Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

North Bristol NHS Trust

Cardiac panel testing

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Sample Required

See Sample requirements page at www.nbt.nhs.uk/genetics for full details

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).
Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

Consent and Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**
DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.
Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

- Heritable myocardial disease and cardiac electrophysiological abnormalities are causes of cardiac-related morbidity and sudden cardiac death (SCD). Gene panel testing may determine the pathogenic basis for SCD and clarify cause and manner of death. For symptomatic patients, identification of a genetic cause can inform choice of treatment, prognosis and disease progression.
- Heritable cardiac diseases with defined genetic aetiologies include: aortopathies; DCM, HCM, LVNC, ARVC/D; congenital heart defects; atrial fibrillation; Brugada Syndrome; Long and Short QT syndromes; ventricular fibrillation / tachycardia; RASopathies; and unclassified cardiomyopathies. These can also be seen in combination.

Service Offered

Cardiac Gene panels

- **Aortopathy panel (29 genes)**
- **Marfan Syndrome (1 gene)**
- **Bicuspid aortic valve panel (9 genes)**
- **Arrhythmia panel (54 genes)**
- **Arrhythmia, Long QT Syndrome only (15 genes)**
- **Cardiomyopathy panel (120 genes)**
- **Hypertrophic cardiomyopathy panel (19 genes)**
- **Congenital heart disease panel (45 genes)**
- **Molecular autopsy (combination of the above)**
- **Pulmonary hypertension (8 genes)**

Genes are analysed as virtual panels using a custom Clinical Exome target enrichment kit, NextSeq (Illumina) sequencing, and GATK best practice variant pipeline. Copy number variation is assessed for the targeted genes using the ExomeDepth algorithm.

- Familial testing is available for known variants (Sanger sequencing). **Predictive tests must be referred from Clinical Genetics.**

Referrals

- Referrals can be accepted nationally from consultants from appropriate disciplines such as clinical geneticists, paediatric cardiologists and paediatric metabolic consultants. **However, it is recommended that discussion in an inherited cardiac conditions MDT is undertaken prior to referral.**

Target reporting Times

Diagnostic screen:	84 days
Familial testing (Including predictives unless urgent):	42 days (by Sanger sequencing)
Urgent:	4-6 weeks on a case by case basis

Please contact the laboratory for up to date prices

Quality

•BGL participates in the following external quality assurance schemes: GenQA arrhythmia and cardiomyopathy; pathogenicity of sequence variants; variant validation and NGS (germline) schemes along with the EMQN DNA Sanger sequencing.

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DETAILS CORRECT AT DATE OF PRINTING ONLY
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North Bristol NHS Trust

Cardiac NGS panel pre-test proforma:

Patient name:		Referring consultant*:
DOB:	Gender:	Department and hospital:
Postcode:		
NHS number:		Hospital number/CG number:
Ethnic origin:		Date requested:
Reviewed at MDT (date):		
Review comments/additional actions:		

*** Please note it is suggested that all referrals should be discussed at an ICC MDT prior to referral**

Panel required:

A combination of the panels below can be requested by ticking more than one box.

AD hoc gene panels can be requested, please contact the lab for further information.

Panel	Tick as appropriate
Aortopathy (29 genes, includes *FBN1*)	
Marfan Syndrome (*FBN1* only)	
Bicuspid aortic valve (9 genes)	
Arrhythmia (54 genes, includes LQT genes)	
Long QT Syndrome (15 genes)	
Cardiomyopathy (120 genes including hypertrophic cardiomyopathy genes)	
Hypertrophic cardiomyopathy (19 genes)	
Congenital heart disease (45 genes)	
Molecular autopsy panel (combination of genes above)	
Pulmonary hypertension (8 genes)	

Indications for testing:

Suspected diagnosis:

Disorder	Tick as appropriate
Aortopathy	
Marfan Syndrome	
Bicuspid aortic valve	
Long QT syndrome	
Torsades de pointes	
Short QT syndrome	

