EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW-PREVALENCE AND COMPLEX DISEASES
Share. Care. Cure.

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NVHVV
Nederlandse Vereniging voor Hart en Vaat Verpleegkundigen

‘Onder spanning inspannen’

Utrecht, 17 April 2018

Plotse hartdood & genetica

European Reference Network
for rare or low prevalence complex diseases

Network Heart Diseases
(ERN GUARD-HEART)

N. Hofman, PhD
Academic Medical Centre
Amsterdam, the Netherlands

Co-funded by
the European Union

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- Network of centres in Europe sharing expertise on (a group of) rare diseases

- Goal: improving the care for patients with rare diseases.

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General criteria (ERN)

- ♥ Involvement patients (they are central)
- ♥ Continuity, durability
- ♥ Education and Research
- ♥ Sharing expertise, information, e-health T
- ♥ Expertise, quality, safety and evaluation.

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Specific criteria (HCP)

- Service, volume criteria (nr of pt/pr per y)
- Results (specific criteria)
- Quality of experts
- Multidisciplenary teams

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24 European Reference Networks

- ERN BOND (bone disorders)
- ERN CRANIO (craniofacial anomalies and ear, nose, and throat disorders)
- Endo-ERN (endocrine conditions)
- ERN EpiCARE (epilepsies)
- ERKNet (kidney diseases)
- ERN-RND (neurological diseases)
- ERNICA (inherited and congenital anomalies)
- ERN LUNG (respiratory diseases)
- ERN Skin (skin disorders)
- ERN EURACAN (adult cancers)
- ERN EuroBloodNet (haematological diseases)
- ERN eUROGEN (urogenital diseases and conditions)
- ERN EURO-NMD (neuromuscular diseases)
- ERN EYE (eye diseases)
- ERN GENTURIS (genetic tumour risk syndromes)
- **ERN GUARD-Heart (diseases of the heart)**
- ERN ITHACA (congenital malformations and rare intellectual disability)
- MetabERN (heridatary metabolic disorders)
- ERN PaedCan (paediatric cancer)
- ERN RARE-LIVER (hepatological diseases)
- ERN ReCONNET (connective tissue and musculoskeletal diseases)
- ERN RITA (immunodeficiency, autoinflammatory and autoimmune diseases)
- ERN TRANSPLANT-CHILD (transplantation in children)
- VASCERN (rare multisystemic vascular diseases)

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ERN GUARD-Heart

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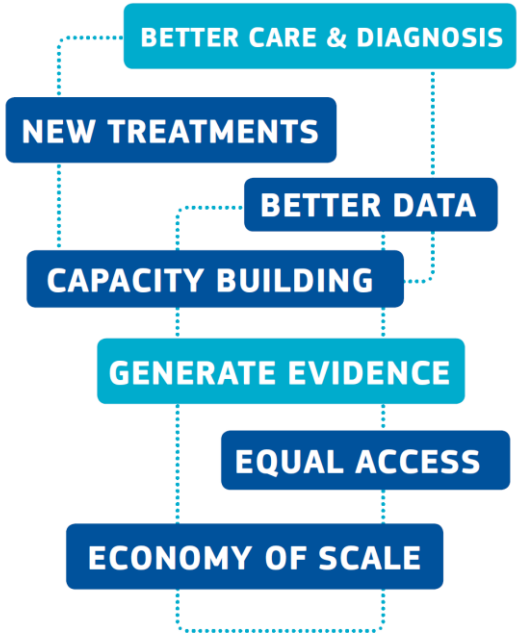

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Healthcare Providers

BE	CZ	DK	DE	ES	FR	IT	NL	RO	FI	SE	UK
2	1	1	1	3	3	6	1	1	1	1	3

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ERN GUARD-Heart

ERN GUARD-Heart Centres

HCP Representatives

1	Arthur Wilde (Amsterdam, NL)	● ● ●	13	Juan Ramon Gimeno (Madrid, ES)	● ● ●
2	Georgia Sarquella-Brugada (Barcelona, ES)	● ●	14	Eric Schulze-Bahr (Munster, DE)	● ●
3	Philippe Charron (Paris, FR)	● ● ●	15	Elijah Behr (London, UK)	● ● ●
4	Silvia Priori (Pavia, IT)	●	16	Philippe Chevalier (Lyon, FR)	● ●
5	Pablo Garcia-Pavia (Madrid, ES)	●	17	Ruxandra Jurcut (Bucharest, RO)	●
6	Vincent Probst (Nancy, FR)	●	18	Guiseppe Limongelli (Naples, IT)	●
7	Jaana Pihkala (Helsinki, FI)	● ● ●	19	Juan Kaski (London, UK)	● ●
8	Jan Janousek (Prague, CZ)	● ● ●	20	Perry Elliot (London, UK)	● ●
9	Rik Willems (Leuven, BE)	● ●	21	Peter Schwartz (Milan, IT)	● ●
10	Fabrizio Drago (Rome, IT)	● ●	22	Eloisa Arbustini (Pavia, IT)	●
11	Annika Rydberg (Umea, SE)	● ●	23	Pedro Brugada (Brussels, BE)	●
12	Jacob Tfelt (Copenhagen, DK)	● ●	24	Sabino Iliceto (Padua, IT)	● ●

Thematic Area Expertise

- ● Familial electrical diseases in adults
- ● Familial electrical diseases in children and special electrophysiology conditions
- ● Familial cardiomyopathies in adults and children

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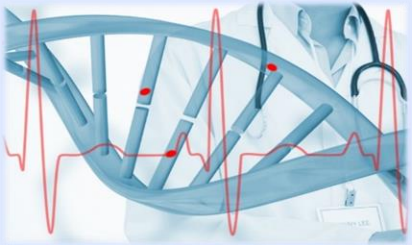
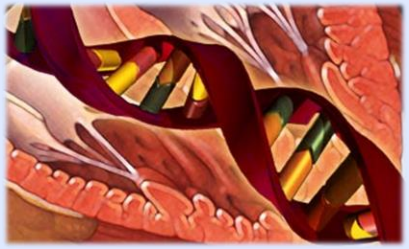
ERN GUARD-Heart Expertise

Familial Electrical Diseases



Silvia Priori

Familial Cardiomyopathies

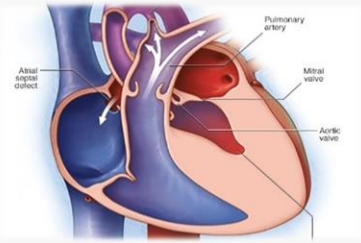


Philippe Charron

Special Electrophysiology Conditions

Georgia Sarquella-Brugada

Congenital Heart Defects (2018)



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ERN GUARD-Heart ; website

http://guardheart.ern-net.eu

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Familial arrhythmia syndromes

Arrhythmogenic substrate

- in the electrical characteristics of the heart (primary)
- in the structural characteristics of the heart (secondary)

Familial arrhythmias

- **Long QT syndrome**
- **ST elevation right precordium, “RBBB”, SCD**
- **Catecholamine-induced polymorphic VT/VF**
- **Short-coupled Torsades de Pointes**
- **Isolated conduction disorders (AVN, BB)**
- **Short QT syndrome**
- **Idiopathic ventricular fibrillation**

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Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, (HRS Chairperson)[1], Arthur A. Wilde, (EHRA Chairperson)[2], Minoru Horie, (APHRS Chairperson)[3], Yongkeun Cho, (APHRS Chairperson)[4], Elijah R. Behr[5], Charles Berul[6], Nico Blom[7*], Josep Brugada[8], Chern-En Chiang[9], Heikki Huikuri[10], Prince Kannankeril[11‡], Andrew Krahn[12], Antoine Leenhardt[13], Arthur Moss[14], Peter J. Schwartz[15], Wataru Shimizu[16], Gordon Tomaselli[17†], Cynthia Tracy[%18]

Document Reviewers: Michael Ackerman (USA), Bernard Belhassen (Israel), N. A. Mark Estes III (USA), Diane Fatkin (Australia), Jonathan Kalman (Australia), Elizabeth Kaufman (USA), Paulus Kirchhof (UK and Germany), Eric Schulze-Bahr (Germany), Christian Wolpert (Germany), Jitendra Vohra (Australia), Marwan Refaat (USA), Susan P. Etheridge (USA), Robert M. Campbell (USA), Edward T. Martin (USA), Swee Chye Quek (Singapore)

