KING'S HEALTH PARTNERS
CARDIOVASCULAR

Pioneering better health for all

Genetic testing in Inherited Cardiac Conditions

Developing the KHP Model

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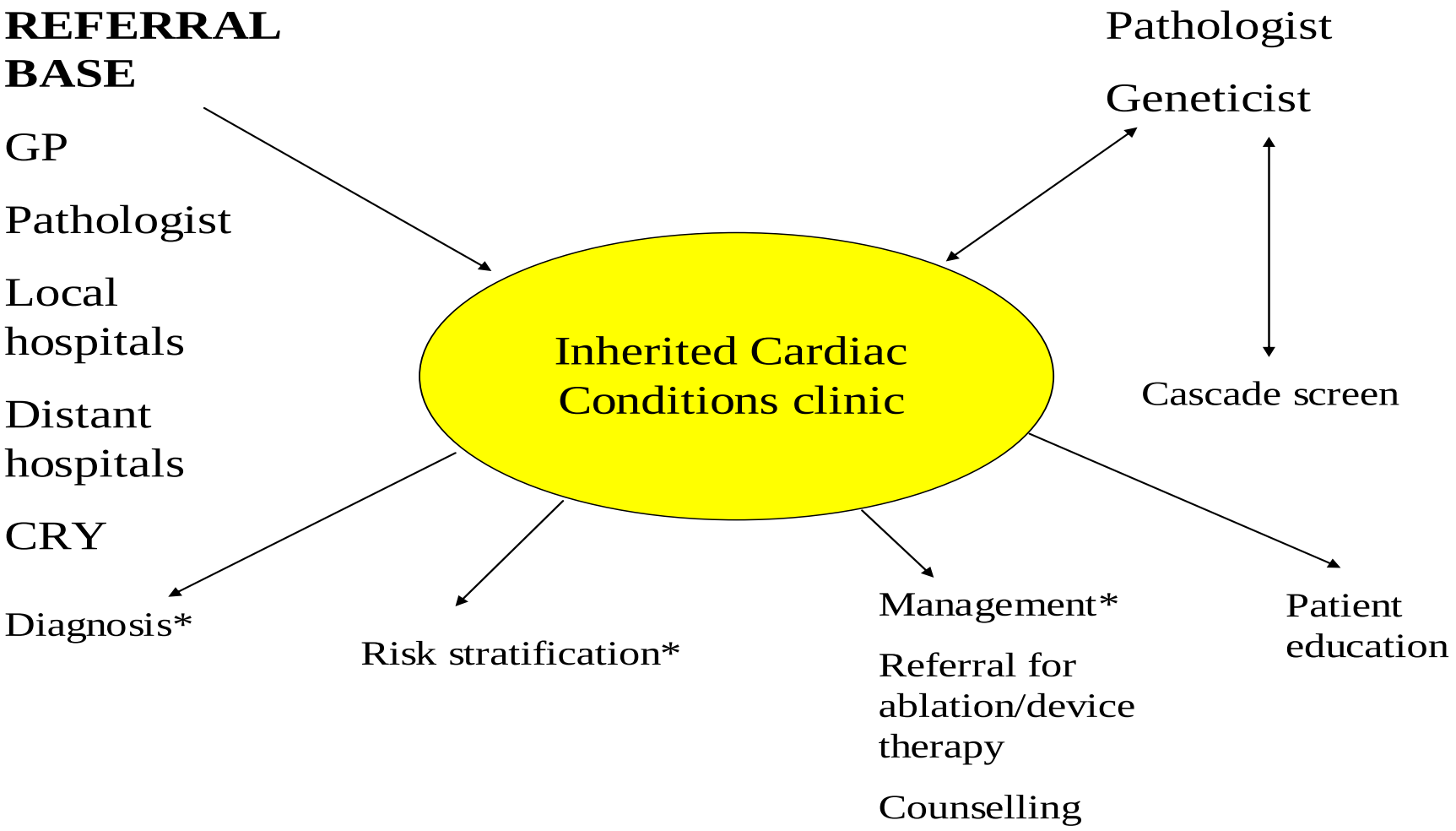
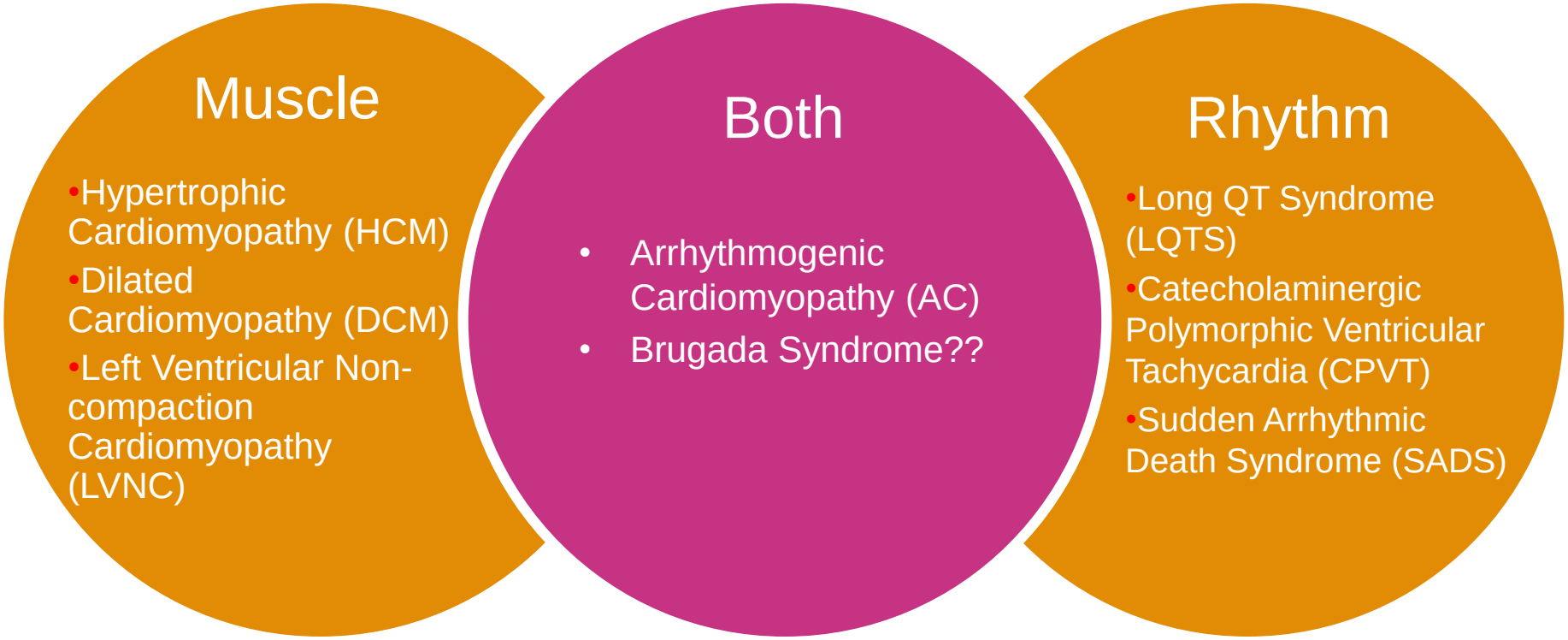

