Facts on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

- ARVD/C is a dominantly inherited disease affecting as many as 1 in 1000 individuals.
  

- ARVD/C is caused by mutations in any one of at least 7 genes, but mutations in one of 4 genes are most commonly found.
  
  Mutations in PKP2, DSG2, DSP2, or DSC2 account for up to 74% of familial ARVD/C.
  
  Bauce B, et al. (2005) Eur Heart Jour 26:1666-75

- ARVD/C is the second most common cause of sudden cardiac death (SCD) in young adults, including trained athletes. Affected individuals are often unaware of their condition.
  
  About 20% SCD in young adults and athletes is due to ARVD/C.
  

- Extensive cardiac screening at regular intervals can identify patients at high risk for SCD, who may benefit from implantation of a cardioverter-defibrillator (ICD).
  
  ICDs averted potentially lethal arrhythmias in 72% of 132 high-risk ARVD/C patients.
  

- Children who are genetically predisposed to ARVD/C may be advised not to participate in certain competitive sports.
  

- Genetic testing can confirm a diagnosis of familial ARVD/C in the index patient for a family and identify family members with a predisposition for ARVD/C at any age.
  
  Family members have a ~50% chance of inheriting ARVD/C.
  
  Hamid MS, et al. (2002) JACC 40: 1445-50
Using Genetic Testing
To Diagnose Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

**Indications:**
- Clinical diagnosis of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)
- Unexplained cardiovascular symptoms such as palpitations and/or history of syncopal episodes in young adults, especially athletes
- Family history of ARVD/C
- Family history of sudden cardiac death in individuals under age 45

**Benefits:**
Genetic testing for ARVD/C can:
- confirm a clinical diagnosis of ARVD/C.
- identify at-risk family members who should undergo regular cardiac screening for ARVD/C.
- identify family members who do not need to undergo regular cardiac screening for ARVD/C.
- help to identify candidates for implantable cardioverter defibrillator (ICD) intervention.

**Background:**
- Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is characterized clinically by right ventricular (RV) arrhythmia and histologically by replacement of normal myocardial tissue in the RV by fibrotic adipose tissue.
- ARVD/C occurs at a prevalence of as high as 1 in 1000 (0.1%) individuals and typically shows a dominant mode of inheritance.¹,²
- ARVD/C is the second leading cause of SCD in young adults, including competitive athletes.³,⁴
- Extensive cardiac screening at regular intervals can identify patients at high risk for SCD, who may benefit from ICD implantation.⁵
- About 50% of ARVD/C cases are familial and are associated with mutations in any one of at least 8 different genes.²,⁶
- Most familial ARVD/C cases are due to mutations in genes encoding components of the cardiac desmosome, a complex of proteins forming intercellular junctions in the myocardium.⁷,⁸

**References:**

**Ordering Information:** Please see other side.
Ordering Information for Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD/C) Testing

**Indications for Testing**
- Clinical diagnosis of Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD/C)
- Unexplained cardiovascular symptoms such as palpitations and/or history of syncopal episodes in young adults, especially athletes
- Family history of ARVD/C
- Family history of sudden cardiac death in individuals under age 45

**Ordering Information for Single Gene Tests**

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>CPT Codes</th>
<th>Test Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKP2</td>
<td>83891(1) 83892(1) 83898(15) 83904(30) 83909(30) 83912(1)</td>
<td>190701</td>
</tr>
<tr>
<td>DSP</td>
<td>83891(1) 83892(1) 83898(38) 83904(76) 83909(76) 83912(1)</td>
<td>190702</td>
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<tr>
<td>DSC2</td>
<td>83891(1) 83892(1) 83898(17) 83904(34) 83909(34) 83912(1)</td>
<td>190703</td>
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<tr>
<td>DSG2</td>
<td>83891(1) 83892(1) 83898(17) 83904(34) 83909(34) 83912(1)</td>
<td>190704</td>
</tr>
</tbody>
</table>

**Ordering Information for Multi-Gene Panels**

*For multi-gene panels, a summary report will be issued in addition to an abbreviated report for each individual gene.*

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>CPT Codes</th>
<th>Test Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKP2, DSP, DSC2, DSG2</td>
<td>83891(1) 83892(1) 83898(87) 83904(174) 83909(174) 83912(4)</td>
<td>190799</td>
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</tbody>
</table>