Europace 2013 - Heart Rhythm 2013 - J of Arrhyth 2013

New guidelines (2013)

Inherited arrhythmia syndromes

- **Long QT syndrome(s)**
- **Brugada syndrome**
- **Catecholaminergic polymorphic VT/VF**
- **Short QT syndrome**
- **Early repolarization syndrome & idiopathic ventricular fibrillation**
- **Progressive cardiac conduction disease**
- **Sudden infant death syndrome/sudden arrhythmia death syndrome**

Heart Rhythm Society

EUROPEAN Heart Rhythm ASSOCIATION
A Registered Branch of the ESC

APHRS

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Familial cardiomyopathies

- **Hypertrophic cardiomyopathy**
- **Dilated cardiomyopathy**
- **Arrhythmogenic cardiomyopathy**
- **Restrictive cardiomyopathy**
- **Non-compaction cardiomyopathy**
- **Unclassified cardiomyopathies**

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European Heart Journal (2014) **35**, 2733–2779
doi:10.1093/eurheartj/ehu284

ESC GUIDELINES

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC)

Authors/Task Force members: Perry M. Elliott* (Chairperson) (UK) Aris Anastasakis (Greece), Michael A. Borger (Germany), Martin Borggrefe (Germany), Franco Cecchi (Italy), Philippe Charron (France), Albert Alain Hagege (France), Antoine Lafont (France), Giuseppe Limongelli (Italy), Heiko Mahrholdt (Germany), William J. McKenna (UK), Jens Mogensen (Denmark), Petros Nihoyannopoulos (UK), Stefano Nistri (Italy), Petronella G. Pieper (Netherlands), Burkert Pieske (Austria), Claudio Rapezzi (Italy), Frans H. Rutten (Netherlands), Christoph Tillmanns (Germany), Hugh Watkins (UK).

Eur Heart J. 2014;35:2733-2779

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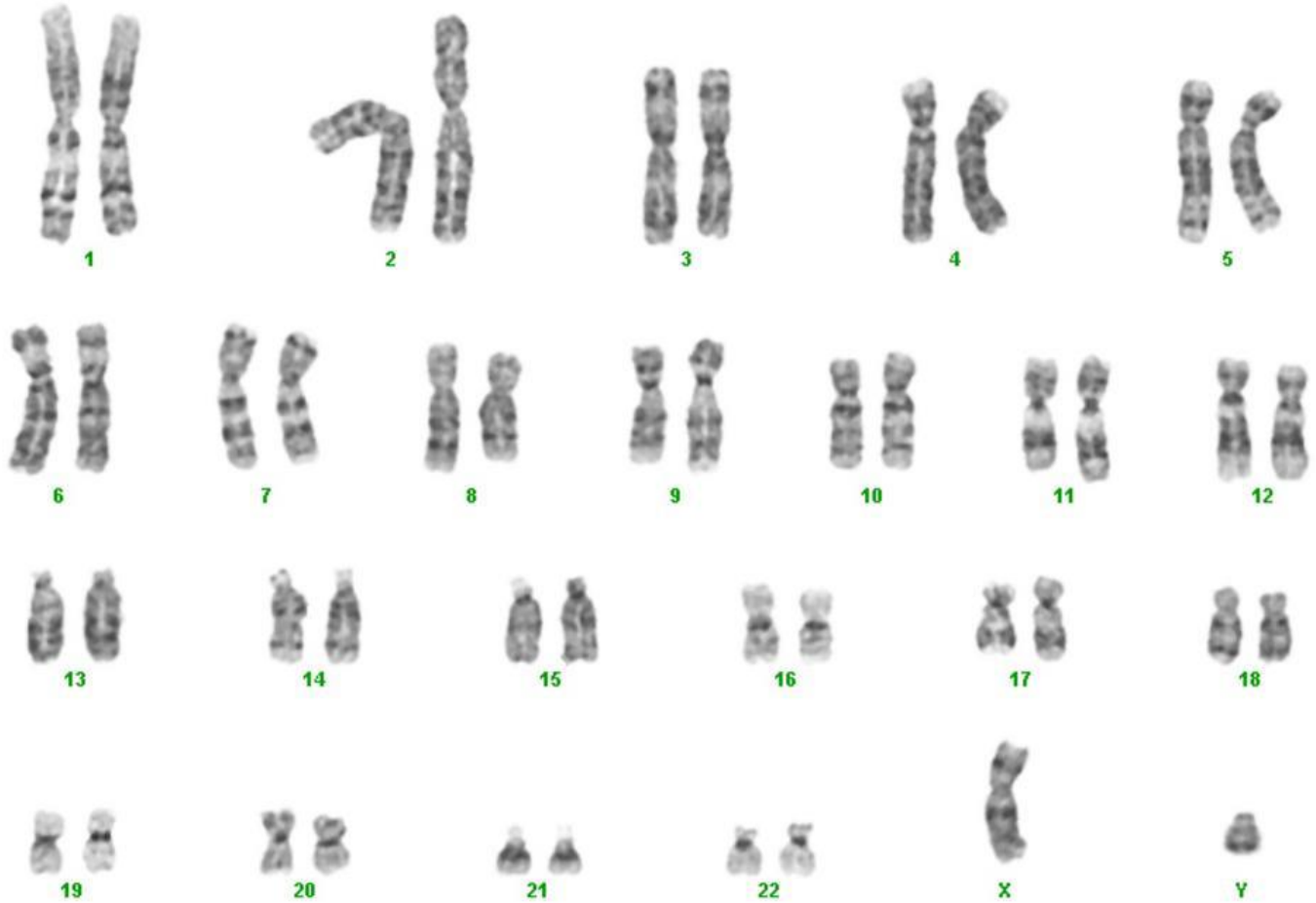
Basics of Inheritance



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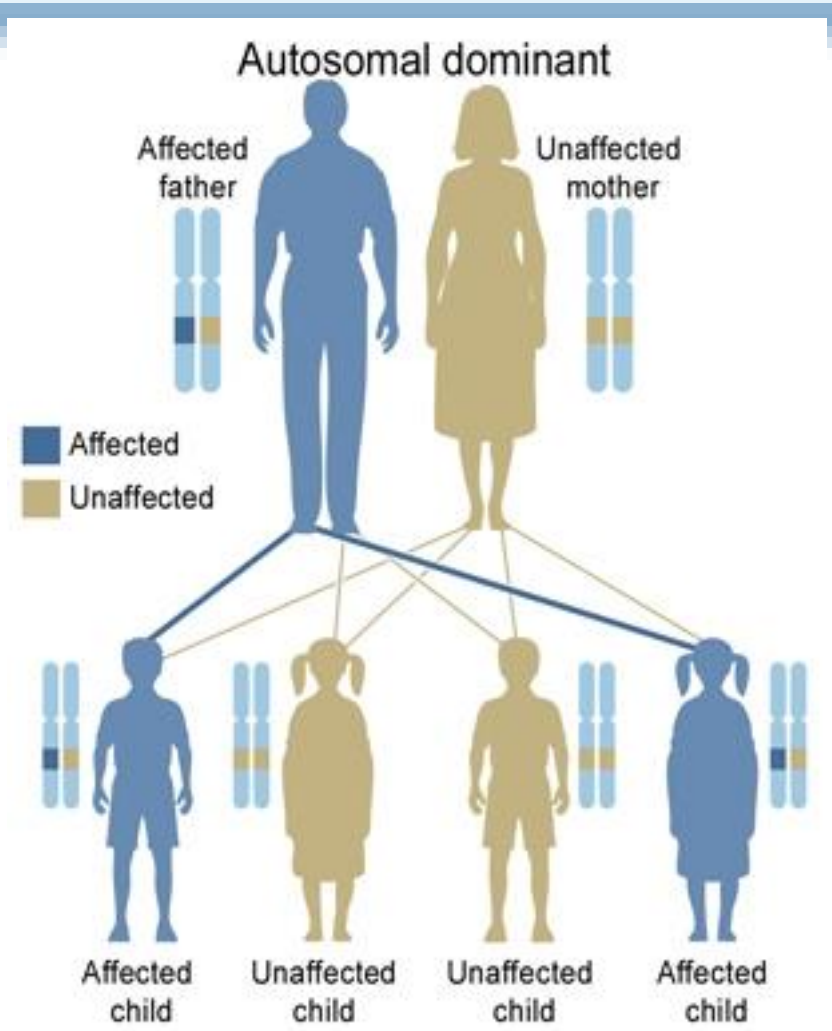
Autosomal dominant inheritance



