Cardiac Sciences Program | Programme des sciences cardiaques

University of Manitoba

Do I need Genetic Testing?

CM Seifer

(S Clarke)

Cardiac Sciences Program | Programme des sciences cardiaques

University of Manitoba

Do I need (to refer my patient for) Genetic Testing?

CM Seifer

(S Clarke)

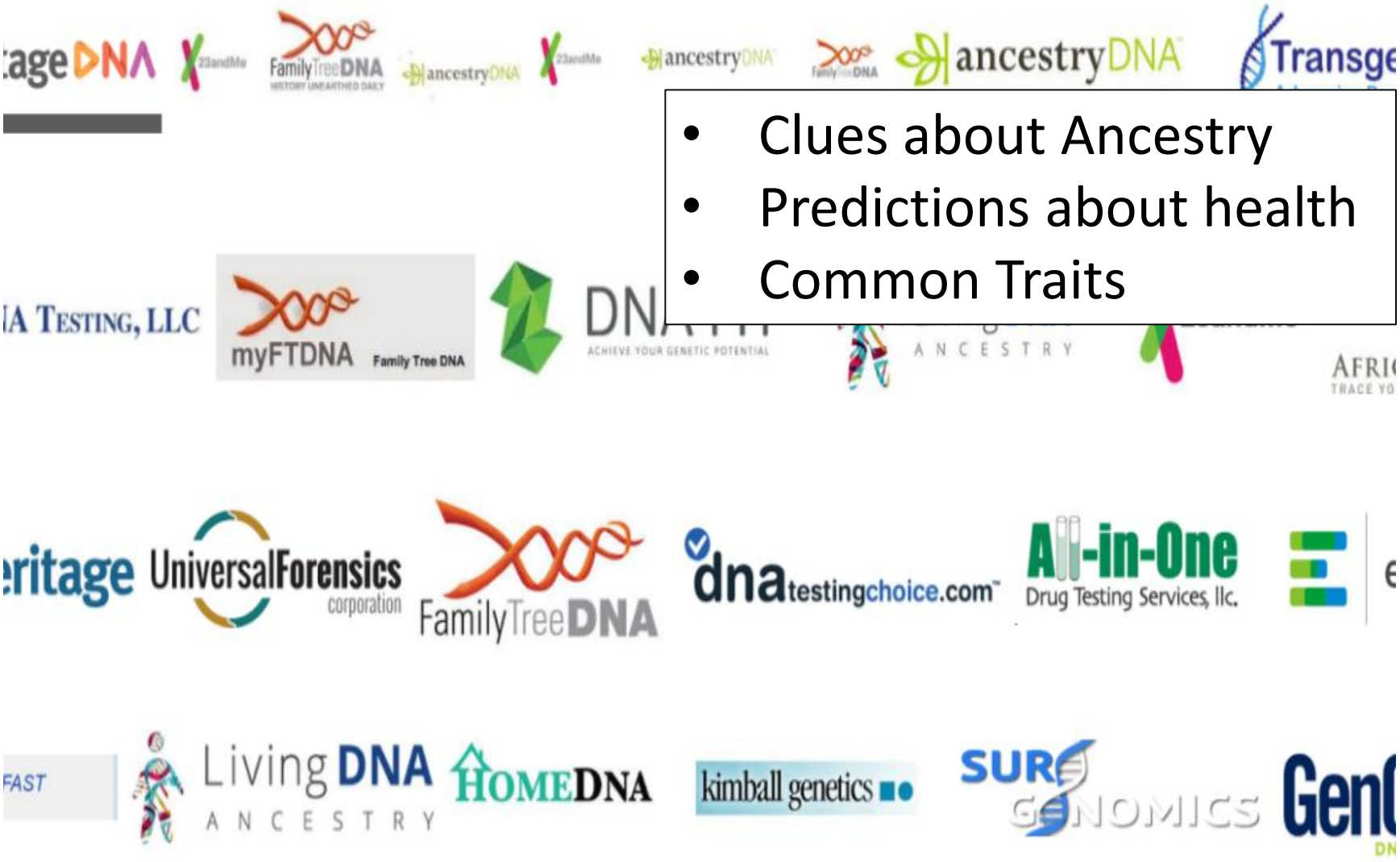
Faculty/Presenter Disclosure

- **Faculty:**

  CM Seifer

- **Relationships with commercial interests:**

  Not Applicable


ancestryDNA
ancestryDNA
Transge
Clues about Ancestry
Predictions about health
Common Traits
myFTDNA
Family Tree DNA
ACHIEVE YOUR GENETIC POTENTIAL
ANCESTRY
UniversalForensics
corporation
FamilyTreeDNA
dnatestingchoice.com
All-in-One
Drug Testing Services, llc.
Living DNA
ANCESTRY
HOMEDNA
kimball genetics

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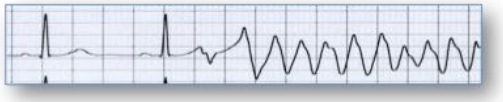
University of Manitoba

Objectives

- Identify who may need genetic testing
- Role of Inherited Arrhythmia and Cardiomyopathy Clinics in investigating patients and families
- Know where to refer patients/families for cardiac assessment of possible inherited conditions

Case 1

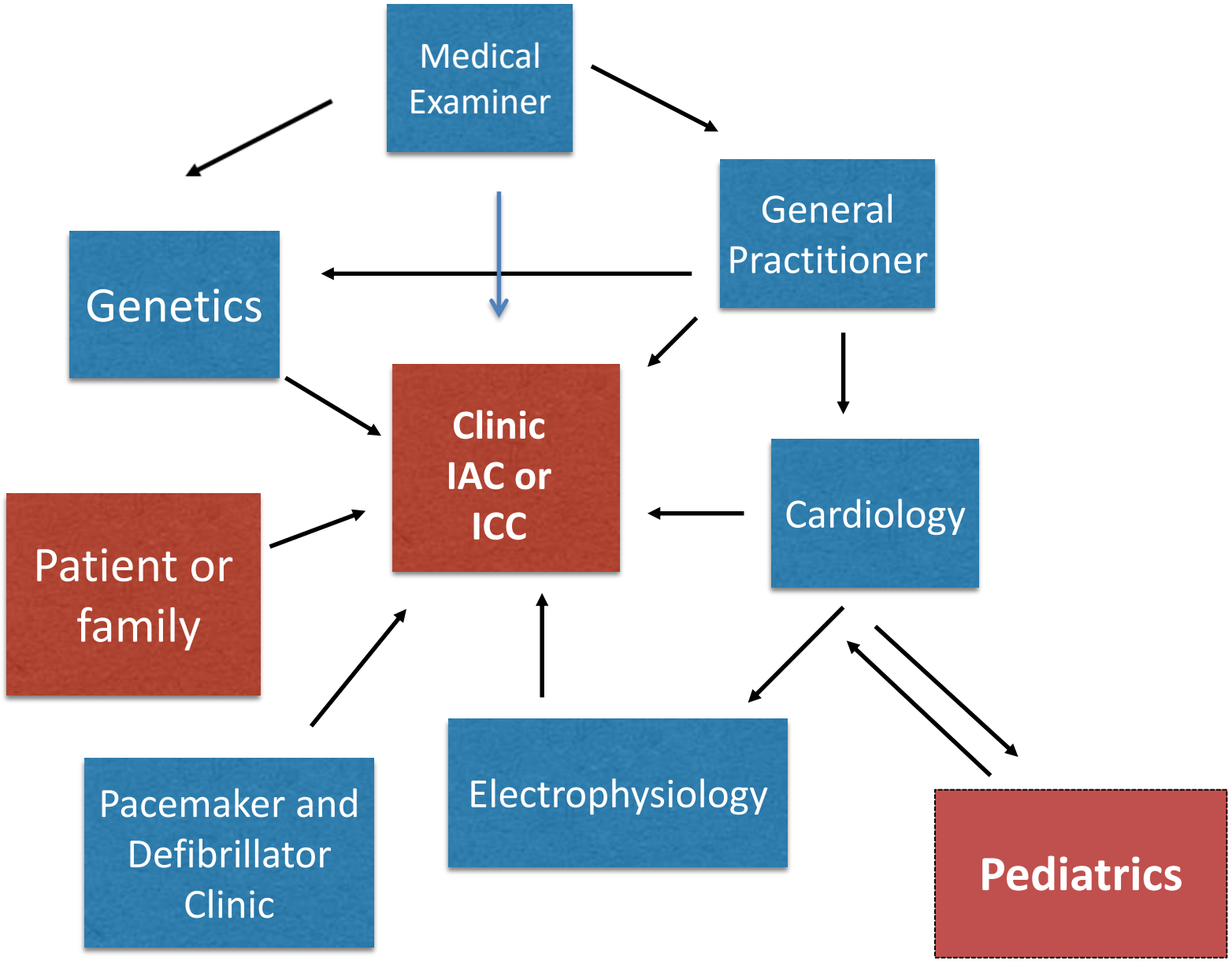
- 21 yo female 6 weeks postpartum
- No significant medical or family history
- Found dead in her bed by her sister at 0800
- Autopsy normal (including toxicology)
- Sudden unexplained death syndrome (SUDS)
- What next?