Disorder	Tick as appropriate
Brugada Syndrome	
Supraventricular Arrhythmias:	
Atrial Fibrillation	
Paroxysmal Supraventricular Tachycardia	
Wolff-Parkinson-White syndrome	
Ventricular Arrhythmias:	
Ventricular Tachycardia	
Ventricular Fibrillation	
Bradyarrhythmias	
Congenital heart disease	
Cardiomyopathy:	
DCM – dilated cardiomyopathy	
HCM – hypertrophic cardiomyopathy	
LVNC - Left ventricular non-compaction	
ARVC – Arrhythmogenic right ventricular cardiomyopathy	
RDM/RCM –restrictive cardiomyopathy	
Mixed features of above please give details below	
Pulmonary arterial hypertension	
Pulmonary hypertension	

Clinical features:

Criteria	Indicate if this patient meets <u>each</u> criteria (Yes/No/Not known)
Sudden cardiac death	
Congestive heart failure	
Syncope	
Palpitations	
Septal hypertrophy	
LV thickening	
Cardiomegaly	
LV dilatation	
LV systolic impairment	
ECG (electrocardiography) results:	
Echocardiography results:	
Ejection fraction < 50%?	
Serum creatine kinase results:	
Atrial septal defect	
Ventricular septal defect	

Patent Ductus Arteriosus	
Tetralogy of Fallot	
Valvular heart defect	
Stenosis – location:	
Atresia – location:	
Regurgitation – location:	
Other congenital heart defect	
Other features e.g. dysmorphism, any facial features of Noonan, CFC (cardio-facio-cutaneous), Costello or LEOPARD syndromes.	
Neuromuscular features	
Metabolic features	
Other investigations carried out including array CGH	
Histology if available	
Connective tissue symptoms (details of)	

Family history (please give details below including relationship and if any consanguinity is reported in the family). Please include any previous genetic testing results:

Please give any further clinical details including any possible suspected diagnoses:

Counselling and consent:

It has been assumed that, in submitting a sample and request for testing, that the referring clinician has counselled the patient appropriately that:

- multiple genes will be targeted and analysed in the proband.
- the test may or may not find the cause of the condition.
- **the test may find changes in included genes associated with either predisposition, syndromic or metabolic disorders (see tables below).**
- that any genetic changes detected will fall into one of the following categories:

  1. Known genetic variants compatible with the patient's phenotype.

  2. Novel genetic variants, which may be clinically relevant but which may require further investigation including family studies.

  3. Novel genetic variants that may be related to the phenotype but which we are unable to interpret the clinical significance of at present.

  4. That the results obtained may have implications for relatives of the proband.

Please note these NGS panels include genes associated with either predisposition, syndromic or metabolic disorders. Genes can be excluded from this test upon request. Further details of individual genes can be obtained from the laboratory on request.

Aortopathy panel (29 genes):
ACTA2, ADAMTS10, ADAMTS17, ADAMTSL4, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, ELN, FBN1, FBN2, FLNA, FOXE3, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SOX18, TGFB2, TGFB3, TGFBR1, TGFBR2.

Bicuspid aortic valve panel (9 genes):
ACTA2, FBN1, FBN2, FLNA, NKX2-5, NOS3, NOTCH1, PLOD1, TGFBR2.

Arrhythmia panel (54 genes):

ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CASQ2, CAV3, CTNNA3, DES, DMPK, DPP6, DSC2, DSG2, DSP, GJA5, GNAI2, GPD1L, HCN4, JUP, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNK3, KCNN3, KCNQ1, LDB3, LMNA, MYH6, NOS1AP, NPPA, PKP2, PLN, PRKAG2, RANGRF, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SNTA1, TGFB3, TMEM43, TRDN, TRPM4.

Long QT syndrome panel (15 genes – included in the Arrhythmia panel also):

AKAP9, ANK2, CACNA1C, CALM1,CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, NOS1AP, SCN4B, SCN5A, SNTA1.

Congenital heart disease panel (45 genes):
ACTC1, ACVR2B, CHD7, CITED2, CRELD1, DNAH11, DNAH5, DNAI1, ELN, EVC, EVC2, FLNA, FOXC1, FOXH1, GATA4, GATA6, GDF1, GJA5, IRX4, JAG1, MED13L, MKKS, MKS1, MYH6, MYH7, NKX2-5, NKX2-6, NODAL, NOTCH1, NOTCH2, PITX2 , RBM10, SEMA3E, SMAD2, SMAD6, STK4, TAB2, TBX1, TBX20, TBX3,TBX5, TFAP2B, TLL1, ZFPM2, ZIC3.