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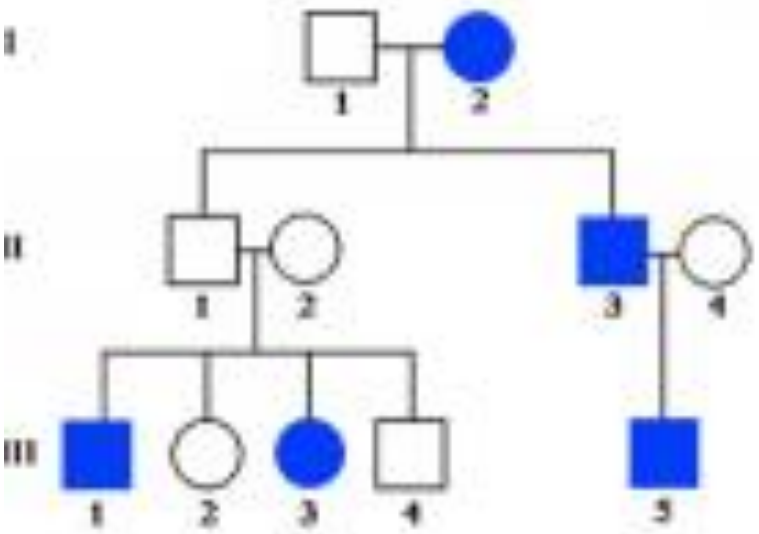
Reduced Penetrance



Family screening after SUD

Van der Werf et al. Heart Rhythm. 2010;7:1383-9.

Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: The experience of a tertiary referral center in The Netherlands

Christian van der Werf, MD,* Nynke Hofman, MSc,† Hanno L. Tan, MD, PhD,*
Pascal F. van Dessel, MD, PhD,* Marielle Alders, PhD,† Allard C. van der Wal, MD, PhD,‡
Irene M. van Langen, MD, PhD,†§ Arthur A.M. Wilde, MD, PhD*

*From the *Heart Failure Research Center, Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands, †Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands, ‡Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands, and §Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

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Family screening after SUD

Van der Werf et al. Heart Rhythm. 2010;7:1383-9.

Definition of Sudden Unexplained Death:

Out-of-hospital death in a previous healthy individual without familial heart disease in whom death within 1 hour after start of complaints or < 24 hours of the victim being seen alive and well, in whom autopsy was not performed or initally did not explain the death.

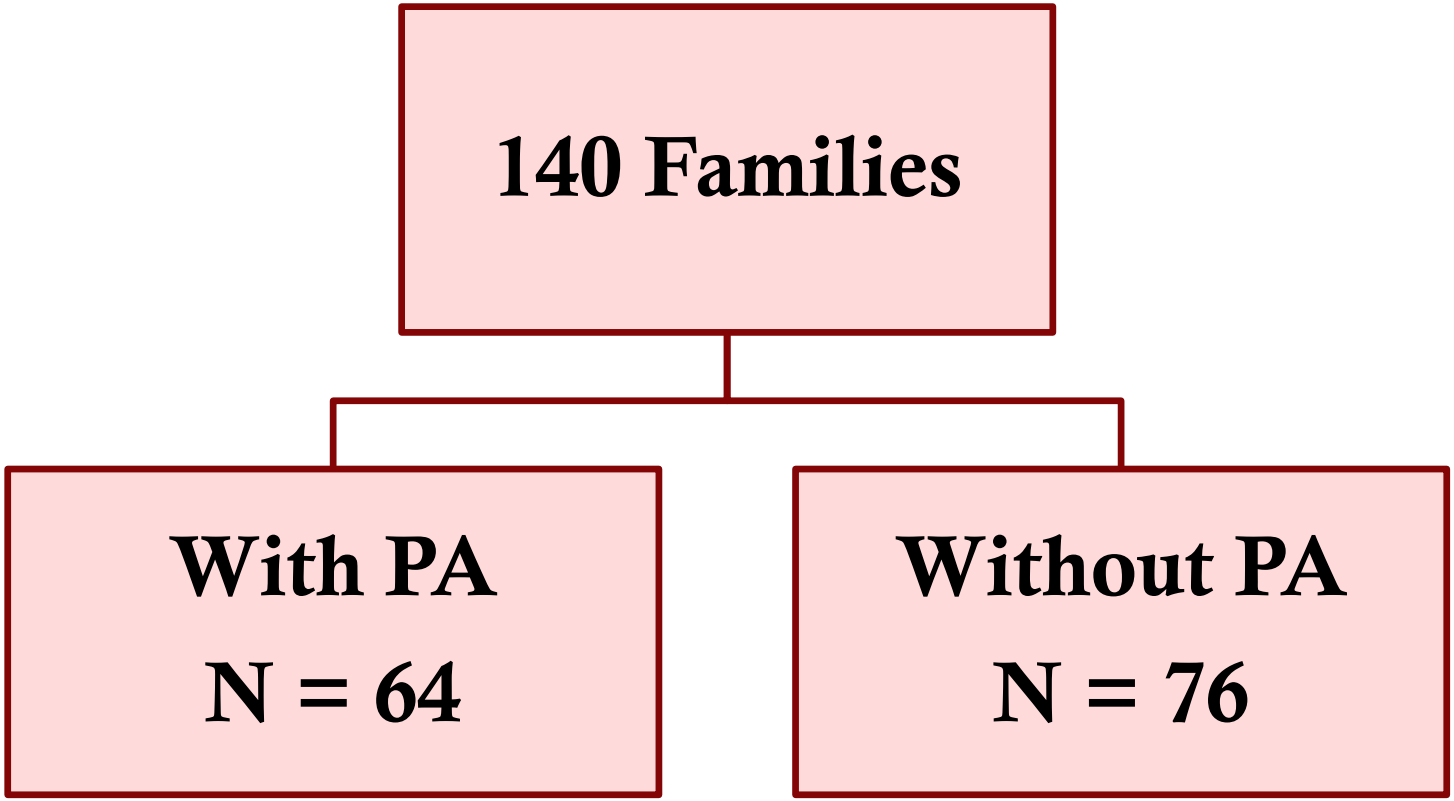
Family screening after SUD

Van der Werf et al. Heart Rhythm. 2010;7:1383-9.

- **140 families with at least 1 S(C)D ≤50 years**
- **No diagnosis in the deceased individual(s)**
- **No diagnosis in family members**
- **Yield of routine cardiologic evaluation**
  - ECG, X-ECG, ECHO, blood testing, (MRI)
  - Patho-anatomical specimens revised
  - Molecular genetic screening (include Troponine T)

Family screening after SCD

Van der Werf et al. Heart Rhythm. 2010;7:1383-9.



