THE PATHCARE NEWS

GENETIC TESTING FOR HEREDITARY CARDIOMYOPATHIES AND ARRHYTHMIAS

Hereditary cardiomyopathy and arrhythmia disorders are genetically heterogeneous meaning that within each category there are multiple disease genes, and many different pathogenic (disease-causing) variants with overlapping phenotypes. Determining the gene and pattern of inheritance for each variant in an individual is critical for accurate risk assessment of other family members.

HEREDITARY CARDIOMYOPATHIES

Hereditary cardiomyopathies are classified clinically according to their functional and morphologic features. These diagnostic classifications can predict major complications and delineate treatment options for each group. Finer resolution of these categories is possible with the aid of molecular genetic testing.

1. DILATED CARDIOMYOPATHY

The main features of dilated cardiomyopathy (DCM) are left ventricular dilatation, systolic dysfunction, myocyte death, and myocardial fibrosis. DCM can be acquired, most commonly through ischemic injury. It may also be part of a multisystem disorder: eg. Duchenne and Becker muscular dystrophy, HFE hemochromatosis or a mitochondrial disorder.

In cases where there is a young age of onset and/or family history, non-syndromic causes should be considered. Variants in more than 30 genes have been identified in up to 30%-35% of individuals with non-syndromic DCM.

Table 1: Non-syndromic DCM genes

Gene	% of DCM Caused by Pathogenic Variants in Gene	Mode of inheritance*
TTN	15%-20%	AD
LMNA	6%	AD
MYH7	4%	AD
FLNC	2%-4%	AD
BAG3	3%	AD
TNNT2	3%	AD
Other	Rare	AD/AR

** AR: Autosomal recessive | AD: Autosomal dominant*

2. HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is characterised by unexplained left ventricular hypertrophy (LVH), often with interventricular septum involvement. The clinical manifestations of HCM are highly variable, ranging from asymptomatic LVH to arrhythmias to refractory heart failure.

HCM may either be acquired, non-syndromic, or part of a syndrome: eg. Fabry disease, Friedreich ataxia, Pompe disease, Hereditary transthyretin amyloidosis or a RASopathy/Noonan spectrum disorder.

Table 2: Non-syndromic HCM genes

Gene	% of HCM Caused by Pathogenic Variants in Gene	Mode of inheritance*
MYBPC3	50%	AD
MYH7	33%	AD
TNNI3	5%	AD
TNNT2	2%-4%	AD
ACTC1	3%	AD
MYL2	3%	AD
MYL3	Rare	AD/AR
Other	Rare	AD/AR

**AR: Autosomal recessive | AD: Autosomal dominant*

3. ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary cardiomyopathy that is often diagnosed after an individual presents with arrhythmia findings.

Table 3: Genes associated with ARVC

Gene	% of ARVC Caused by Pathogenic Variants in Gene	Mode of inheritance*
PKP2	34%-74%	AD
DSG2	5%-26%	AD/AR
DSP	4%	AD
DSC2	1%-2%	AD/AR
JUP	0.5%-2%	AD
TMEM43/ DES/PLN	Rare	AD
Other	Rare	AD/AR

** AR: Autosomal recessive | AD: Autosomal dominant*

A pathogenic variant in one of the genes associated with ARVC is identified in up to 66% of individuals with a clinical diagnosis of ARVC. Approximately 2%-4% of individuals with ARVC have more than one pathogenic variant identified. Individuals with more than one ARVC-related pathogenic variant have a propensity to more severe disease, including a younger age of onset, arrhythmias, and progression to cardiomyopathy.

4. RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is a very rare but severe disease, accounting for ~ 5% of all cardiomyopathy cases. Three of the leading causes of RCM are cardiac amyloidosis, cardiac sarcoidosis, and cardiac hemochromatosis. Genes associated with RCM include: *TNNI3, TNNT2, TNNC1, TPM1, TTN, MYH7, MYL2, MYBPC3, MPN, DES, FLNC, LMNA, BAG3.*

HEREDITARY ARRHYTHMIAS

The main inherited cardiac arrhythmia syndromes are: Long QT syndrome (LQTS), Short QT syndrome (SQTS), Catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS).

These rare diseases are often the underlying cause of sudden cardiac death in young individuals and result from pathogenic variants in several genes encoding ion channels or proteins involved in their regulation.

Gene	Associated disorder	Mode of inheritance*
KCNQ1	LQTS	AD
	Jervell and Lange-Nielsen syndrome	AR
	SQTS	AD
KCNH2	LQTS and SQTS	AD
KCNE1	Jervell and Lange-Nielsen syndrome	AR
KCNJ2	Andersen–Tawil syndrome/SQTS	AD
SCN5A	LQTS	AD
	BrS	Complex
CALM1	LQTS and CPVT	AD
CALM2	LQTS and CPVT	AD
CALM3	LQTS	AD
ANK2	CPVT	AD
TRDN	CPVT	AD
CACNA1C	Timothy syndrome	AD
RYR2	CPVT	AD
CASQ2	CPVT	AR
TECRL	CPVT	AR

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GENETIC TESTING

Individuals with clinical symptoms of inherited arrhythmia or cardiomyopathy may benefit from genetic testing to establish or confirm a diagnosis, clarify risks, or inform management options. For asymptomatic individuals within a family with a known pathogenic variant, the biggest benefit to testing is early clinical management (e.g. in the form of medication or ICD implant), and the avoidance of certain activities and medications that can trigger symptoms.

