline genetic testing should be managed conservatively and undergo clinical surveillance.



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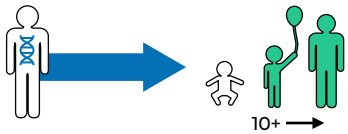
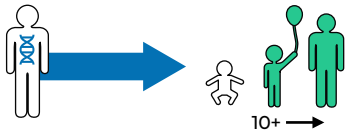
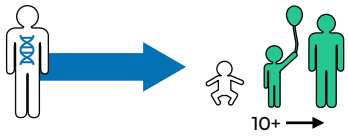
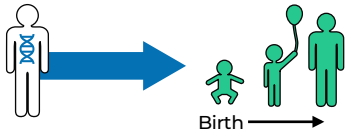
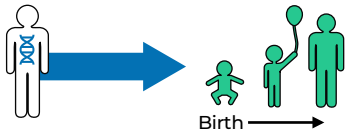
Cardiomyopathies

Management Implications Key

- Management information for patients
- Prognostic information for patients
- Early interventions for asymptomatic
- Identify at-risk relatives

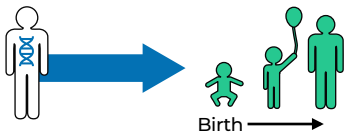
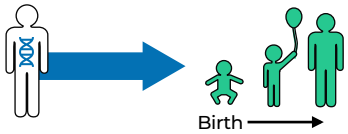
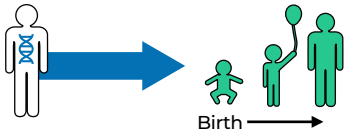
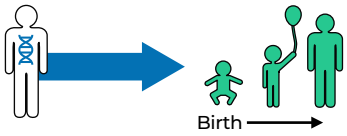
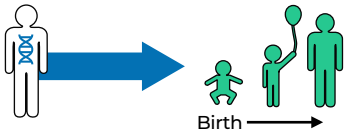
Genetic Testing Recommendations	Management Implications			
Arrhythmogenic right ventricular cardiomyopathy				
Recommended for all diagnosed individuals[1,2] 	●	●	●	●
Dilated cardiomyopathy				
Recommended for all diagnosed individuals[2] 	●	●		●
Hypertrophic cardiomyopathy				
Recommended for all diagnosed individuals[1,2] 	●	●	●	●
Left ventricular non-compaction cardiomyopathy				
Can be considered in diagnosed individuals if associated with other cardiomyopathies and LV dysfunction, syndromic features, and/or strong family history[1] 		●		●
Restrictive cardiomyopathy				
Recommended for all diagnosed individuals with cardiac TTR amyloidosis and can be considered for other diagnosed individuals with syndromic features and/or family history[1] 	●	●		●

Innovative Gx Health

Arrhythmias

Management Implications Key

- Management information for patients
- Prognostic information for patients
- Early interventions for asymptomatic
- Identify at-risk relatives

Genetic Testing Recommendations	Management Implications			
Brugada syndrome type 1				
Recommended for all individuals diagnosed with type 1. Not recommended for isolated type 2 or type 3 Brugada syndrome[1] 	●	●	●	●
Catecholaminergic polymorphic ventricular tachycardia				
Recommended for all diagnosed individuals[1] 	●	●	●	●
Long QT syndrome				
Recommended for all diagnosed individuals[1] 	●	●	●	●
Progressive cardiac conduction disease				
Recommended for diagnosed individuals when there is early age of diagnosis, suspicion of laminopathy and/or family history[1] 	●	●		●
Short QT syndrome				
Recommended for all diagnosed individuals[1] 	●	●		●

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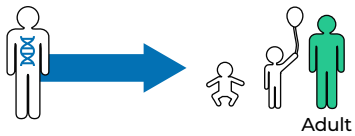
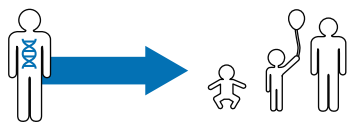
Familial thoracic aortic aneurysm and dissection

Management Implications Key

- Management information for patients
- Prognostic information for patients
- Early interventions for asymptomatic
- Identify at-risk relatives

Genetic Testing Recommendations	Management Implications
Patients with a thoracic aortic aneurysm (≥45 mm) or dissection AND • Age at diagnosis <50 years, OR • Age at diagnosis 50-60 years with no hypertension, OR • At least one first- or second-degree relative with a thoracic aortic aneurysm or dissection, OR • An aneurysm or dissection elsewhere in the arterial tree diagnosed <60 years of age, OR • A left-sided congenital heart defect (e.g. congenital aortic valve stenosis or bicuspid aortic valve) or patent ductus arteriosus, OR • Sudden death below 45 years of age. ***Patients with an aortic diameter between 40-45 mm should be judged on a case-by-case basis***[5]  Adult or 10 years before earliest case in family	● ● ●

Sudden cardiac death

Genetic Testing Recommendations	Management Implications
Recommended when death remains unexplained despite an autopsy and toxicology, or when attributable to a likely genetic cause[1]  Age to offer genetic testing depends on gene/disease identified	● ● ●