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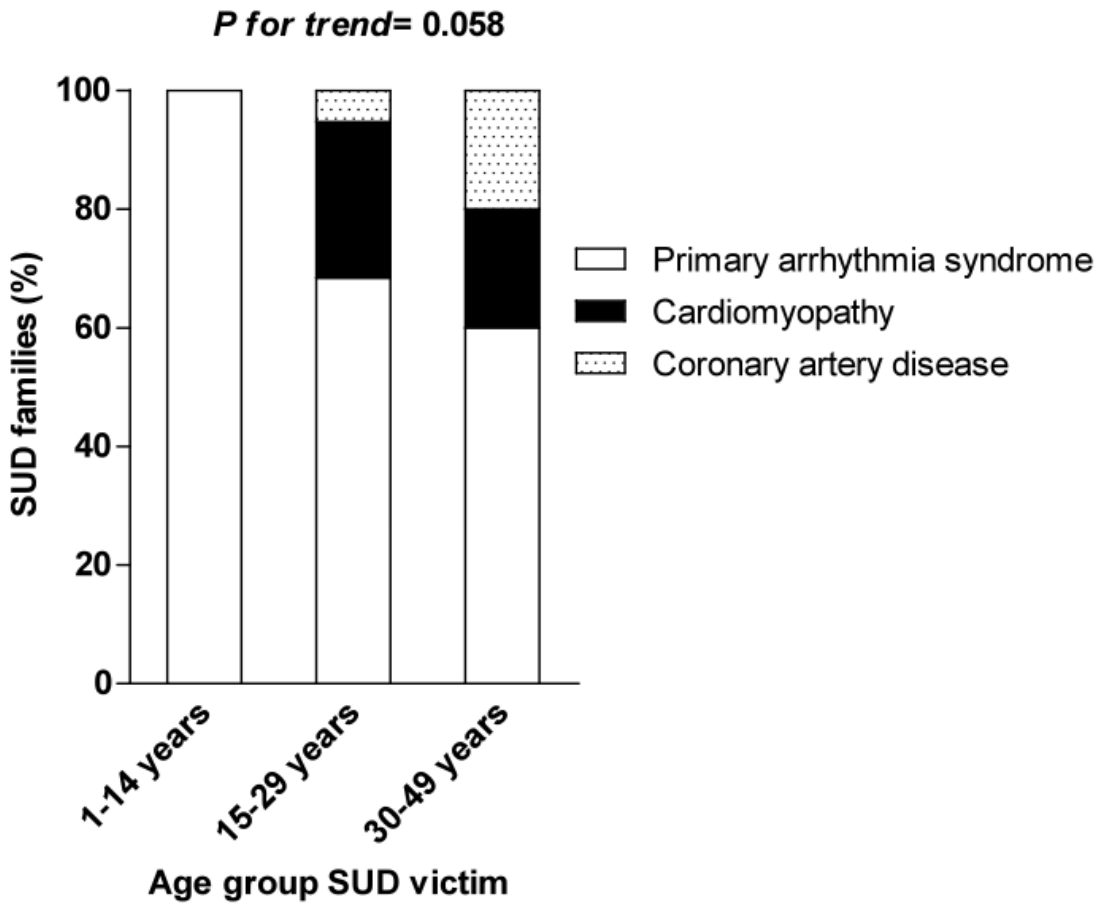
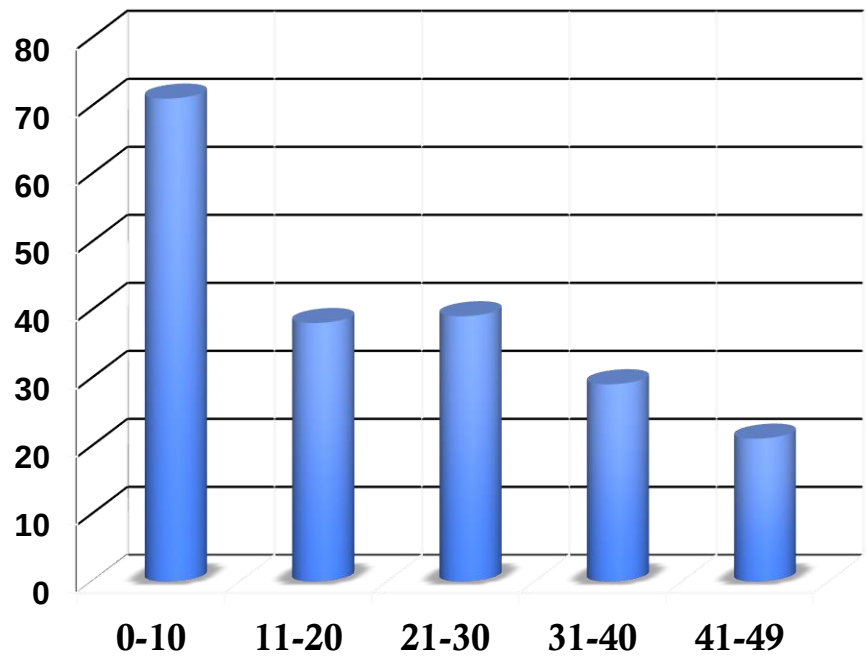
Family screening after SCD

Van der Werf et al. Heart Rhythm. 2010;7:1383-9.



Total yield: 47 families (33%)



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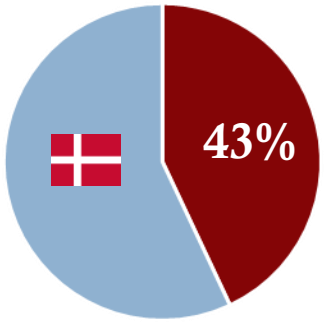
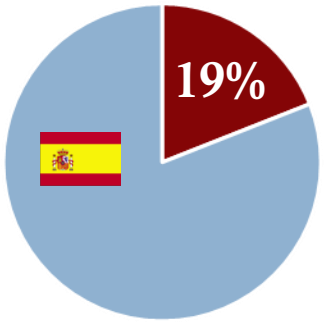
SADS is a common cause of SCD

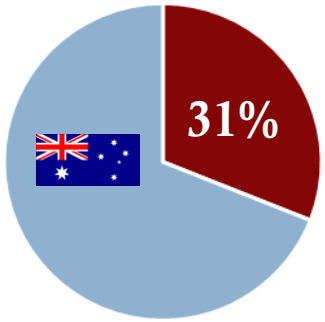
Courtesy Dr. Elijah Behr



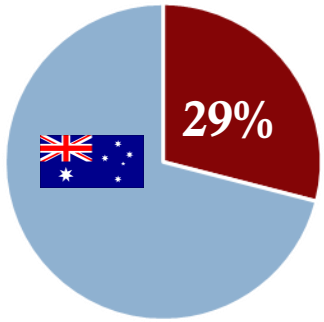
Winkel et al. 2011



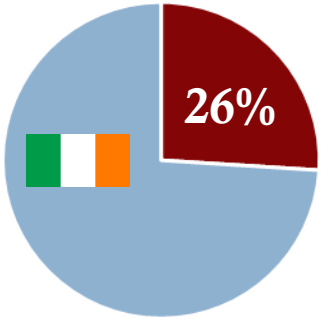
Morentin et al. 2003



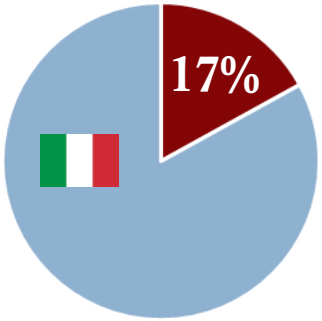
Doolan et al. 2004



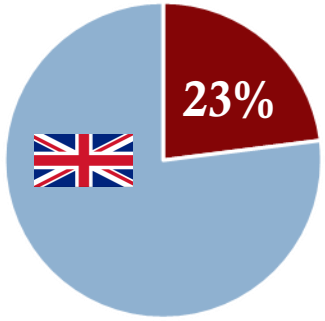
Puranik et al. 2005



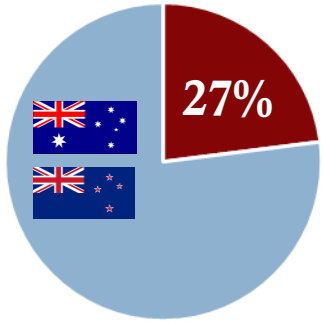
Margey et al. 2011



Corrado et al. 2001



de Noronha et al. 2009



Bagnall et al. 2016

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SCD and autopsy findings

Circulation
Arrhythmia and Electrophysiology

American Heart Association®

Sudden Cardiac Death With Autopsy Findings of Uncertain Significance: Potential for Erroneous Interpretation

Michael Papadakis, Hariharan Raju, Elijah R. Behr, Sofia V. De Noronha, Nicholas Spath, Alexandros Kouloubinis, Mary N. Sheppard and Sanjay Sharma