**Family Testing (single amplicon)**

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>CPT Codes</th>
<th>Test Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKP2</td>
<td>83891(1) 83892(1) 83898(2) 83904(2) 83909(2) 83912(1)</td>
<td>use single-gene test code</td>
</tr>
</tbody>
</table>

**Test Methodology and Sample Requirements**

- Amplification by polymerase chain reaction (PCR); sequencing of entire protein-coding region
- For blood samples:
  - 2 mL whole blood in EDTA tube (lavender top)
  - Samples can be stored briefly at 4°C, but should be shipped on day of collection.
- For buccal swab samples:
  - (only accepted for family testing)
  - Please contact client services at 1-866-647-0735 for instructions.
- All sample types should be shipped overnight at room temperature.
- To request a sample shipping kit, please call 1-866-647-0735.

**Turn- around Times**

Turn-around times typically range from 7 to 21 days of receipt of sample and all required forms, but may vary depending on test volume and test-specific technical difficulties. Current TATs are posted on our website. Please schedule patient follow-up appointments for discussion of test results conservatively at 6 weeks.

For more information, please contact Correlagen Diagnostics, Inc., at 1-866-647-0735 or visit us on the web at www.correlagen.com.
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy – an Overview

Introduction

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C), which occurs at an estimated prevalence of as high as 1:1000 individuals (1), is characterized clinically by ventricular arrhythmia, most commonly arising from the right ventricle (RV), and histologically by replacement of normal myocardial tissue in the RV by fibrotic adipose tissue. Ventricular arrhythmias associated with ARVD/C account for about 20% of sudden cardiac death (SCD) in young individuals and athletes (2, 3). SCD can be prevented through use of an implantable cardioverter defibrillator (ICD), and occurrence of SCD events may be reduced by avoidance of mechanical stress due to physical exertion. However, at-risk individuals who may benefit from an ICD and lifestyle adjustments may be difficult to identify, since SCD can be the presenting symptom. Genetic testing can facilitate detection of at-risk individuals in familial forms of ARVD/C, which account for nearly 50% of all cases (4). Family members carrying the familial mutation detected in the index patient for the family are at highly increased risk of ARVD/C, while family members not carrying the familial mutation are not at increased risk. In the index patient, genetic testing can help to establish whether a specific case of ARVD/C is familial or not, by screening for presence of a germline mutation in the genes known to be associated with ARVD/C. A familial versus a sporadic nature of ARVD/C may otherwise not always be clear, since ARVD/C shows variable expressivity and penetrance, ranging from 20-60% (5-8).

Familial ARVD/C typically shows autosomal dominant inheritance and has been associated with mutations in any one of at least eight genes (see Table 1). Rare autosomal recessive forms of familial ARVD/C usually occur in the context of non-cardiac manifestations, such as palmoplantar keratoderma and woolly hair in Carvajal syndrome (9) and Naxos disease (10).

| Table 1: Genetic Causes of Familial ARVD/C (8-20) |
|-------------------------------|-----------------|-----------------|-----------------|
| **Gene (Protein)**            | **% ARVD/C**    | **Inheritance** |
| PKP2 (plakophilin 2)         | 10-43%          | (AD)            |
| DSG2 (desmoglein 2)          | 10%             | (AD)            |
| DSP (desmoplakin)            | 6-16%           | (AD); <1% (AR)* |
| DSC2 (desmocollin 2)         | 1-5%            | (AD)            |
| JUP (plakoglobin)            | <1%             | (AR)*           |
| RYR2 (cardiac ryanodine      | <1% (AR)*       | receptor 2)     |
| TGF-B3 (transforming growth  | 3%              | (AD)            |
| factor beta 3)               |                 |                 |
| TMEM43 (transmembrane protein 43) | <1% (AD)*     |

AD (autosomal dominant); AR (autosomal recessive) *presumed rare; reported as founder mutations in single population

Molecular Pathophysiology

Among the ARVD/C-associated genes, PKP2, DSG2, DSP, DSC2, and JUP code for desmosomal proteins while the RYR2, TGF-B3, and TMEM43 code for non-desmosomal proteins. Desmosomes are specialized multi-protein complexes that make up intercellular junctions mainly in tissues subject to mechanical stress, including the epidermis and myocardium. By providing cell-cell adhesion, desmosomes serve as the "cement" that holds cells together. In addition, they participate in cell signaling networks which are known to affect cell fate, proliferation, and apoptosis. Disruption of either function has been proposed to underlie the disease mechanism of ARVD/C. In a simple model, loss of cell adhesion results in apoptosis of myocytes and localized fibrosis (21). A more complex model (22) proposes that defects in gap-junction signaling give rise
to abnormal electrical conductivity that leads to arrhythmias.