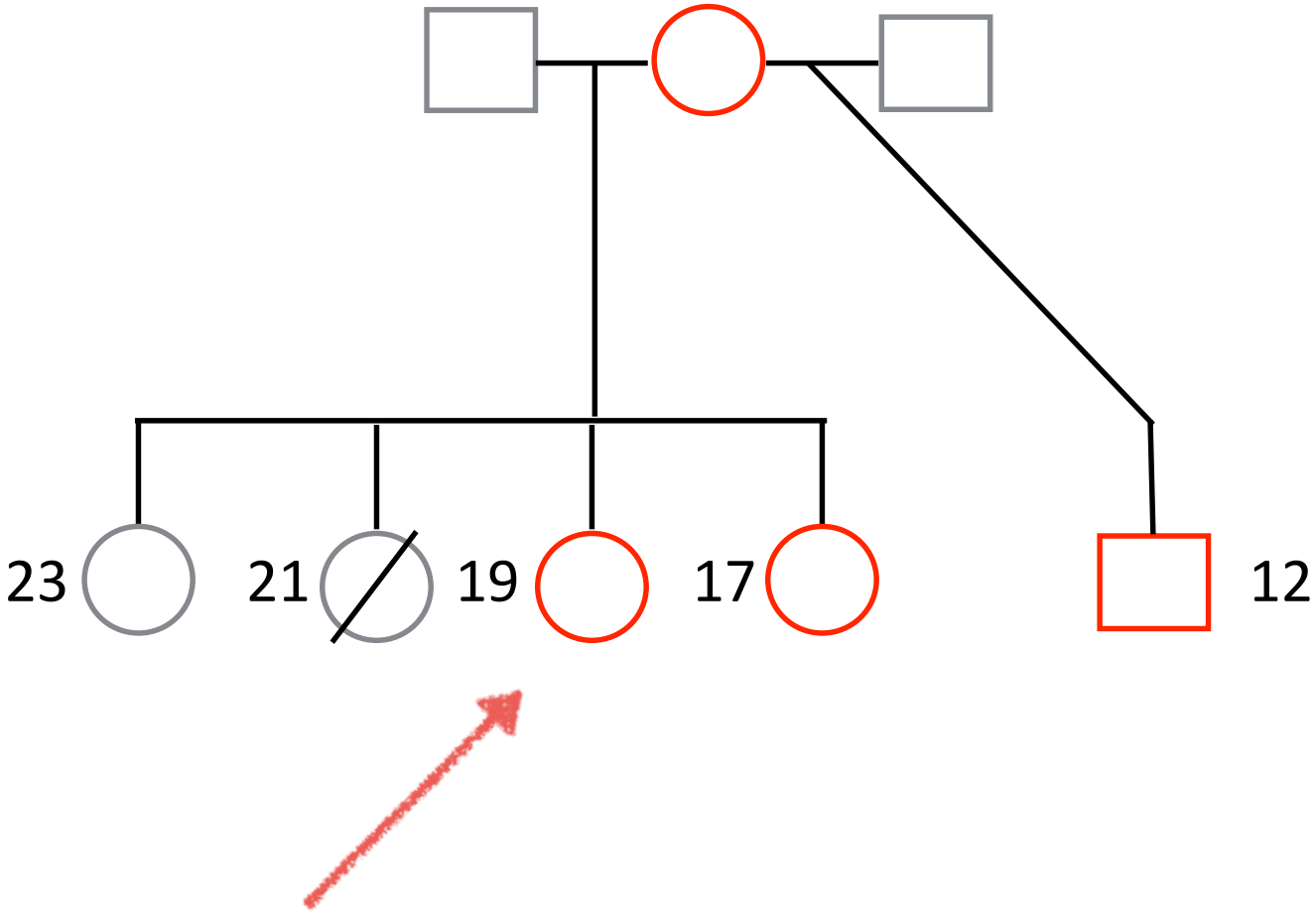
*Expert Consensus Recommendations on **Sudden Unexplained Death Syndrome Therapeutic Interventions***

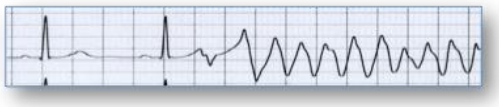
Class I	1. Genetic screening of the first-degree relatives of a SUDS victim ***is recommended*** whenever a pathogenic mutation in a gene associated with increased risk of sudden death is identified by molecular autopsy in the SUDS victim.
	2. Evaluation of first-degree blood relatives of all SUDS victims with resting ECG with high right ventricular leads, exercise stress testing and echocardiography ***is recommended.*** Assessment of obligate carriers and relatives with a history of palpitations, arrhythmias or syncope should be prioritized.
	3. Follow-up clinical assessment ***is indicated*** in young family members of SUDS victims who may manifest symptoms and/or signs of the disease at an older age and in all family members whenever additional SUDS or SUDI events occur.
Class IIa	4. Evaluation of first-degree relatives of SUDS victims with ambulatory and signal-averaged ECGs, cardiac MRI and provocative testing with Class Ic antiarrhythmic drugs ***can be useful.***
Class IIb	5. Evaluation of first-degree relatives of SUDS victims with epinephrine infusion ***may be considered.***