Cardiomyopathy panel (120 genes):
A2ML1, ABCC9, ACADVL, ACTC1, ACTN2, AGL, ANKRD1, ATP5E, BAG3, BRAF, CALR3, CASQ2, CAV3, CBL, COA5, CPT2, CRYAB, CSRP3, CTF1, CTNNA3, DES, DMD, DMPK, DNAJC19, DNM1L, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FHL1, FHL2, FKTN, FLNC, FOXRED1, GAA, GATAD1, GBE1, GLA, GLB1, GUSB, HFE, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, MAP2K1, MAP2K2, MIB1, MMACHC, MRPL3, MUT, MYBPC3, MYH11, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, NF1, NRAS, PCCA, PCCB, PDLIM3, PIK3CA, PIK3R2, PKP2, PLN, PNPLA2, PRDM16, PRKAG2, PTPN11, RAF1, RASA1, RBM20, RIT1, RYR2, SCN5A, SCO2, SGCD, SHOC2, SLC22A5, SLC25A20, SLC25A3, SLC25A4, SOS1, SPRED1, STAMBP, STK4, SYNE1, SYNE2, TAZ, TCAP, TGFB3, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TRIM63, TSFM, TTN, TTR, TXNRD2, VCL, XK.

Hypertrophic cardiomyopathy panel (19 genes):
ACTC1, ACTN2, ANKRD1, CSRP3, FHL1, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Molecular autopsy panel:
A2ML1, ABCC9, ACADVL, ACTC1, ACTN2, ACVR2B, AGL, AKAP9, ANK2, ANKRD1, ATP5E, BAG3, BRAF, CACNA1C, CACNA2D1, CACNB2, CALM1, CALR3, CASQ2, CAV3, CBL, CBS, CHD7, CITED2, COA5, CPT2, CRELD1, CRYAB, CSRP3, CTF1, CTNNA3, DES, DMD, DMPK, DNAH11, DNAH5, DNAI1, DNAJC19, DNM1L, DOLK, DPP6, DSC2, DSG2, DSP, DTNA, EMD, EVC, EVC2, EYA4, FHL1, FHL2, FKTN, FOXC1, FOXH1, FOXRED1, GAA, GATA4, GATA6, GATAD1, GBE1, GDF1, GJA5, GLA, GLB1, GNAI2, GPD1L, GUSB, HCN4, HFE, HRAS, ILK, IRX4, JAG1, JPH2, JUP, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNK3, KCNN3, KCNQ1, KRAS, LAMA4, LAMP2, LDB3, LMNA, LOX, MAP2K1, MAP2K2, MED13L, MIB1, MKKS, MKS1, MMACHC, MRPL3, MUT, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOM1,

MYOZ2, MYPN, NEBL, NEXN, NF1, NKX2-5, NKX2-6, NODAL, NOS1AP, NOS3, NOTCH1, NOTCH2, NPPA, NRAS, PCCA, PCCB, PDLIM3, PIK3CA, PIK3R2, PITX2, PKP2, PLN, PNPLA2, PRDM16, PRKAG2, PTPN11, RAF1, RANGRF, RASA1, RBM10, RBM20, RIT1, RYR2, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SCO2, SEMA3E, SGCD, SHOC2, SLC22A5, SLC25A20, SLC25A3, SLC25A4, SMAD2, SMAD6, SNTA1, SOS1, SPRED1, STAMBP, STK4, SYNE1, SYNE2, TAB2, TAZ, TBX1, TBX20, TBX3, TBX5, TCAP, TFAP2B, TLL1, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TRIM63, TRPM4, TSFM, TTN, TTR, TXNRD2, VCL, XK, ZFPM2, ZIC3.

Pulmonary hypertension panel (8 genes):

ACVRL1, BMPR1B, BMPR2, CAV1, EIF2AK4, ENG, KCNK3, SMAD9.