**Clinical Presentation**

ARVD/C typically presents with palpitations and/or syncope, although cardiac arrest may also be the presenting manifestation (reviewed in 23). A higher occurrence of cardiac arrest has been associated with DSP-related ARVD/C (16). Characteristic of ARVD/C, an EKG usually shows RV arrhythmias triggered by physical effort. There may also be left ventricular (LV) arrhythmias, making the disease look more like dilated cardiomyopathy (23). DSG2- and DSC2-related ARVD/C may present with predominant LV involvement (7, 8, 14). Age-of-onset of ARVD/C is usually in the thirties, but PKP2-related ARVD/C often shows a significantly lower (by ~8 years) age-of-onset than other forms of ARVD/C (12). In addition, PKP2 mutations that lead to early-disease onset are usually also associated with higher penetrance, i.e., they cause disease in most mutation carriers. However, penetrance of PKP2-related ARVD/C can remain incomplete even above 70 years of age (24).

**Diagnosis**

Diagnosis of ARVD/C is based on so-called Task Force Criteria (TFC – see Table 2; refs. 4, 25). A positive diagnosis is indicated by presence of two major criteria, one major plus two minor criteria, or four minor criteria. Major criteria include family history of ARVD/C, electrocardiogram depolarization/conduction abnormalities, structural alterations, and presence of fibro-fatty tissue in the heart. Minor criteria generally constitute milder versions of the major criteria. A clinical diagnosis of familial ARVD/C can be confirmed through genetic testing, since published studies have shown a causal relationship to certain variants in PKP2, DSG2, DSP, and DSC2 (reviewed in 21). Once the familial mutation is known, genetic testing can also distinguish asymptomatic mutation carriers from non-carriers in an affected family. This distinction is important since mutation carriers, even if asymptomatic, are at high risk of ARVD/C and should be closely monitored for development of ARVD/C, while non-carriers are not at increased risk of ARVD/C. Depending on the family history and the type of mutation present, asymptomatic mutation carriers may even be candidates for ICD implantation.

**Treatment**

ARVD/C is typically treated with antiarrhythmic drugs, such as sodium blockers, beta-blockers, sotalol, amiodarone, or verapamil alone or in combinations. Risk of SCD may also be reduced by certain lifestyle adjustments, such as avoiding physical exertion. ICD implantation is commonly considered for patients who have been diagnosed with ARVD/C and have had an aborted SCD or are at high risk of SCD, based on presence of severe RV dysfunction, LV involvement, hemodynamically unstable VT/VF, pleomorphic VT, epsilon potential, late potential, and family history of SCD and/or ARVD/C (26). In a study tracking the efficacy of ICD in prevention of cardiac arrest, ICD intervention averted SCD in 72% patients with severe ARVD/C over a 36-month period (27). However, since ICD implantation is invasive, requires frequent clinical follow-up, and may cause side effects such as inappropriate defibrillation/shock, the risk-benefit ratio has to be carefully considered. In severe cases of ARVD/C, heart transplantation may be necessary.
Table 2: ARVD/C Diagnostic Criteria (TFC)

<table>
<thead>
<tr>
<th>Group</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural/Functional RV abnormality</td>
<td>Severe RV dilation with little or no LV involvement; localized RV aneurysm</td>
<td>Mild RV dilation with normal LV; regional RV hypokinesia</td>
</tr>
<tr>
<td>Tissue characterization</td>
<td>Replacement of myocardium by fibro-fatty infiltrate</td>
<td>No criteria reported</td>
</tr>
<tr>
<td>EKG depolarization/conduction abnormality</td>
<td>Epsilon waves or localized prolongation (&gt;110ms) of QRS complex in right precordial leads</td>
<td>Late potentials on signal-averaged EKG</td>
</tr>
<tr>
<td>EKG repolarization abnormality</td>
<td>No criteria reported</td>
<td>Inverted T waves on EKG; aged &gt;12 years; absence of right bundle branch block</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>No criteria reported</td>
<td>Left bundle branch block type ventricular tachycardia on EKG; frequent ventricular extrasystoles (&gt;1000/24h) on Holter monitoring</td>
</tr>
<tr>
<td>Family History of ARVD/C</td>
<td>Family history confirmed by autopsy or surgery</td>
<td>Family history of SCD (&gt;35 years of age) due to suspected ARVD/C; family history of ARVD/C clinically diagnosed based on TFC</td>
</tr>
</tbody>
</table>