Heart Rhythm 2013

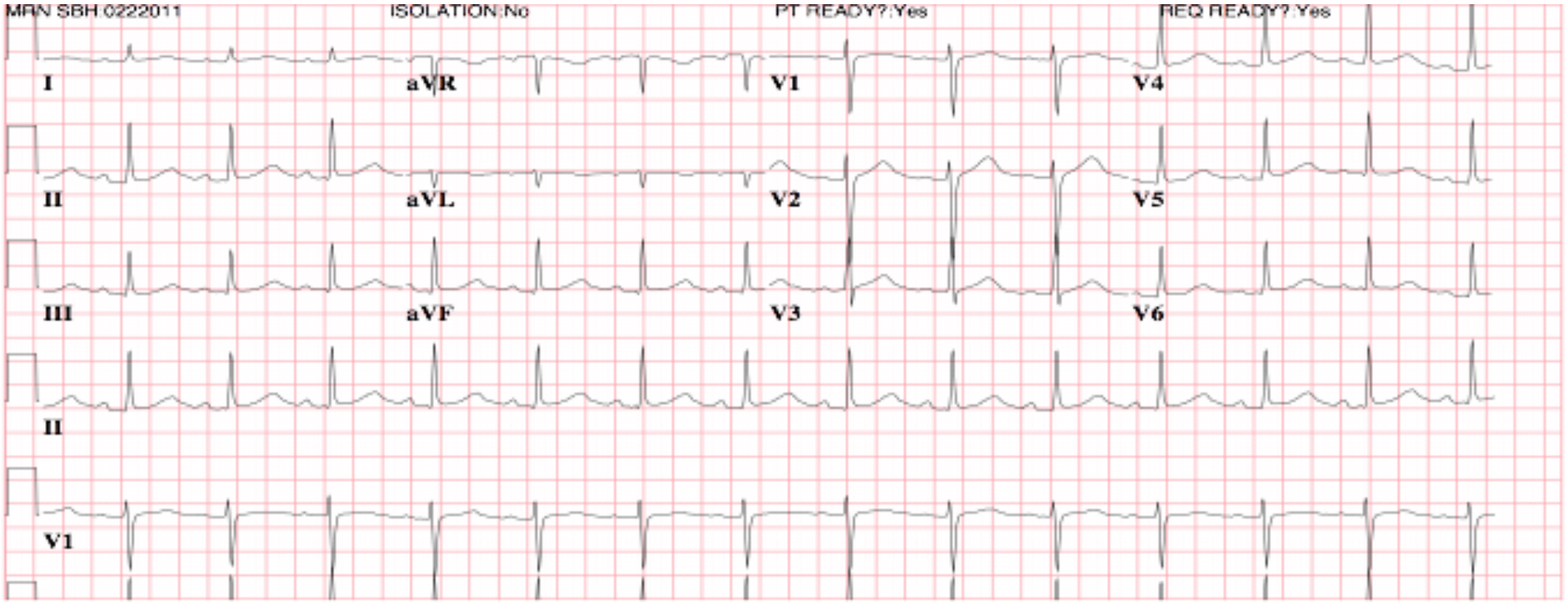

Medical Examiner
General Practitioner
Genetics
Clinic IAC or ICC
Cardiology
Patient or family
Pacemaker and Defibrillator Clinic
Electrophysiology
Pediatrics

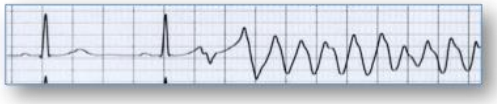
Case 1





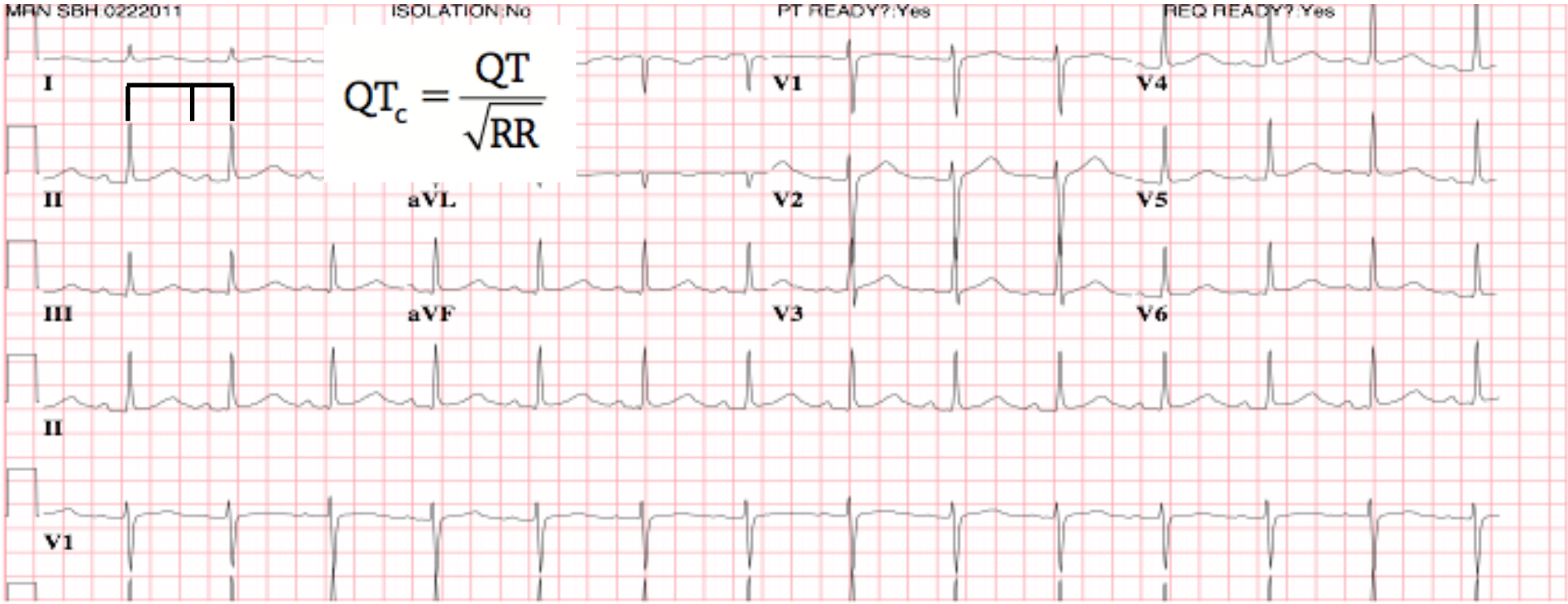
Case 1 - First Degree Relative

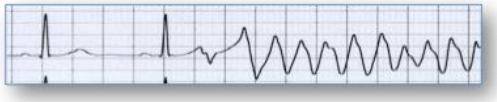




Case 1 - First Degree Relative

QTc = 540 ms





2. Long QT Syndrome (LQTS) *Expert Consensus Recommendations on* ***LQTS Diagnosis***

1. LQTS is diagnosed:
   a. In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation *and/or*
   b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes *or*
   c. In the presence of a QT interval corrected for heart rate using Bazett's formula (QTc) ≥500 ms in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.
2. LQTS can be diagnosed in the presence of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.