Circ Arrhythm Electrophysiol. 2013;6:588-596; originally published online May 13, 2013;
doi: 10.1161/CIRCEP.113.000111

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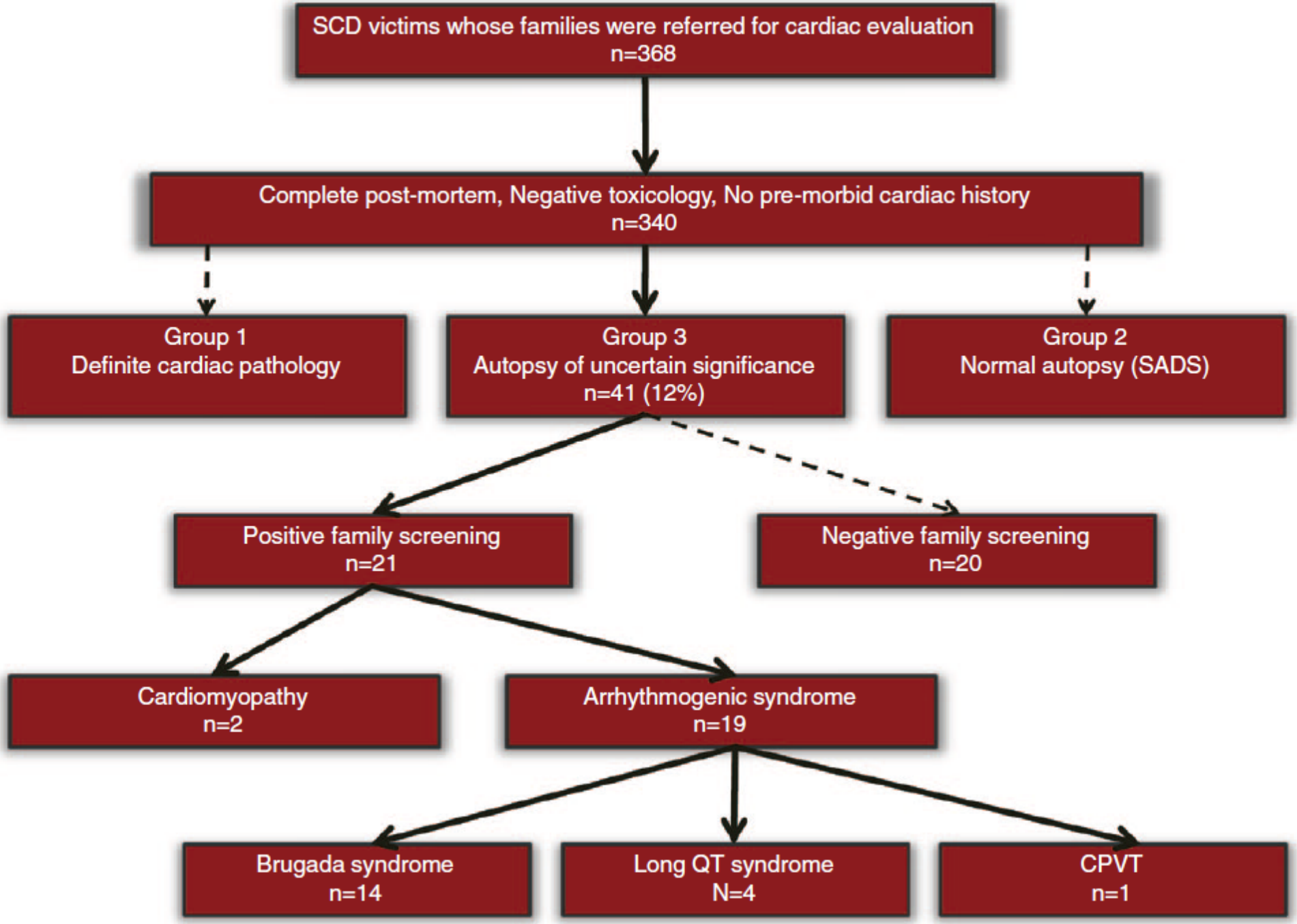
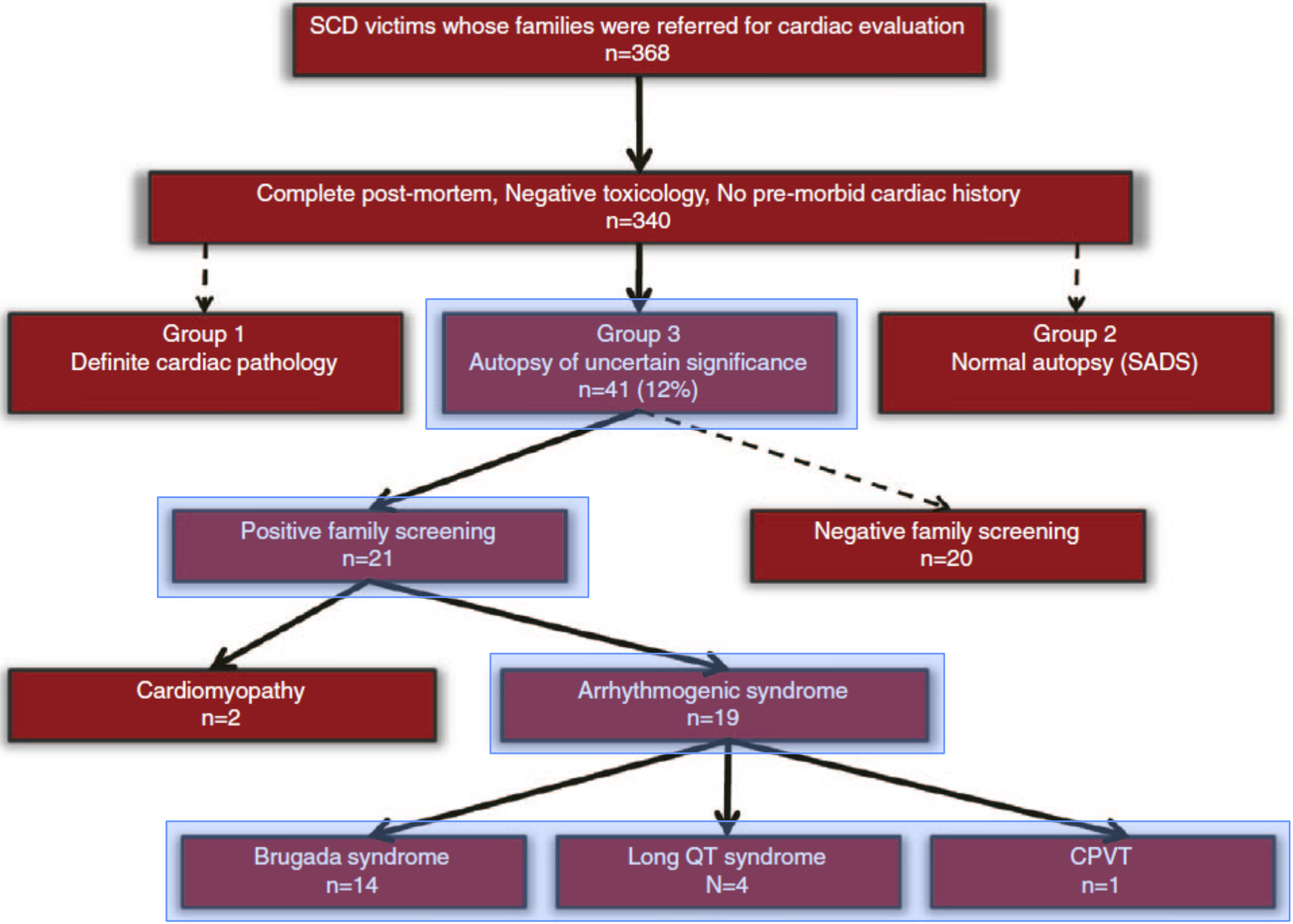