Due to the extensive clinical overlap between different arrhythmia and cardiomyopathy conditions, comprehensive genetic testing can be requested as it enables a more efficient evaluation of multiple conditions based on a single indication for testing. For some conditions, for example Brugada syndrome, a more targeted approach is recommended.

INTERNATIONAL SEND-AWAY SERVICE
INVITAE

PathCare offers a referral service to Invitae Laboratory in the USA. Invitae offers an extensive genetic test menu over a broad range of clinical areas, including cardiology: https://www.invitae.com/en/providers/test-catalog/cardiology?tab=tests

Invitae offers testing via single-gene or multi-gene panels at a fixed patient-pay price of 349 USD**, with the additional benefits of re-requisitioning a sample for additional genes at no extra cost (within the same clinical area), and free-of-charge family variant testing to blood relatives, within 150 days of the initial patient's report (PathCare handling fee will still apply). PathCare charges an international handling fee (R1000**) which is paid upfront when providing the sample The turnaround time for Invitae tests is approximately 4 weeks.

CENTOGENE

PathCare offers a referral service to Centogene Laboratory in Germany. Centogene offers NGS Hereditary Diagnostic Panels, as well as whole exome sequencing (WES) and other options.

The cost of Centogene panels varies; however, standard NGS multigene panel testing starts at USD 435**. PathCare charges a R750** handling fee for Centogene testing. The turnaround time for Centogene testing is approximately 6 weeks for panels and 7-8 weeks for exomes.

*(** Pricing is correct and valid as of February 2024. Costs are subject to change)*

GENETIC COUNSELLING

It is internationally recognised and strongly recommended that genetic testing be offered in the context of appropriate pre- and post-test genetic counselling by a genetics professional.

PathCare does not offer a clinical genetic counselling service but is able to provide you with contact details for genetic counsellors in South Africa. Please contact our Genetics Team for a list of HPCSA-registered genetic counsellors who you can refer your patients to. Most genetic counsellors would be able to arrange online consultations if necessary.

Please feel free to contact our PathCare Genetics Team if you have any questions on 021 596 3655 or geneticconsult@pathcare.net

QUICK GUIDE TO TESTING

	INVITAE	CENTOGENE
Location	United States of America	Germany
Tests	Invitae Hypertrophic Cardiomyopathy panel (~44 genes) Invitae Dilated Cardiomyopathy and Left Ventricular Noncompaction Panel (~80 genes) Invitae Arrhythmogenic Cardiomyopathy Panel (~27 genes) Invitae Cardiomyopathy Comprehensive panel (~121 genes) Invitae Long QT Syndrome Panel (~17 genes) Invitae Short QT Syndrome Panel (~6 genes) Invitae Catecholaminergic Polymorphic Ventricular Tachycardia Panel (~7 genes) Invitae Brugada Syndrome Test (~20 genes) Invitae Arrhythmia Comprehensive Panel (~80 genes) Invitae Arrhythmia and Cardiomyopathy Comprehensive panel (~168 genes)	CentoCardio panel, disorders covered: Arrhythmogenic right ventricular cardiomyopathy / Brugada syndrome / Catecholaminergic polymorphic ventricular tachycardia / Congenital heart defects / Dilated cardiomyopathy / Dolichoectasia / Hereditary arrhythmia syndromes / Hereditary hemorrhagic telangiectasia / Heterotaxy syndrome / Hypertrophic cardiomyopathy / Hypomagnesemia / Long QT syndrome / Short QT syndrome
Test cost	USD 349**	USD 435**
Handling fee	ZAR 1000**	ZAR 750**
Turn around time	~4 weeks	Panels ~ 6 weeks
Sample type	4 ml EDTA whole blood	4 ml EDTA whole blood
Additional benefits	Family variant testing at no additional charge, following pre-test counselling, for all blood relatives of patients who undergo gene/panel testing at Invitae and are found to have a pathogenic or likely pathogenic variant. The PathCare handling fee will still apply. This order must be placed within 150 days of the original patient's test report. Re-requisition: If you don't get the answers you need from the initial test, you can add additional genes or panels within the same clinical area within 150 days at no additional charge if clinically indicated.	

References

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3. Hershberger & Jordan. Dilated Cardiomyopathy Overview. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1309/
4. McNally et al. Arrhythmogenic Right Ventricular Cardiomyopathy Overview. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1131/
5. Schwartz et al. Inherited cardiac arrhythmias. Nat Rev Dis Primers. 2020 Jul. doi: 10.1038/s41572-020-0188-7