Adapted from (21, 23)

References


Requisition Form

Please send sample and completed forms to ➔
(Ship sample overnight at room temperature.)

Is this a family test for a known familial mutation? □ □ yes no

Familial mutation ____________________________
Gene (eg, MYH7) ____________________________ Variant (eg, c.746G>A) ____________________________ Exon (eg, x9)

Was the index patient* tested at Correlagen? □ □ yes no
(*Family member in whom familial mutation was identified.)

If yes: Please complete Index Patient Section on right.

Relationship of current patient to index patient ____________________________

Patient Information (current patient)

Name ____________________________ First Name MI Last Name ____________________________
Date of Birth / / month day year Sex □ ♀ □ ♂
Social Security # ____________________________
Address Number Street Apt. ____________________________
Address City State Zip ____________________________
Phone day ( ) evening ( ) ____________________________

Physician’s Identifier for Patient ____________________________

Physician Information

Medical Specialty ____________________________
Name ____________________________ First Name Last Name ____________________________
Institution Name ____________________________
Address Number Street Building/Suite ____________________________
Address City State Zip ____________________________
Phone ( ) Fax ( ) ____________________________ e-mail ____________________________

Cancellation Policy:
Cancellation requests must be submitted in writing by the ordering physician. Cancellation requests will only be accepted if received before specimen testing begins.

* For testing in the fields of endocrinology and metabolism, please order from Athena Diagnostics, Inc.

Information on Index Patient

(if other than current patient)

Name: ____________________________ First Name MI Last Name ____________________________
Date of Birth / / month day year
Accession # ____________________________

Ordering* Check List:

☐ Requisition Form (required)
☐ Survey (requested)
☐ Test Selection Form (required)
☐ Payment Form (required)
☐ Letter of Medical Necessity (requested) for patients with commercial insurance
☐ Clinical Information Form (recommended)
☐ Informed Consent (required)
☐ Catalogue Page and FAQ Flier (for your information only)

For more information, please call: 1-866-647-0735

Sample Specifications

Date and Time of Sample Collection (required):

/ / month day year am pm

Sample Type (check one):

☐ Blood samples:
  o 2 mL whole blood in EDTA (lavender-top tube)
  o Can be stored briefly at 4°C, but should be shipped on day of collection

☐ Buccal swabs:
  o Please contact client services at 1-866-647-0735 for instructions.

☐ DNA samples:
  Preferably ≥1 µg at 50 ng/µl in TE
  Actual total amount of DNA: µg
  Actual DNA concentration: ng/µl

Accession Number (internal use) ____________________________

Correlagen Diagnostics, Inc.
307 Waverley Oaks Road, Suite 101
Waltham, MA 02452

(Sample receipt Mo-Fri only)
Dear client,

Please take a moment to fill out this survey. Your responses will help us to serve you even better in the future.

Thank you from your Correlagen team.

How did you hear about us?
- Through a colleague
- Through a patient
- Through a patient advocacy group
- Through the news media
- Through the internet
  - Search engine (such as Google, Yahoo, etc)
  - Google Ad
  - Other:
- Through an e-mail from us
- Through a phone call from us
- Other:

Have you ordered from us before?
- Yes
  How would you rank our services?
  
  Please circle one number (1=unsatisfactory; 5=excellent)
  
  Client services
  1  2  3  4  5
  Billing
  1  2  3  4  5
  Turn-around times
  1  2  3  4  5
  Result reports
  1  2  3  4  5
  Informational material
  1  2  3  4  5

- No

Which other genetic tests would you like us to offer?