TABLE 2. 1993 LQTS Diagnostic Criteria

		Points
ECG findings*		
A.	QT_c†	
	≥480 $msec^{1/2}$	3
	460-470 $msec^{1/2}$	2
	450 $msec^{1/2}$ (in males)	1
B.	Torsade de pointes‡	2
C.	T-Wave alternans	1
D.	Notched T wave in three leads	1
E.	Low heart rate for age§	0.5
Clinical history		
A.	Syncope‡	
	With stress	2
	Without stress	1
B.	Congenital deafness	0.5
Family history‖		
A.	Family members with definite LQTS#	1
B.	Unexplained sudden cardiac death below age 30 among immediate family members	0.5

- LQTS risk score = 3.5
- Unequivocally pathogenic mutation (?)
- QTc ≥ 500 ms

Schwartz et al, Circulation 1993

Case 1 - first degree relative (sister with prolonged QT interval)

CPA
Accredited Medical Laboratory Reference No: 0745
Oxford University Hospitals NHS
NHS Trust
Genetics Laboratories, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Head of Laboratory: Dr Anneke Seller ☎ +44 (0)1865 225594 www.ouh.nhs.uk/geneticslab

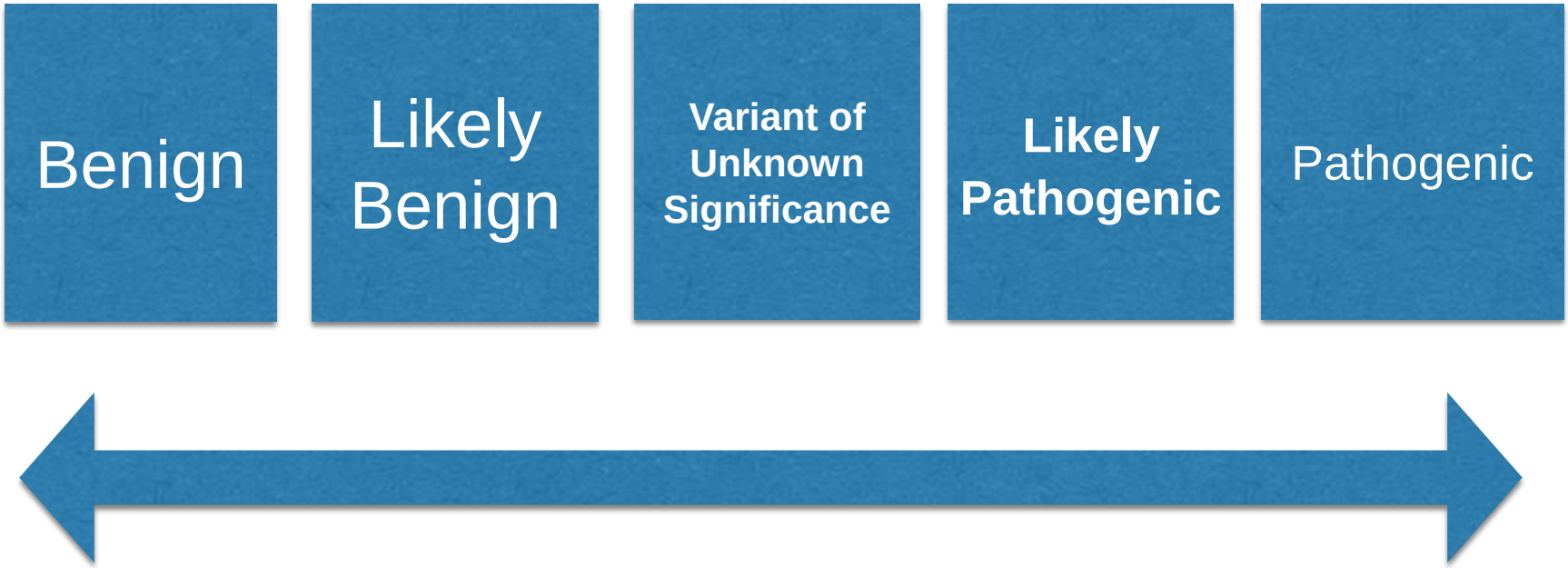
Molecular analysis of the *KCNQ1*, *KCNH2, KCNE1, KCNE2* and *SCN5A*

Analysis of *KCNH2, KCNE1, KCNE2*	Analysis of *KCNQ1*	Analysis of *SCN5A*
No pathogenic variant detected	Heterozygous for c.671C>T (p.Thr224Met)	Heterozygous for the unclassified variant c.5948C>G (p.Ala1983Gly

KCNQ1 (C to T nucleotide substitution in exon 4): This variant has previously been detected in individuals with LQTS…..as far as we are aware, this variant has not been seen in normal control or population based cohorts. **There is evidence to suggest this variant is pathogenic however in the absence of further evidence, we are uncertain and molecular analysis of other affected family members is recommended.**

SCN5A (exon 28): has not been described in the literature and has not been detected in normal control or population based cohorts. **The pathogenicity of this variant is uncertain.**

Classifying a gene change



Case 1 - 21 yo female RIP 6/52 postpartum (Proband)

CPA Accredited Medical Laboratory Reference No: 0745
Oxford University Hospitals NHS
NHS Trust
Genetics Laboratories, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Head of Laboratory: Dr Anneke Seller ☎ +44 (0)1865 225594 www.ouh.nhs.uk/geneticslab

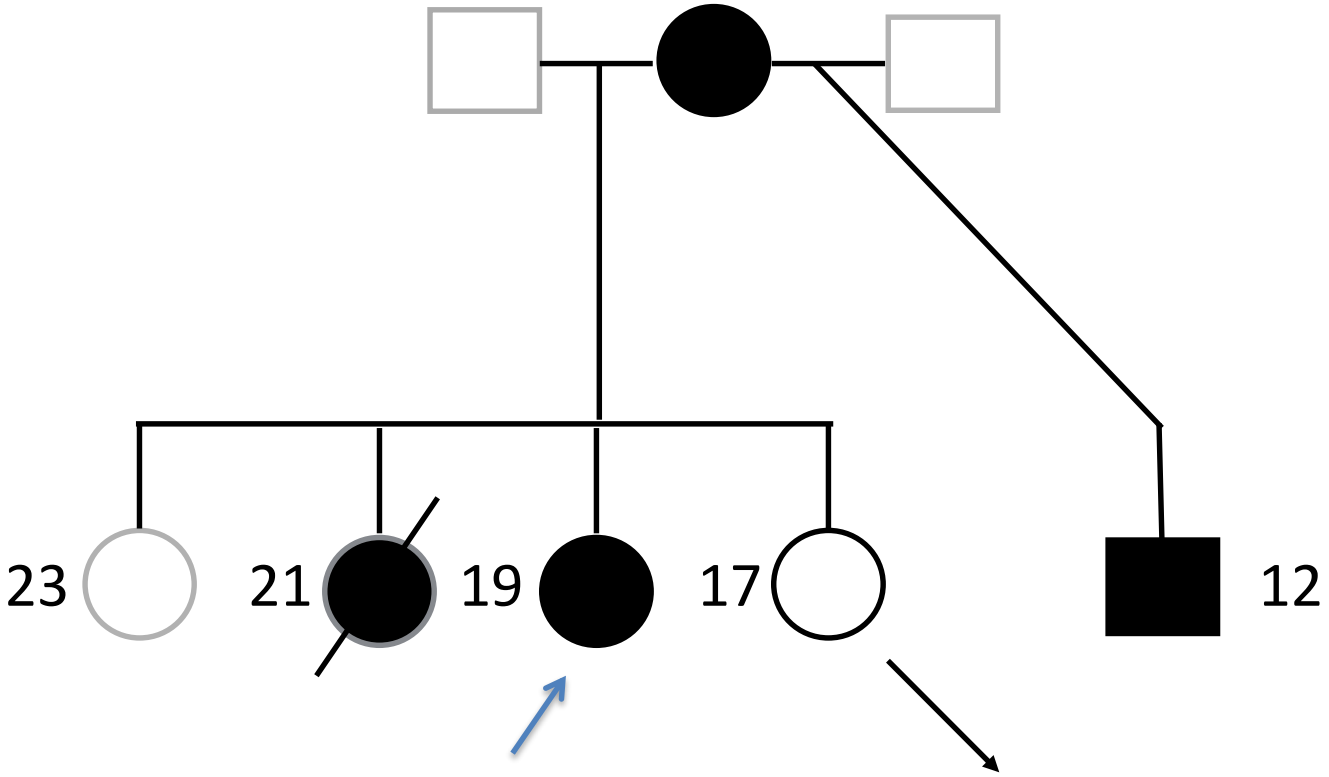
Molecular analysis of the *KCNQ1*, *KCNH2, KCNE1, KCNE2* and *SCN5A*