Inherited Cardiovascular Disease Testing

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Diagnosis	Recommended Panel	Genes
Arrhythmogenic right ventricular cardiomyopathy (ARVC/D)	**Arrhythmogenic Right Ventricular Cardiomyopathy Panel**	*ACTN2, AKAP9, ANK2, ANKRD1, CACNA1C, CACNB2, CASQ2, CAV3, CTNNA3, DES, DSC2, DSG2, DSP, EMD, FLNC, GPD1L, HCN4, JUP, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LDB3, LMNA, NKX2-5, PDLIM3, PKP2, PLN, PRKAG2, RANGRF, RBM20, RYR2, SCN1B, SCN3B, SCN4B, SCN5A, SNTA1, TGFB3, TMEM43, TNNI3, TNNT2, TTN (46 genes)*
Dilated Cardiomyopathy	**Dilated Cardiomyopathy Panel**	*ABCC9, ACADVL, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, CASQ2, CAV3, CAVIN4, CHRM2, CPT2, CRYAB, CSRP3, CTF1, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FHL2, FKRP, FKTN, FLNC, GATA4, GATA6, GATAD1, GLA, ILK, JUP, LAMA4, LAMP2, LDB3, LMNA, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEBL, NEXN, NKX2-5, NPPA, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN5A, SDHA, SGCD, SLC22A5, TAZ, TBX20, TCAP, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TTN, TTR, TXNRD2, VCL (78 genes)*
Hypertrophic Cardiomyopathy	**Hypertrophic Cardiomyopathy Panel**	*A2ML1, ABCC9, ACADVL, ACTC1, ACTN2, AGL, ANKRD1, BAG3, BRAF, CACNA1C, CALR3, CAV3, CBL, CPT2, CRYAB, CSRP3, CTF1, DES, DMD, DSC2, DSG2, DSP, DTNA, ELAC2, EMD, FHL1, FKTN, FLNC, FXN, GAA, GATA4, GATAD1, GLA, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, NF1, NRAS, PDLIM3, PKP2, PLN, PRKAG2, PTPN11, RAF1, RASA1, RBM20, RIT1, RRAS, RYR2, SCN5A, SGCD, SHOC2, SOS1, SOS2, SPRED1, TAZ, TCAP, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL (86 genes)*
Restrictive cardiomyopathy	**Dilated Cardiomyopathy Panel + Hypertrophic Cardiomyopathy Panel** [1]	*Dilated Cardiomyopathy Panel + Hypertrophic Cardiomyopathy Panel genes*
Brugada syndrome CPVT Long QT syndrome Short QT syndrome	**Inherited Arrhythmias Panel**	*ABCC9, ACTN2, AKAP9, ANK2, ANKRD1, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CPT1A, CTNNA3, DEPDC5, DES, DSC2, DSG2, DSP, EMD, FLNC, GJA5, GPD1L, GYG1, HCN4, JUP, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNE5, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNK3, KCNQ1, KCNQ2, KCNQ3, KCNT1, LDB3, LMNA, NKX2-5, NPPA, PCDH19, PDLIM3, PKP2, PLN, PRKAG2, PRRT2, RANGRF, RBM20, RYR2, SCN10A, SCN1A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SCN8A, SCN9A, SLC25A20, SLC2A1, SLMAP, SNTA1, TBX5, TGFB3, TMEM43, TNNI3, TNNT2, TRDN, TRPM4, TTN (76 genes)*
Familial thoracic aortic aneurysm and dissection	**Marfan Syndrome and Thoracic Aortic Aneurysm and Dissection Panel**	*ABL1, ACTA2, ADAMTS10, ADAMTS17, BGN, CBS, COL1A1, COL3A1, COL5A1, COL5A2, EFEMP2, ELN, FBN1, FBN2, FLNA, FOXE3, HCN4, IPO8, LOX, LTBP3, MAT2A, MED12, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TAB2, TGFB2, TGFB3, TGFBR1, TGFBR2 (39 genes)*

Test Specifics:

Sequencing and copy number variant analysis performed via next-generation sequencing. All panels have turnaround time of approximately 3-5 weeks. 96% at 20x coverage.

References:

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2. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, Morales A, Taylor MRG, Vatta M, Ware SM. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. 2018 May;24(5):281-302. doi: 10.1016/j.cardfail.2018.03.004. Epub 2018 Mar 19. PMID: 29567486.
3. Hershberger, R.E., Givertz, M., Ho, C.Y. et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 20, 899–909 (2018). https://doi.org/10.1038/s41436-018-0039-z.
4. Campuzano O, Sarquella-Brugada G, Cesar S, Arbelo E, Brugada J, Brugada R. Recent Advances in Short QT Syndrome. Front Cardiovasc Med. 2018;5:149. Published 2018 Oct 29. doi:10.3389/fcvm.2018.00149
5. Verhagen JMA, Kempers M, Cozijnsen L, Bouma BJ, Duijnhouwer AL, Post JG, Hilhorst-Hofstee Y, Bekkers SCAM, Kerstjens-Frederikse WS, van Brakel TJ, Lambermon E, Wessels MW, Loeys BL, Roos-Hesselink JW, van de Laar IMBH; National Working Group on BAV & TAA. Expert consensus recommendations on the cardiogenetic care for patients with thoracic aortic disease and their first-degree relatives. Int J Cardiol. 2018 May 1;258:243-248. doi: 10.1016/j.ijcard.2018.01.145. Epub 2018 Feb 7. PMID: 29452988.