________________________________________________________

________________________________________________________

Other comments:

________________________________________________________

________________________________________________________

Would you like someone to call you to discuss your responses?
- Yes
- No
Test Selection Form - Cardiology

Patient Name: 

Accession Number (internal use)

Atrial Septal Defect with Atroventricular Block

☐ # 190401  NKX2-5

Dilated Cardiomyopathy

☐ # 190599  TNNT2, MYBPC3, MYH7, TPM1, ACTC
☐ # 190501  TNNT2
☐ # 190502  TNNI3
☐ # 190503  TPM1
☐ # 190504  MYBPC3
☐ # 190505  MYH7
☐ # 190506  ACTC

Early-Onset Coronary Heart Disease

☐ # 190199  LDLR, APOB
☐ # 190101  LDLR
☐ # 190102  APOB

Hypertrophic Cardiomyopathy

☐ # 190398  TNNT2, MYBPC3, MYH7
☐ # 190397  TPM1, TNNI3, MYL2, MYL3, ACTC
☐ # 190396  TNNT2, MYBPC3, MYH7, TPM1, TNNI3, MYL2, MYL3, ACTC
☐ # 190395  PRKAG2, LAMP2
☐ # 190350  Reflexive-testing option:  TNNT2, MYBPC3, MYH7
If no (probable) disease variant found:  TPM1, TNNI3, MYL2, MYL3, ACTC
☐ # 190301  TNNT2
☐ # 190302  TNNI3
☐ # 190303  TPM1
☐ # 190304  MYBPC3
☐ # 190305  MYH7
☐ # 190306  MYL2
☐ # 190307  MYL3
☐ # 190308  ACTC
☐ # 190309  PRKAG2
☐ # 190310  LAMP2

Arrhythmogenic Right Ventricular Dysplasia

☐ # 190799  PKP2, DSP, DSC2, DSG2
☐ # 190701  PKP2
☐ # 190702  DSP
☐ # 190703  DSC2
☐ # 190704  DSG2

Marfan Syndrome

☐ # 190601  FBN1

Pulmonic Stenosis

☐ # 190201  PTPN11

Use same testcode for full gene test or single variant test.
# Payment Form

**Commercial Insurance**

Correlagen has established the Capped Patient-Payment Plan (CPPP) to assist patients covered by most commercial insurance. The CPPP limits the financial responsibility of the patient to 15% of the total cost plus any portion of the test cost that is applied by the insurance company to the patient’s annual deductible. To participate in the CPPP, patients must be pre-qualified prior to testing (contact a Client Services Representative to get pre-qualified). Once pre-qualified, patients need to complete the information below and provide the 15% payment before testing is initiated. Patients choosing not to participate in the CPPP will be responsible for all charges not covered by their insurance carrier within 60 days of claim submission. Note: a higher CPPP rate applies for family testing. See [http://www.correlagen.com/resources/billing.jsp](http://www.correlagen.com/resources/billing.jsp) for CPPP details and exceptions.

1 Commercial insurance does not include programs such as Medicare, Medicare HMOs, Medicaid, or Tricare/Champus.

**Authorization to Release Information and Pay Benefits:** I authorize Correlagen Diagnostics, Inc., to release all information necessary for reimbursement to my designated insurance carrier. I authorize that benefits under this claim be paid directly to Correlagen Diagnostics and will remit any insurance payments that I receive to Correlagen. I acknowledge responsibility for 100% of the service price if I fraudulently represent insurance. In the event of underpayment or denial by my insurance carrier, I authorize Correlagen or its designee to appeal on my behalf to overturn the denial or receive reimbursement for the underpaid claim.

2 Correlagen and/or its designee may perform this appeal on my behalf, but is not obligated to do so.

- [ ] I choose to participate in Correlagen's Capped Patient-Payment Plan (please fill out the Check/Credit Card section below)
- [ ] I waive the opportunity to participate in Correlagen's Capped Patient-Payment Plan

**Payment by Check/Credit Card** *(Credit card charges may be applied for self-pay, CPPP co-pays and any applicable deductibles)*

- [ ] Check or money order enclosed $ 
- [ ] Credit Card
  - [ ] Master Card
  - [ ] Visa
  - Card Number ____________________________
  - Expiration Date ________________________
  - [ ] Name as it appears on card ____________________________
  - Billing Address ____________________________
  - Number __________________ Street __________________ City __________________ State __________________ Zip __________________
  - Please bill my credit card for the amount of $ __________________