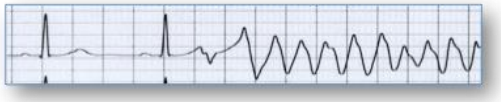
Analysis of *KCNH2, KCNE1, KCNE2*	Analysis of *KCNQ1*	Analysis of *SCN5A* (variant c.5948C>G (p.Ala1983Gly)
No pathogenic variant detected	Heterozygous for c.671C>T (p.Thr224Met)	Not detected

KCNQ1 (C to T nucleotide substitution in exon 4): There is evidence to suggest that c.671C>T (p.Thr224Met) is pathogenic and therefore this is consistent with a diagnosis of familial long QT syndrome.

This result provides further evidence in the support of pathogenicity of c.671C>T (p.Thr224Met)

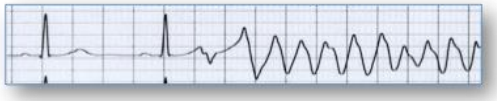
Case 1 - LQTS


23
21
19
17
12
Normal QT interval
unaffected, negative genetic testing



Case 1 LQTS family

- 19 yo sister is maintained on nadolol; dose aimed at 30% reduction in heart rate on exercise
- 45 yo mother (intermittently) maintained on nadolol; declined follow-up
- 12 yo brother is maintained on nadolol and followed by pediatric EP



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http://dx.doi.org/10.1016/j.jacc.2012.07.046

Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Propranolol has a significantly better QTc shortening effect compared to metoprolol and nadolol, especially in patients with prolonged QTc. Propranolol and nadolol are equally effective, whereas symptomatic patients started on metoprolol are at a significantly higher risk for BCEs. Metoprolol should not be used for symptomatic LQT1 and LQT2 patients. (J Am Coll Cardiol 2012;60:2092–9) © 2012 by the American College of Cardiology Foundation

Case 2

Autopsy Report Form

Office of the
Chief Medical Examiner

File No _____
For Office Use Only

Preliminary Report ☐ Final Report ☒

Name of Deceased _____ Sex M Age 20

Home Address _____ Place of Death _____

Date and Time of Admission NA _____ Place of Autopsy _____
(if applicable)

Date and Time Pronounced _____

Name of Police Department Winnipeg Police Service Name of Medical Examiner _____

NARRATIVE SUMMARY OF FINDINGS RELATED TO DEATH: (Include only relevant history, laboratory and anatomical findings)

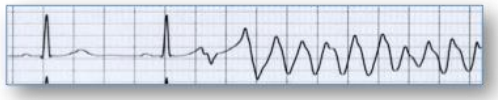
History obtained from Preliminary Report of Death.

The deceased was found collapsed at home. EMS attended and he was found to be in ventricular fibrillation. Three attempts to defibrillate were administered and full ACLS protocol was initiated. He was transported to HSC where he was pronounced dead. [redacted]

AUTOPSY FINDINGS:

1. Thinly built adult male (BMI 18).
2. Dilated right atrium and right ventricle.
3. Fibrofatty infiltration of left and right ventricles.
4. Normal coronary artery circulation.
5. [redacted]

OFFICE OF THE



Case 2

Autopsy Report Form

Office of the
Chief Medical Examiner

File No _____
For Office Use Only

Preliminary Report ☐ Final Report ☒

Name of Deceased _____ Sex M Age 20

Home Address _____

Date and Time of Admissio

Date and Time Pronounced

Name of Police Departmen

AUTOPSY FINDINGS:

1. Thinly built adult male (BMI 18).
2. Dilated right atrium and right ventricle.
3. Fibrofatty infiltration of left and right ventricles.
4. Normal coronary artery circulation.
5. Pulmonary congestion and edema.

NARRATIVE SUMMARY OF FI

History obtained from

The deceased was found collapsed at home. EMS attended and he was found to be in ventricular fibrillation. Three attempts to defibrillate were administered and full ACLS protocol was initiated. He was transported to HSC where he was pronounced dead.

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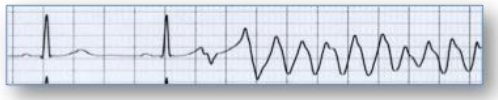


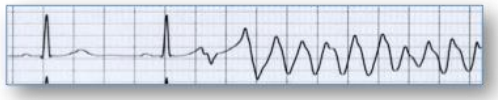
Case 2

Cause of Death

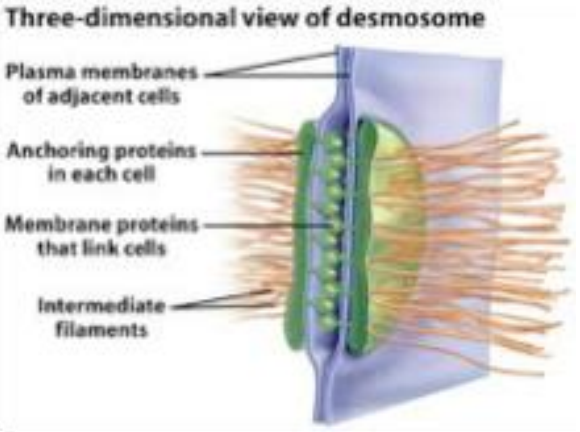
Arrhythmogenic cardiomyopathy.

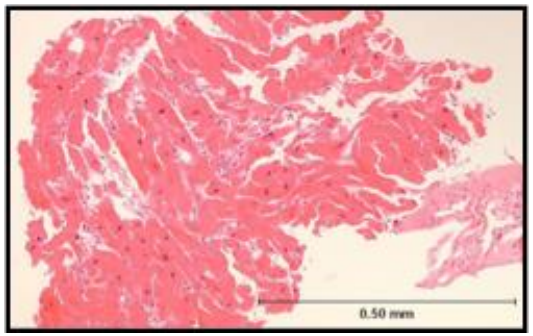
Comment:

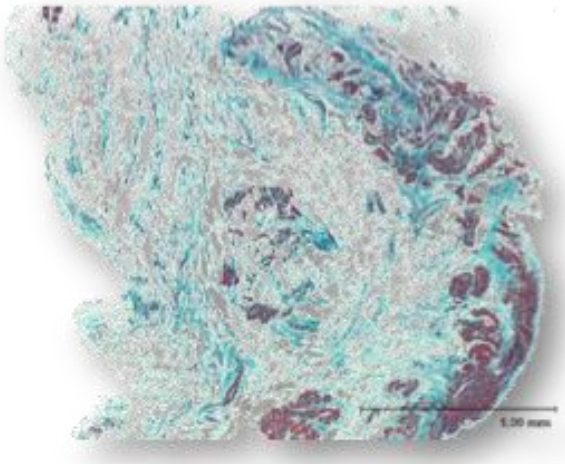
Arrhythmogenic cardiomyopathy (also known as arrhythmogenic right ventricular dysplasia) is a familial disease in at least 50% of cases and after hypertrophic heart disease is the number one cause of sudden cardiac death in young persons under 35 and accounts for up to 10% of deaths from undiagnosed cardiac disease in the over 65 age group. For these reasons, it is strongly recommended that genetic counselling be considered for the family. DNA was successfully extracted from the deceased's blood at autopsy and has been banked.