SCD victims whose families were referred for cardiac evaluation
n=368
Complete post-mortem, Negative toxicology, No pre-morbid cardiac history
n=340
Group 1
Definite cardiac pathology
Group 3
Autopsy of uncertain significance
n=41 (12%)
Group 2
Normal autopsy (SADS)
Positive family screening
n=21
Negative family screening
n=20
Cardiomyopathy
n=2
Arrhythmogenic syndrome
n=19
Brugada syndrome
n=14
Long QT syndrome
N=4
CPVT
n=1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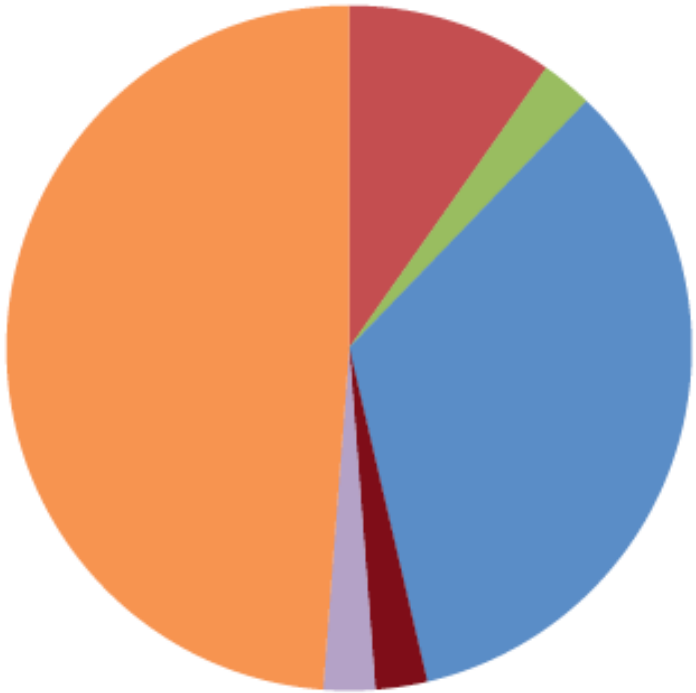
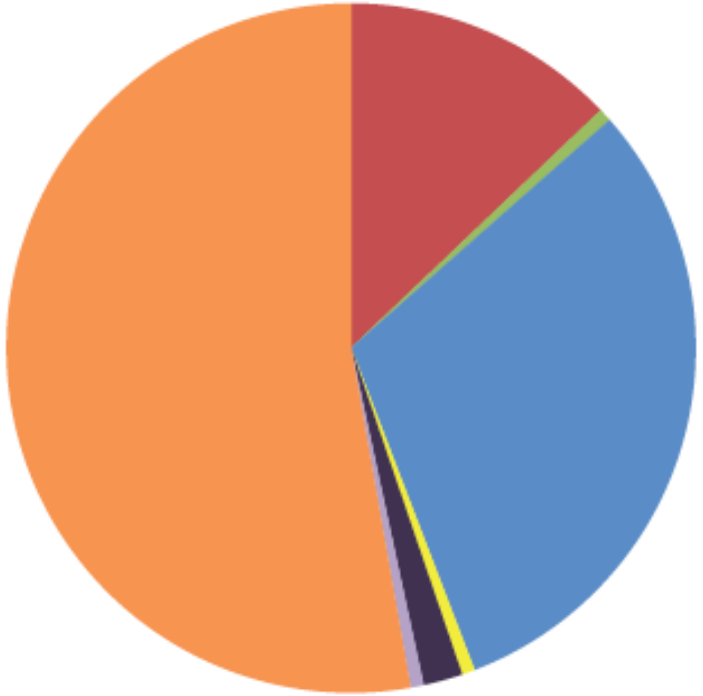
N=4
CPVT
n=1

SCD and autopsy findings

Autopsy of uncertain significance



Normal autopsy (SADS)



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Familial arrhythmia syndromes

♥ Long QT syndrome(s)	17 genes
♥ ST elevation right precordium, “RBBB”, SCD	20+ genes
♥ Catecholamine-induced polymorphic VT/VF	6 genes
♥ Short-coupled Torsades de Pointes	1 gene
♥ Isolated conduction disorders (AVN, BB)	3 genes
♥ Short QT syndrome	3 genes
♥ Idiopathic ventricular fibrillation	1 gene

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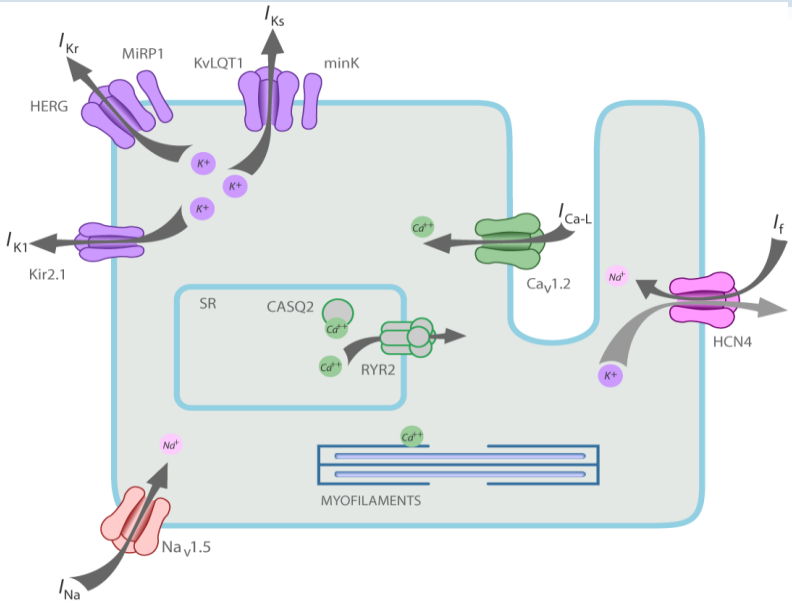
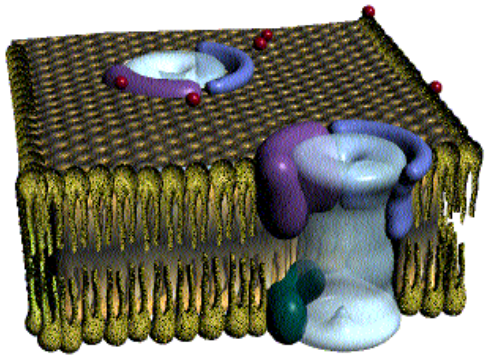
Genetics of sudden cardiac death

Mendelian Arrhythmia Syndromes

- Long QT syndrome
- Short QT syndrome
- Cardiac conduction disease
- Brugada syndrome
- Sinus node dysfunction
- Familial atrial fibrillation
- Catecholaminergic polymorphic VT