**Signature (required) Date**
To  
Name of Insurance Company: ________________________________

Request for coverage of diagnostic DNA-sequence analysis of the genes

PKP2  DSP  DSG2  DSC2

For the purpose of

confirming a diagnosis of arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C)
identifying the mutation leading to ARVD/C in a specific family (familial mutation)
identifying family members of a confirmed patient who do not need ongoing clinical screening for the development of ARVD/C because they do not harbor the familial mutation

Indicated by

Clinical diagnosis of ARVD/C
Unexplained cardiovascular symptoms such as palpitations and/or history of syncopal episodes in young adults, especially athletes:

Family history of ARVD/C

Regarding my patient

Name of patient: __________________________________________

Insurance number of patient: ________________________________

Name of primary insurance holder: __________________________

Group Policy Number: ______________________________________

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C), which occurs at an estimated prevalence of as high as 1:1000 individuals, is characterized clinically by ventricular arrhythmia, most commonly arising from the right ventricle (RV), and histologically by replacement of normal myocardial tissue in the RV by fibrotic adipose tissue. Ventricular arrhythmias associated with ARVD/C account for about 20% of sudden cardiac death (SCD) in young individuals and athletes. Since ARVD/C has been associated with mutations in any one of a number of genes, genetic testing can confirm a clinical diagnosis of ARVD/C. Genetic testing can also inform prognosis and genetic counseling, which may vary with the underlying genetic cause. Once the familial mutation has been identified through genetic testing of the index patient for a family, genetic testing can identify family members who are not at increased risk for ARVD/C (non-mutation carriers). No other test can reliably differentiate unaffected family members, who do not require further screening, from presymptomatic affected family members, who must regularly undergo extensive cardiac screening.

I am choosing Correlagen Diagnostics as the provider of genetic testing services, since this CLIA-certified testing laboratory offers reliable sequencing services, consistent variant analysis, and detailed result reporting with short turn-around times. Since known ARVD/C-associated mutations are spread throughout the genes linked to ARVD/C, Correlagen sequences the entire coding region of each specified gene in the index patient. Coding regions are amplified and sequenced in segments (amplicons). If the familial ARVD/C-associated mutation is known, only the amplicon harboring the familial mutation is amplified and sequenced. Nearly 50% of all ARVD/C cases are familial and mutations in the following genes account for up to a combined 74% of familial ARVD/C: PKP2 (10-43%), DSG2 (10%), DSP (6-16%), and DSC2 (1-5%).

In summary, I believe that genetic testing for ARVD/C will allow me to provide better care for my patient and will prove to be a cost-effective measure. Please let me know if you have any further questions.

Sincerely,

_____________________________    __________________ ___________           _______________       _____
Signature    Name (printed)    Tel. No. Date
Clinical Information Form for Cardiomyopathies (HCM, DCM, ARVD/C)

**Patient:**

<table>
<thead>
<tr>
<th>First Name</th>
<th>MI</th>
<th>Last Name</th>
</tr>
</thead>
</table>

**Medical History:**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Age at onset</th>
<th>Comments</th>
</tr>
</thead>
</table>

- h/o Cardiac arrest
- Chest pain / dyspnea / syncope
- h/o Heart murmur
- h/o Cardiac arrhythmias
- Exercise intolerance
- Diagnosis of cardiomyopathy
- Other (please specify)

**Physical Examination Data:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Value (circle units)</th>
<th>Comments</th>
</tr>
</thead>
</table>

- Height MM/DD/YY cm/inches
- Weight MM/DD/YY kg/pounds
- Blood pressure MM/DD/YY Systolic: mm Hg Diastolic: mm Hg
- Heart murmur
- Skeletal myopathy

**Laboratory Test Results:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Results</th>
</tr>
</thead>
</table>

- EKG MM/DD/YY
- -- ? Ventricular pre-excitation
- -- ? Epsilon waves
- Echocardiogram/MRI MM/DD/YY
- -- ? Right ventricular dilation
- Ambulatory EKG (Holter) monitoring MM/DD/YY
- Blood pressure response during exercise MM/DD/YY
- Creatine kinase [U/L] MM/DD/YY
- Other (please specify) MM/DD/YY