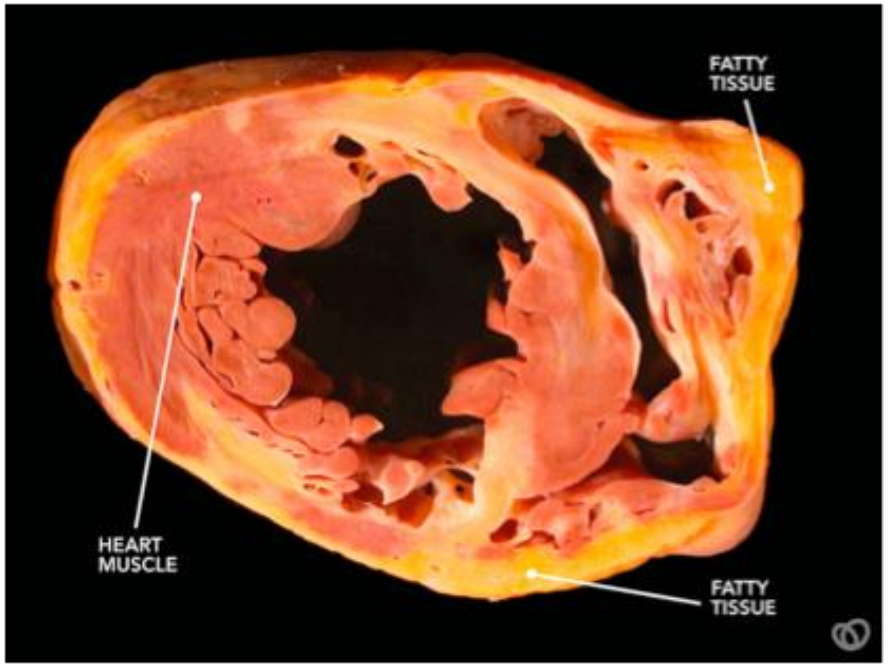


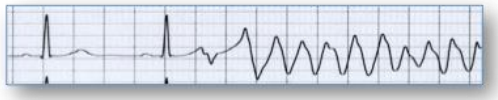
ARVC


Three-dimensional view of desmosome
Plasma membranes of adjacent cells
Anchoring proteins in each cell
Membrane proteins that link cells
Intermediate filaments