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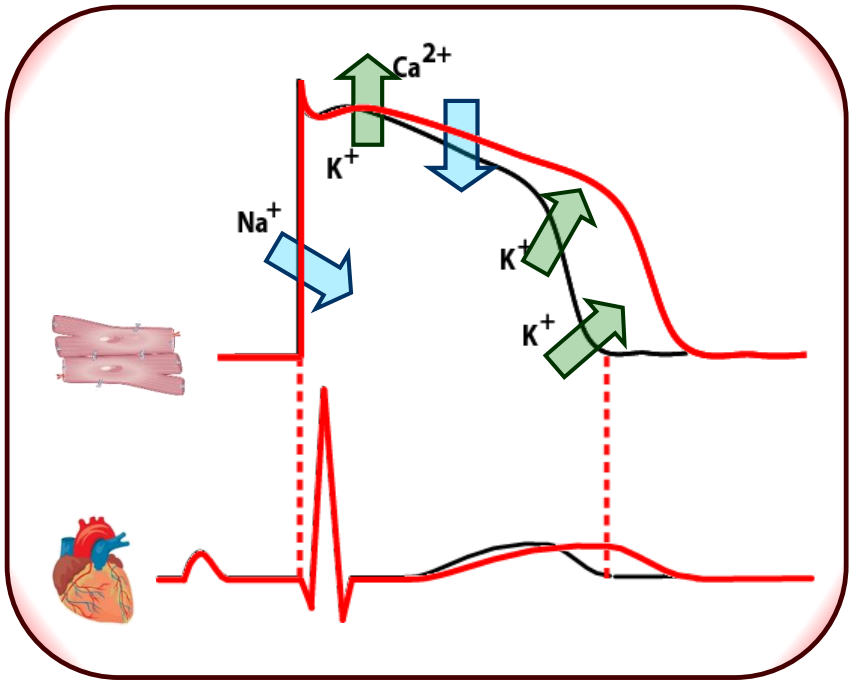
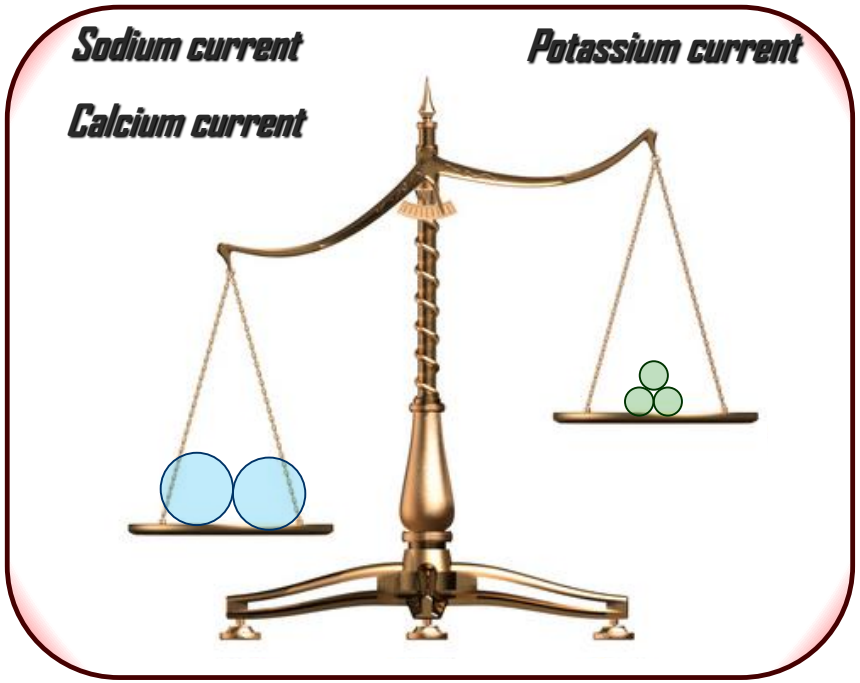
Molecular mechanism of channelopathies





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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Yield of Molecular and Clinical Testing for Arrhythmia Syndromes: Report of a 15 Years' Experience

Nynke Hofman, Hanno L. Tan, Mariëlle Alders, Iris Kolder, Simone de Haij, Marcel Mannens, Maria Paola Lombardi, Ronald L. Lekanne dit Deprez, Irene van Langen and Arthur A. M. Wilde

Circulation. published online August 20, 2013;

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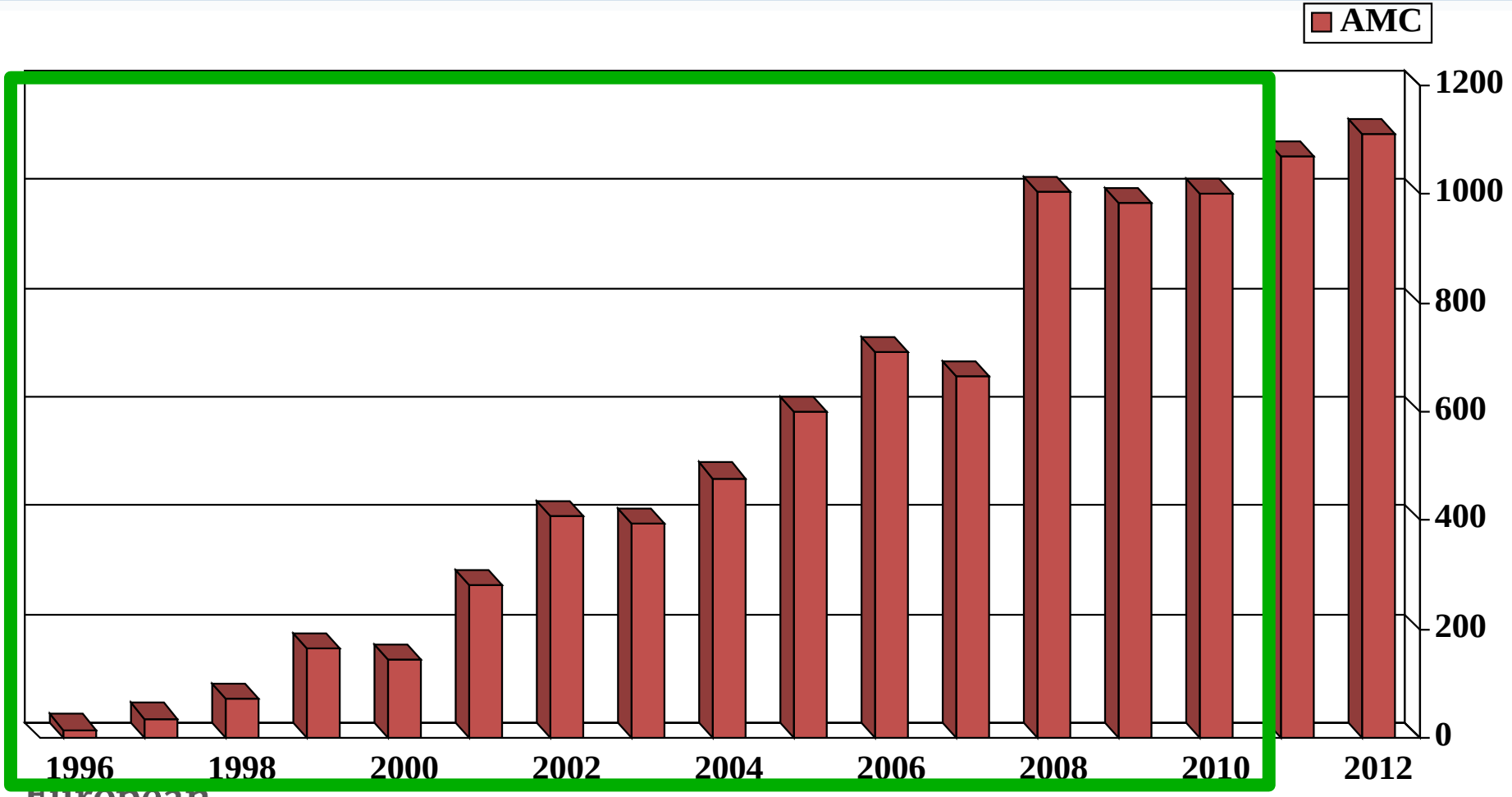
Genetic counseling in AMC