**Current Therapy:**

- Implantable cardioverter-defibrillator MM/DD/YY
- Pacemaker MM/DD/YY
- Other (please specify) MM/DD/YY

**Family History:**

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Cardio-myopathy Age at onset</th>
<th>Cardiac Arrhythmias Age at onset</th>
<th>Sudden Cardiac Death Age at occurrence</th>
<th>Other Cardiac Symptoms (please specify)</th>
</tr>
</thead>
</table>

- □
- □
- □
- □

**Comments:**

- □
- □
- □
Informed Consent for Genetic Testing

I hereby request genetic testing by DNA analysis for the following condition:

I understand that the purpose of the DNA test is to look for the presence of abnormalities (often called “variants” or “mutations”) in one or more genes that may be associated with the condition specified above.

I understand that a sample of blood will be obtained from me and/or individuals for whom I am authorized to make medical decisions by removing blood from a vein, a procedure that carries very little risk. I give permission to collect blood samples from the individuals named below, to be used for DNA testing for the condition specified above:

<table>
<thead>
<tr>
<th>Child’s Name</th>
<th>Date of Birth</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I understand and agree that:

1. By signing this consent, I authorize my doctor to forward my blood, DNA, or tissue sample as well as relevant clinical information about me and about members of my family to Correlagen Diagnostics, Inc. I understand that the testing laboratory needs this clinical information to provide the most accurate interpretation of my test results.

2. While genetic testing is a valuable tool, it does not always give a definite answer. In some cases, the DNA test may not detect an abnormality, although an abnormality may still be present. This event may be due to an inability of the current technology to identify certain types of abnormalities in the gene(s). In other cases, the significance of an abnormality detected by the DNA test for the condition specified above may be uncertain. Thus, the DNA test is not 100% accurate, and the significance of the results will be reported as a probability of association with the condition specified above. Consulting a doctor or genetic counselor is recommended to learn the full meaning of the results.

3. DNA testing performed on a child and a child’s parents might discover non-paternity (a situation where the acknowledged father is not the biological father) or some other previously unknown information about family relationships, such as adoption.

4. The results of this test will be released only to the physician ordering the test or to persons designated by me, in writing, unless otherwise required by law.
5a. Correlagen Diagnostics, Inc, may contact me if it subsequently learns new information that affects the interpretation of previously reported test results. Correlagen Diagnostics, Inc, will make reasonable efforts to contact me through the physician that ordered the test, unless I designate in writing another person authorized to be contacted.

5b. I indicate my desire to opt out of being contacted if Correlagen Diagnostics, Inc, subsequently learns new information that affects the interpretation of previously reported test results, by checking this box: ☐

6a. The sample will be retained after testing for the condition specified above is completed, to allow testing for other conditions. Testing for other conditions requires written authorization by the patient or an individual authorized to make medical decision for the patient.

6b. I indicate my desire to opt out of having my sample retained for more than sixty days after the sample was taken by checking this box: ☐

7a. After DNA testing is completed, a portion of my sample may be used anonymously for research purposes. Prior to use in research, all identifiers will be removed from a portion of my sample and from my clinical information. I understand that the use of my anonymized sample and clinical information for research purposes may contribute to the identification of new genes, the creation of new diagnostic tests or new medicines, or other events that may be commercially valuable and that I will not receive any financial benefits from such developments.

7b. I indicate my desire to opt out of having my anonymized sample and clinical information used for research purposes by checking this box: ☐. Refusal to permit use of my anonymized sample and clinical information for research purposes will not affect this test procedure.

8. Participation in DNA testing is completely voluntary, and the decision to consent to or to refuse the above testing is entirely mine.

9. My signature below indicates that I have read, or had read to me, the above information and that I understand it. I have had the opportunity to discuss the information, including the purposes and possible risks of genetic testing, with my doctor or someone my doctor has designated. I know that I may obtain professional genetic counseling before signing this consent if I wish. I have all the information I want, and all of my questions have been answered.

________________________  _______________________
Signature                           Date

________________________
Printed Name

Witnessed by:

________________________  _______________________
Signature                           Printed Name

Physician/Counselor Statement: I have explained DNA testing to this individual. I have addressed the limitations outlined above, and I have answered the person’s questions.

________________________  _______________________
Signature                           Date

________________________
Printed Name