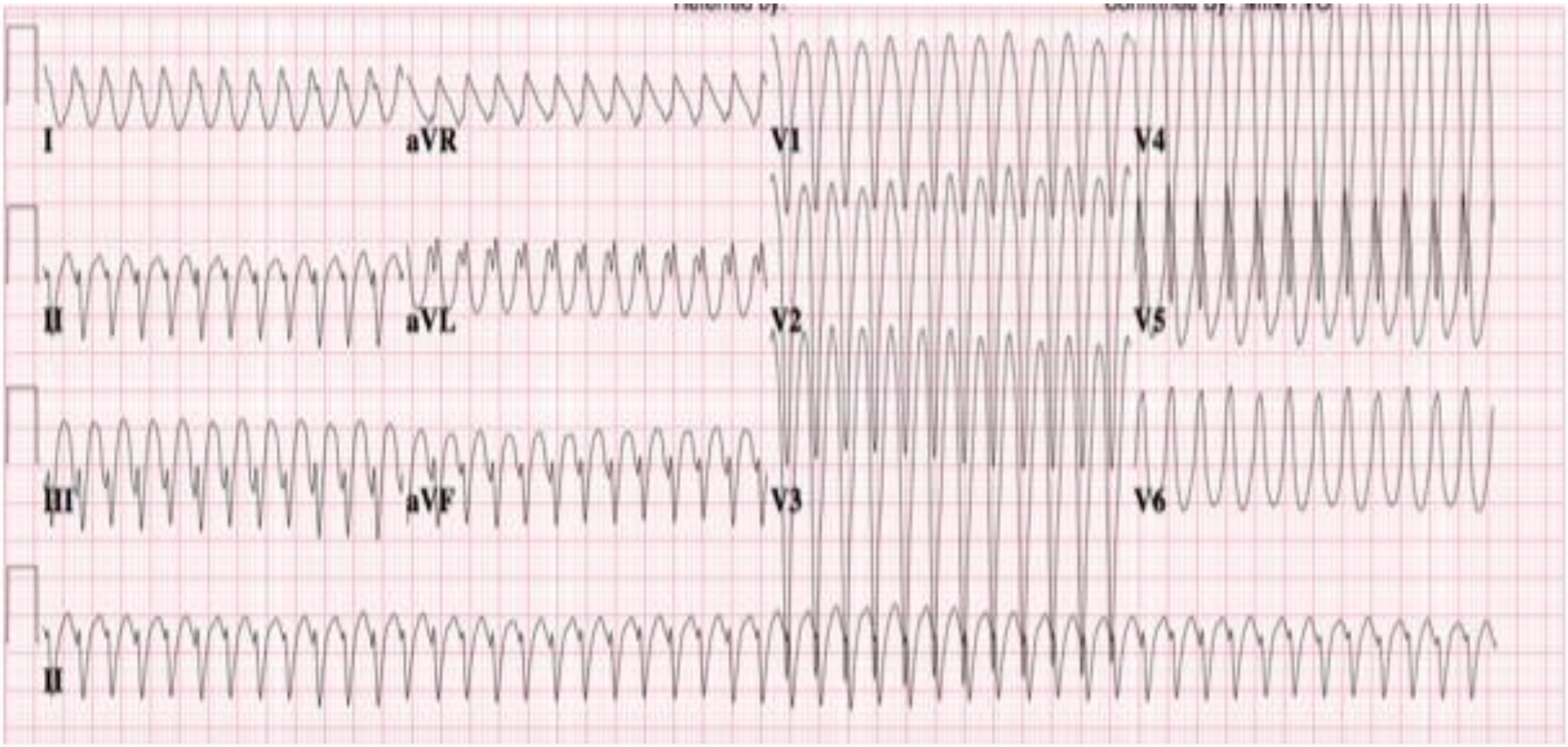

0.50 mm

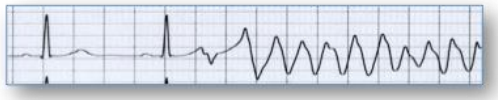



FATTY TISSUE
HEART MUSCLE
FATTY TISSUE

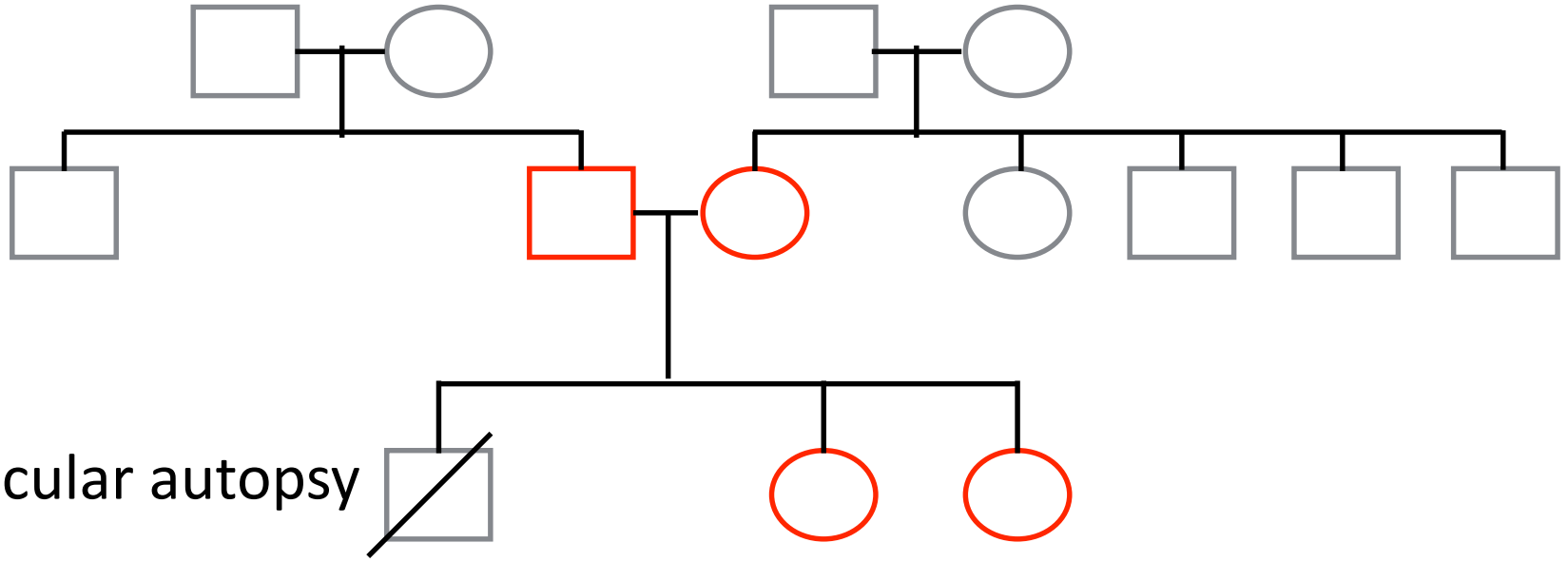


ARVC

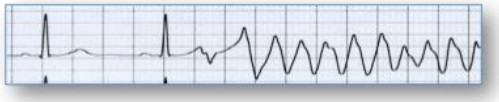




Case 2 - 20 yo male (ARVC)



molecular autopsy
DNA



Case 2 - 20 yo male (ARVC) (Proband)

CPA
Accredited Medical Laboratory
Reference No: 0745

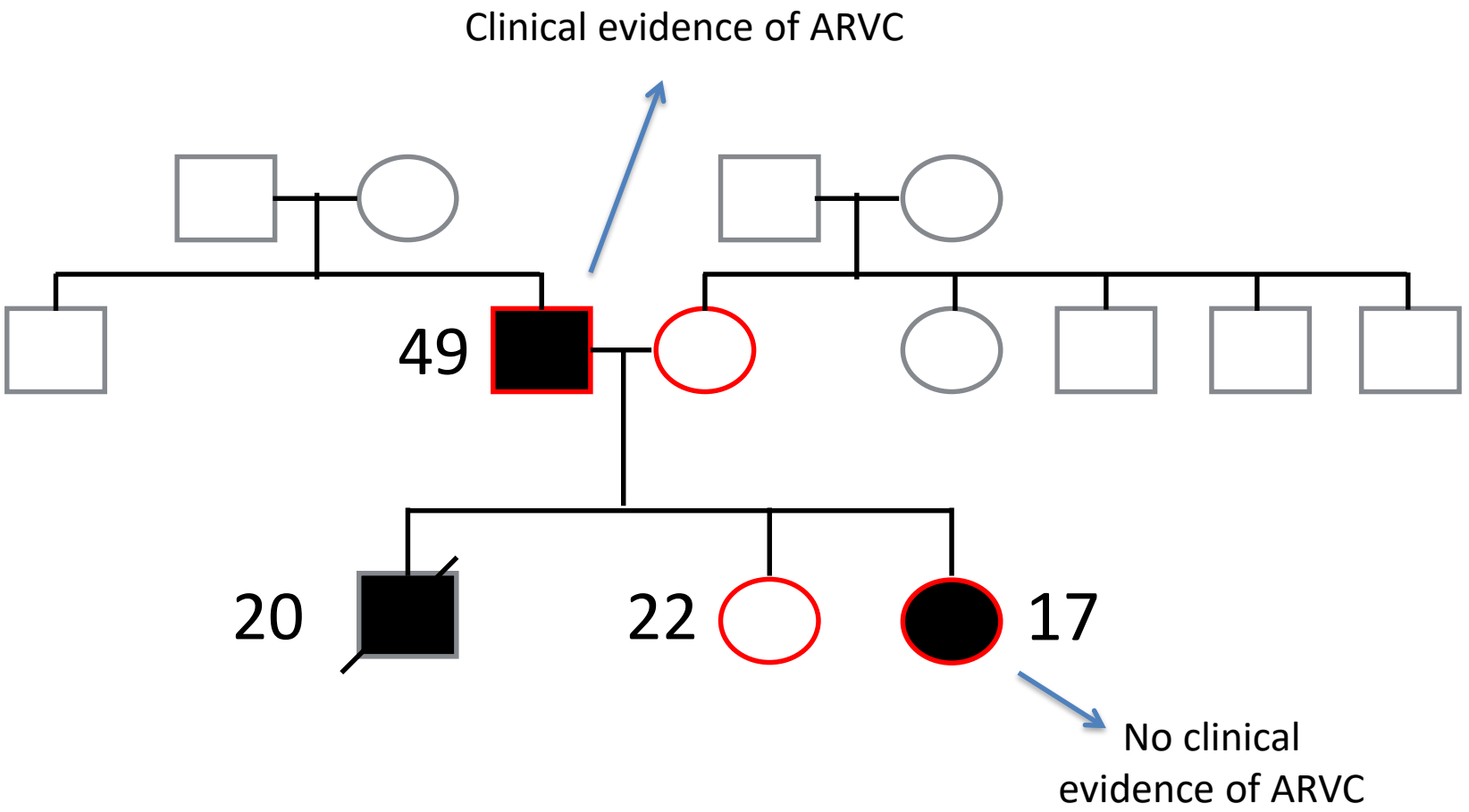
Oxford University Hospitals NHS
NHS Trust

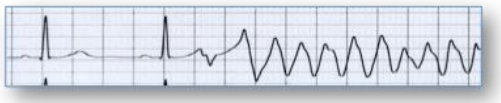
Genetics Laboratories, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LE
Head of Laboratory: Dr Anneke Seller ☎ +44 (0)1865 225594 www.ouh.nhs.uk/geneticslab

RESULTS & VARIANT INTERPRETATION	Sequence analysis of the *DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2* and *TMEM43*
Sequence Analysis: 8 Gene ARVC Panel	Dosage Analysis of *PKP2*
No pathogenic variant detected	Duplication of exons 8 and 9 detected

This variant is predicted to be pathogenic

Case 2 - 20 yo male (ARVC)

