INTRODUCTION
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterised by progressive loss and fibro-fatty replacement of the ventricular myocardium. It is associated with ventricular tachycardia and an increased risk of sudden death. It is estimated to affect 1-5 per 5,000 individuals. It is familial in up to 50% of cases and is usually inherited in an autosomal dominant manner with incomplete penetrance. Mutations in >9 genes are known to predispose to ARVC, with the vast majority found in genes that encode protein components of the cardiac desmosome. Whilst the vast majority are point mutations, large-scale deletions and/or duplications involving the PKP2 gene are detected in ~2% of affected individuals.

The Oxford Medical Genetics Laboratory provides molecular genetic testing for nine ARVC-related genes (see table below). The overall clinical sensitivity for probands screened on this panel is ~40%.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Primary Related Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>Desmin</td>
<td>ARVC, DCM, myofibrillar myopathy</td>
</tr>
<tr>
<td>DSC2</td>
<td>Desmocollin 2</td>
<td>ARVC</td>
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<tr>
<td>DSG2</td>
<td>Desmoglein 2</td>
<td>ARVC</td>
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<tr>
<td>DSP</td>
<td>Desmoplakin</td>
<td>ARVC, Carvajal syndrome, DCM</td>
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<tr>
<td>JUP</td>
<td>Junction Plakoglobin</td>
<td>ARVC, Naxos syndrome</td>
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<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>DCM, skeletal myopathy, other laminopathies</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>ARVC, DCM, HCM</td>
</tr>
<tr>
<td>PKP2</td>
<td>Plakophilin 2</td>
<td>ARVC</td>
</tr>
<tr>
<td>TMEM43</td>
<td>Transmembrane Protein 43</td>
<td>ARVC</td>
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</table>

REFERRAL PROCEDURE
• Diagnostic referrals are accepted for probands with a suspected or confirmed diagnosis of ARVC.
  o Referrals are accepted from Cardiology, Clinical Genetics and Consultants from other relevant medical specialities.
  o 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 (ARVC pre-referral form).

• Family test referrals are only accepted from Clinical Genetics specialists.
  o Referrals for affected family members (i.e. segregation analysis) must be accompanied by appropriate clinical information.
  o 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).

SAMPLE REQUIREMENTS
• This analysis requires >4 μg of DNA at >30 ng/μl.
• DNA from formalin-fixed paraffin-embedded (FFPE) tissue may be suitable.
  o >300 ng (preferably >1,000 ng) at >30 ng/μl is required.
  o Total gene coverage may be lower due to the poor quality of DNA obtained from FFPE tissue.

STRATEGY AND TECHNICAL INFORMATION
• Diagnostic Screens:
  o Gene target enrichment is undertaken using Agilent’s HaloPlex Target Enrichment System.
  o Libraries are sequenced on an Illumina MiSeq Desktop Sequencer.
    ▪ This will involve sequence data generation in-house or by the High Throughput Genomics Group at the Wellcome Trust Centre for Human Genetics, Oxford.
  o Sequence data are analysed on a custom-designed bioinformatic pipeline.
  o Where possible, regions of interest (ROIs) in all nine genes are 100% covered either by >30 reads or by Sanger sequencing.
  o MLPA targeted at the PKP2 gene is also undertaken.

• Family Tests:
  o Familial variants are targeted for analysis by Sanger sequencing of the relevant exon, with DNA from a family member used as a positive control where possible.

TARGET REPORTING TIMES
• Diagnostic screens: 60-80 working days
• Family tests: 10 working days
• Urgent analysis: Please contact the laboratory.

PRICING
Please see the current price list on the Oxford Genetics Laboratories Molecular Genetics page.

N.B. Details are correct for the date of printing only. Updated 12/10/2015.