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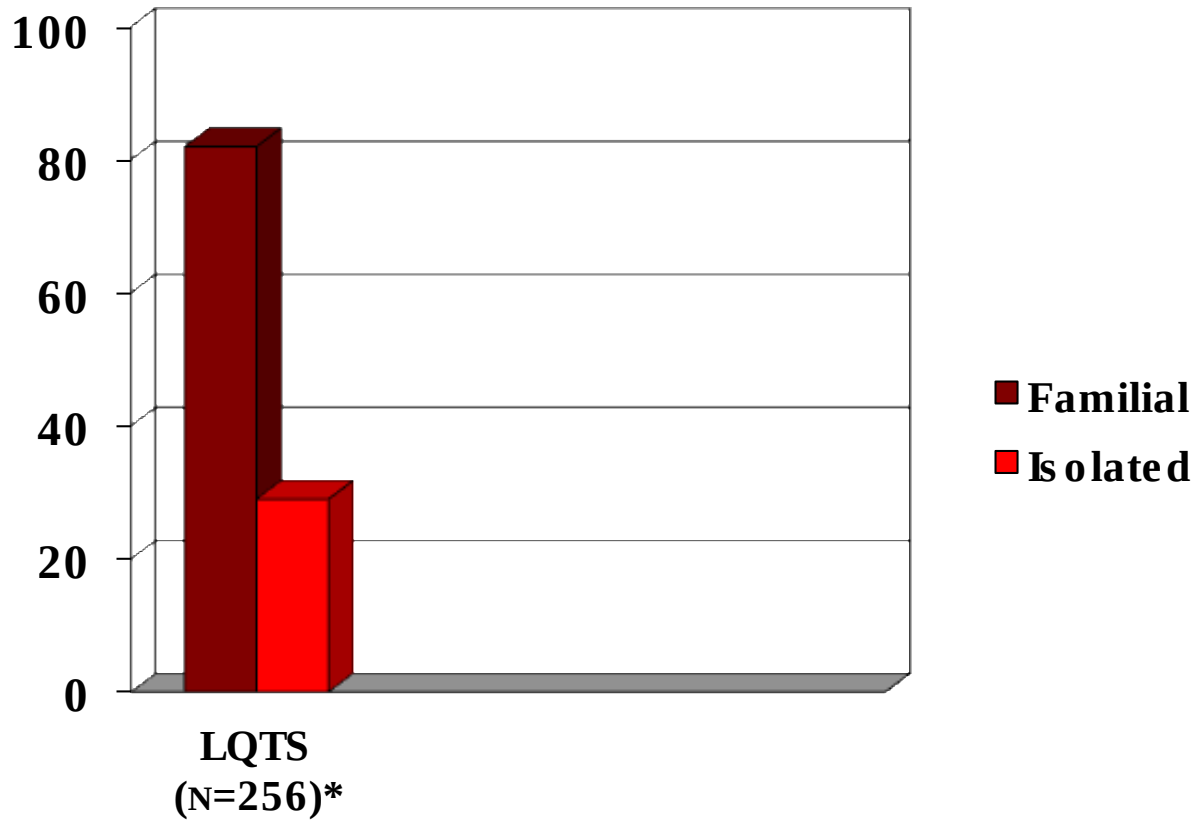
Yield of molecular diagnosis

- Depends on family history, which is defined as:
  - At least 2 clearly affected patients in the family
  - Sudden death of patient in the family ≤40 years

Yield of molecular diagnosis



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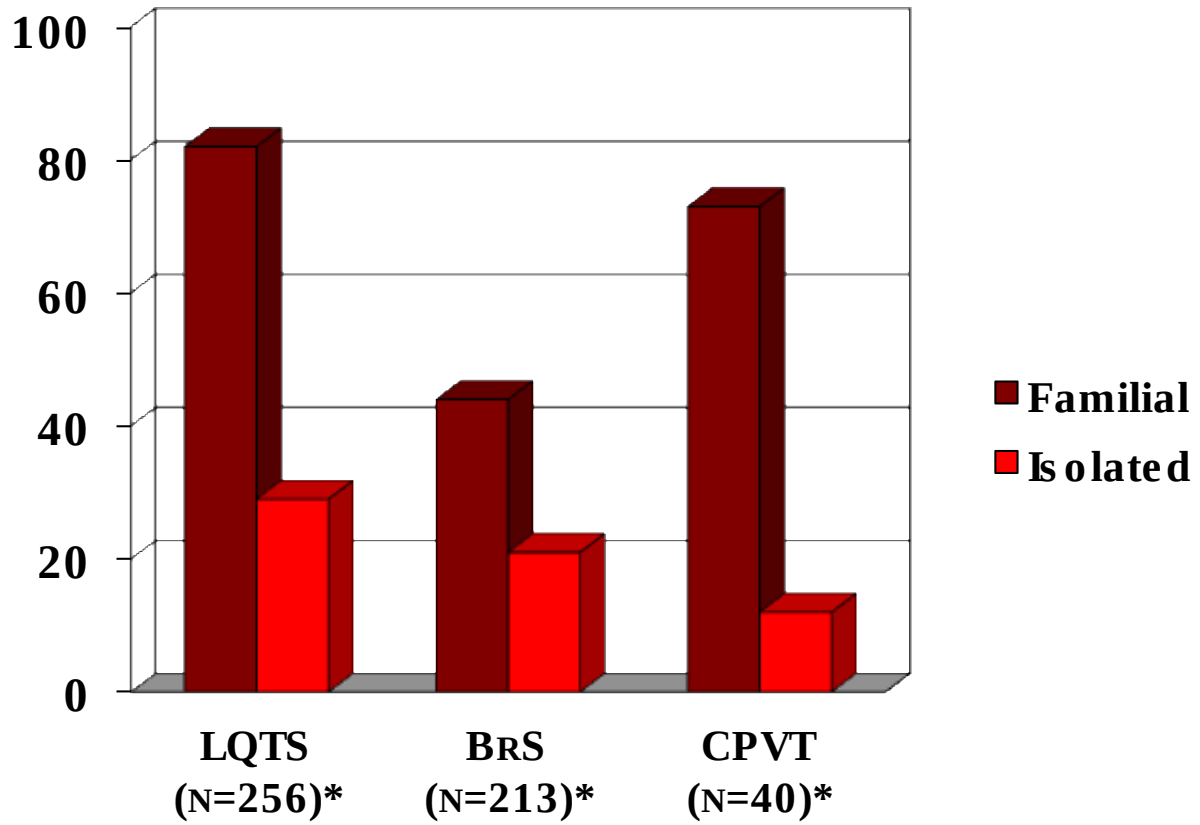
Yield of molecular diagnosis



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In conclusion

Inherited arrhythmia syndromes

- ♥ are important to recognize
- ♥ because they can be treated effectively
- ♥ genetic testing is mandatory in some
- ♥ inherent gene-specific treatment

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Inherited arrhythmias and SCD

Genetic testing post SCD:

- ♥ significant yield
- ♥ significant impact on family (members)
- ♥ significant impact on therapy choices
- ♥ multidisciplinary approach

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Psychological and quality of life implications of ICD therapy

Psychological wellbeing and posttraumatic stress associated with implantable cardioverter defibrillator therapy in young adults with genetic heart disease

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Heart Rhythm 2010;7:1383-1389

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Psychological and quality of life implications of ICD therapy - Methods

- Patients with a clinical diagnosis of a genetic heart disease (cmp or arrhythmias), and an ICD implanted at least 12 months prior
- < 15 years old
- 90/139 (65%)HADS-surveys were returned
- Patients in 'ICD-shock group' (34%) also completed the 'Impact of Events Scale-revised'
- Mean age: 49 ± 14 years
- 73 (81%) had ICD implanted for primary prevention

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Psychological and quality of life implications of ICD therapy- Results

- Mean sores for anxiety and depression were within 'normal' range
- A significant subgroup reported symptoms of anxiety (38%), depression (17%) and posttraumatic stress (31%)
- Greater distress was associated with female gender, a history of syncope, other comorbid medical consitions, and reporting of other distressing events (i.e. ICD complications)
- In those with ICD-shock, higher posttraumatic stress scores were associated with female gender and longer time to first shock.

Clinical course and quality of life in high-risk HCM patients

Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Clinical Course and Quality of Life in High-Risk Patients With Hypertrophic Cardiomyopathy and Implantable Cardioverter-Defibrillators

Circulation, april 2018, Barry J. Maron et al.

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Clinical course and quality of life in high-risk HCM patients - methods

- Cohort of 486 patients with ICDs from 8 international centers
- 94/486 (19%) experienced appropriate ICD interventions
- Clinical course and device interventions were addressed, and survey questionnaires (Florida Shock Anxiety Scale & Hospital Anxiety and Depression Scale) assessed patient anxiety level and psychological well-being.

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Clinical course and quality of life in high-risk HCM patients – clinical results

- 250 (51%) patients completed 720 surveys, of whom 89 (36%) had an (in)appropriate ICD intervention before enrollment in the survey section of the study.
- 94/486 (19%) experienced ≥ 1appropriate primary (n=76) or secondary (n=18) prevention ICD discharge. 87 had no or only mild heart failure symptoms (NYHA I or II).
- 96 (20%) experienced inappropriate shocks (including 29 who also had an appropriate intervention)

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Clinical course and quality of life in high-risk HCM patients – patient reported psychological outcomes

- Patients with ICD interventions reported higher levels of shock anxiety. No difference in the level of anxiety experienced when patients with appropriate shocks were compared to those with inappropriate shocks.
- No significant difference among ICD patient subgroups in terms of general health status and well-being.

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‘Onder spanning inspannen’

Utrecht, 17 April 2018

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