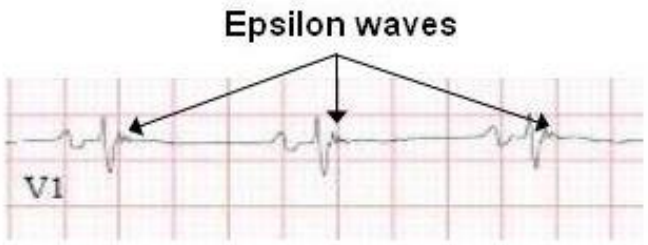


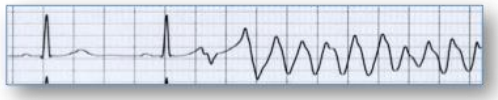


ARVC – 2010 Task Force Criteria

Syncope
Sustained VT
ECG criteria:
T wave abnormality
Epsilon wave
Holter:
PVC's on 24 hour holter
ECHO
MRI
SAECG

RV Biopsy
Family History
-pathogenic mutation

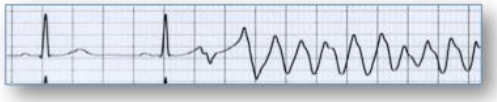




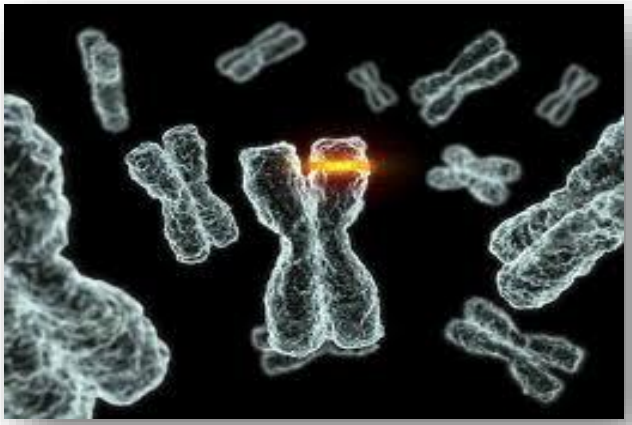
ARVC Task Force, Circulation 2010

Case 2 ARVC family

- 17 yo sister will have periodic follow-up in adult arrhythmia clinic with intermittent ECG, Holter monitor, imaging (likely every 1-2 years until 25 and then q5 years)
- 49 yo father has declined further follow-up at this time



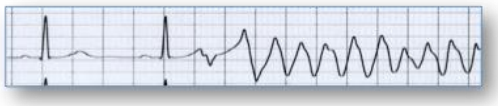
Role of Genetic Testing



- 3 situations that warrant testing
  - Clear diagnosis in **proband** and a positive genetic test aids in prognosis and Rx
  - Proband results facilitate family screening
  - Borderline case may help as a tie breaker
- Not a useful screen in every patient with minimal evidence of a disease
- Counseling before testing and complex interpretation afterwards
- Yield 20-75% in these conditions

10. Inherited Arrhythmia Clinics *Expert Consensus Recommendations on* ***Inherited Arrhythmia Clinic***	
Class I	Patients (probands) and first-degree relatives with a diagnosed or suspected inherited cardiovascular disease as a potential cause of SCD (SUDS/SUDI) ***should be evaluated*** in a dedicated clinic with appropriately trained staff.

Inherited Heart Rhythm Clinics (2015):



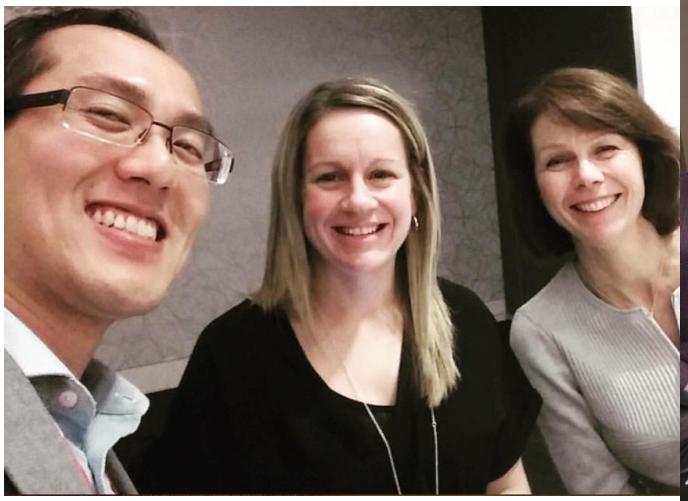
10. Inherited Arrhythmia Clinics *Expert Consensus Recommendations on* ***Inherited Arrhythmia Clinic***

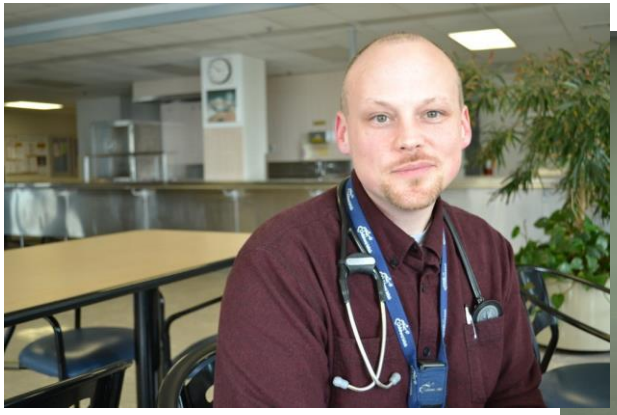
Class I	Patients (probands) and first-degree relatives with a diagnosed or suspected inherited cardiovascular disease as a potential cause of SCD (SUDS/SUDI) ***should be evaluated*** in a dedicated clinic with appropriately trained staff.

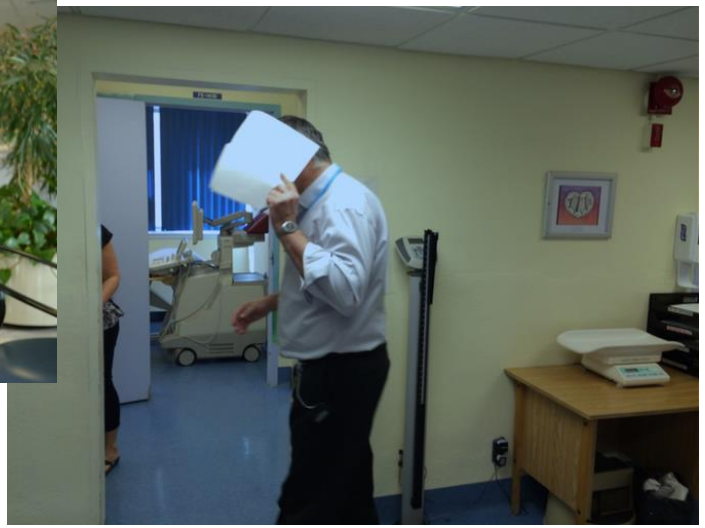
Inherited Heart Rhythm Clinics (2016)

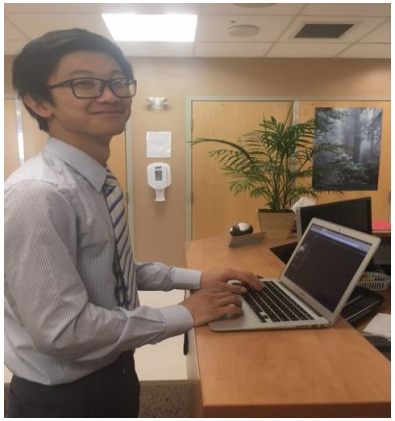
Summary

- Genetic testing is a component of patient assessment and management
- Genetic test interpretation needs a specialty team approach
- The yield of genetic testing is variable depending on the condition
- Positive genetic test does not always = disease
- Negative genetic test does not always = no disease









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