INTRODUCTION
The Oxford Medical Genetics Laboratory offers a molecular testing service for a number of cardiac arrhythmia conditions. Most tests utilise next generation sequencing technology (NGS) although Sanger sequencing is undertaken for tests that only require analysis of 1 or 2 genes. Diagnostic samples undergoing NGS are processed using the full panel of 43 genes. Samples are then tailored at the analysis and interpretation stage to only analyse a specific sub panel of genes that are implicated with the specific phenotype. This approach enables subsequent retrospective analysis of other genes on the panel at a later date. The NGS methodology used does not provide 100% “coverage” of all genes and therefore some genes (those called genes of higher interest) are covered to 100% by Sanger sequencing the under-covered bases i.e. “gap filling”.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>APPROACH</th>
<th>GENES</th>
<th>GENES OF HIGHER INTEREST</th>
<th>MLPA ANALYSIS (on request)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)</td>
<td>NGS Panel</td>
<td>DES, DSG2, DSC2, DSP, JUP, LMNA, PKP2, PLN, TMEM43 (N.B., also offered as subpanel within cardiomyopathy panel)</td>
<td>-</td>
<td>PKP2 (N.B.: Probes for DSP, JUP, DSC2, DSG2 and TGFβ3 and RYR2 are also included in this test)</td>
</tr>
<tr>
<td>Andersen Tawil Syndrome (ATS)</td>
<td>Sanger sequencing</td>
<td>KCN2</td>
<td>-</td>
<td>KCN2 (N.B.: Probes for KCNQ1, KCN2, KCN1, and KCN2 are also included in this test)</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>NGS Panel</td>
<td>SCN1B, SCN2B, SCN3B, SCN5A, SCN10A, SLMAP, TRPM4, CACNA1C, CACNA2D1, CACNB2, DLG1, GPDL1, HCN4, KCN3, KCNE1L, KCNJB8</td>
<td>SCN5A Key domains of HCN4</td>
<td>SCN5A available as separate test</td>
</tr>
<tr>
<td>CPVT</td>
<td>NGS Panel</td>
<td>CASQ2, CALM1, CALM2, CALM3, KCNJ2, RYR2, TRDN</td>
<td>Key domains of RYR2</td>
<td>-</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>NGS Panel</td>
<td>ANK2, AKAP9, CACNA1C, CALM1, CALM2, CALM3, CASQ2, CAV3, DH1, GPD1L, HCN4, KCN4, KCN3, KCNE1, KCNE1L, KCNE2, KCNE3, KCNE4, KCNE2, KCNJ5, KCNJ8, KCNJ1, PKP2, RYR2, SCN1A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SLMAP, SNTA1, TRDN, TRPM4</td>
<td>SCN5A, KCNJ2, KCNQ1</td>
<td>SCN5A = one test KCON1, KCN2, KCN4, KCN2 second test</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen syndrome (ULNS)</td>
<td>Sanger sequencing</td>
<td>KCNQ1 and KCNE1</td>
<td>-</td>
<td>KCNQ1 and KCNE1 (N.B.: Probes for KCNQ1, KCNE2 and KCNJ2 are also included in this test)</td>
</tr>
<tr>
<td>Timothy Syndrome (TS)</td>
<td>Sanger sequencing</td>
<td>Selected regions of CACNA1C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>General arrhythmia or Sudden Cardiac / Arrhythmic Death</td>
<td>NGS Panel</td>
<td>AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CASQ2, CAV3, DLG1, GPD1L, HCN4, KCN4, KCN3, KCNE1, KCNE1L, KCNE2, KCNE3, KCNE4, KCNE2, KCNJ5, KCNJ8, KCNJ1, PKP2, PLN, RYR2, SCN1A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SLMAP, SNTA1, TMEM43, TRDN, TRPM4</td>
<td>Can be arranged on case by case basis at a separate cost.</td>
<td>-</td>
</tr>
<tr>
<td>General Arrhythmia or sudden cardiac / Arrhythmic death with a clinical indication of ARVC</td>
<td>NGS Panel</td>
<td>AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CALM2, CASQ2, CAV3, DES, DLG1, DSC2, DSG2, DSP, GPDL1, HCN4, JUP, KCN3, KCNE1, KCNE1L, KCNE2, KCNE3, KCNE4, KCNE2, KCNJ5, KCNJ8, LMNA, PKP2, PLN, RYR2, SCN1A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SLMAP, SNTA1, TMEM43, TRDN, TRPM4</td>
<td>Can be arranged on case by case basis at an additional cost.</td>
<td>-</td>
</tr>
</tbody>
</table>

REFERRAL PROCEDURE
- Diagnostic referrals are accepted for probands with a suspected or confirmed diagnosis of specific types of cardiac arrhythmia (see table above) and may include a clinical suspicion of ARVC.
  - Referrals are accepted from Cardiology, Clinical Genetics and Consultants from other relevant medical specialties.
  - Clinical information and details of relevant family history should be provided with all referrals either on the original request form or on a separate pre-referral form (Cardiac arrhythmia pre-referral form).
  - Family test referrals are only accepted from Clinical Genetics specialists.
  - Referrals for affected family members (i.e. segregation analysis) must be accompanied by appropriate clinical information.
  - Referrals for unaffected family members will only be considered for variants with clear evidence for pathogenicity.
  - Clinical advice is available from Dr Edward Blair, Consultant Clinical Geneticist, at the Churchill Hospital (Ed.Blair@ouh.nhs.uk).
  - Further information about the test can be obtained from the laboratory (OxfordCardiac@nhs.net).

STRATEGY AND TECHNICAL INFORMATION
- Diagnostic Screens:
  - Gene target enrichment is undertaken using Agilent’s HaloPlex Target Enrichment System.
  - Libraries are sequenced on an Illumina MiSeq Desktop Sequencer.
  - Sequence data are analysed on a custom-designed bioinformatic pipeline.
  - Coverage varies but is typically 88–100% at >30 reads.
  - Where possible, genes of higher interest are covered to 100% by Sanger sequencing (see table above).
  - MLPA dosage analysis may be undertaken as a separate test on request (see table above).
  - Diagnostic screens for small gene numbers i.e., JLNS are undertaken by Sanger sequencing
  - Family tests involve targeted analysis by Sanger sequencing of the relevant exon.

TARGET REPORTING TIMES
Diagnostic test: 84-112 calendar days
Family test: 14 calendar days
MLPA Dosage Analysis: 14 calendar days
- Please see the current price list on the Oxford Genetics laboratory Molecular genetics page


N.B. Details are correct for the date of printing only. Last updated February, 2017