REFERRAL BASE
GP
Pathologist
Local hospitals
Distant hospitals
CRY
Inherited Cardiac Conditions clinic
Pathologist
Geneticist
Cascade screen
Diagnosis*
Risk stratification*
Management*
Referral for ablation/device therapy
Counselling
Patient education

Inherited cardiac conditions



- Mitochondrial disorders
- Inherited neuromuscular diseases

Role of Genetic Testing in ICCs

- Genetic confirmation of phenotype
- May inform medical management
- Can facilitate cascade testing
- Can facilitate prenatal testing and pre-implantation genetic diagnosis

- To arrive at a diagnosis

Video

hidden risk of genetic testing

By Jacqueline Howard, CNN

Updated 1448 GMT (2248 HKT) October 31, 2016

Genetic testing: Good medicine or TMI? 05:32

Story highlights

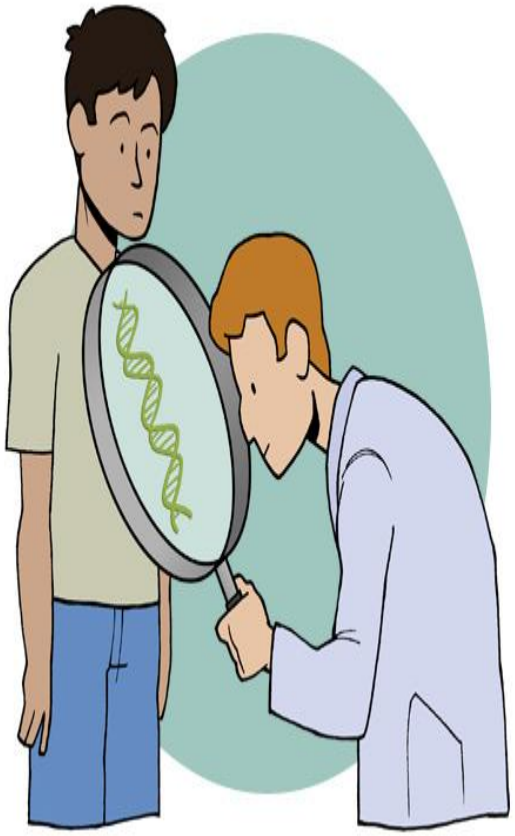
After a boy's sudden death, his family got genetic tests for heart conditions

Twenty family members received false positive test results

(CNN) — After a 13-year-old boy's heart failed suddenly, his family arrived at Dr. Michael Ackerman's doorstep with questions. He was determined to find them answers.

Since the boy's autopsy report seemingly failed to explain his death, more than 20 of his relatives underwent genetic testing for heart conditions that could put them at increased risk of the same fate. The tests diagnosed the family members, including the boy's brother, as having a potentially deadly genetic heart rhythm condition called

Considerations for genetic testing of proband (affected person)



- Fulfillment of diagnostic criteria
- Genetic testing guidelines

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)
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- Availability of test
- Readiness of the patient & ethical considerations

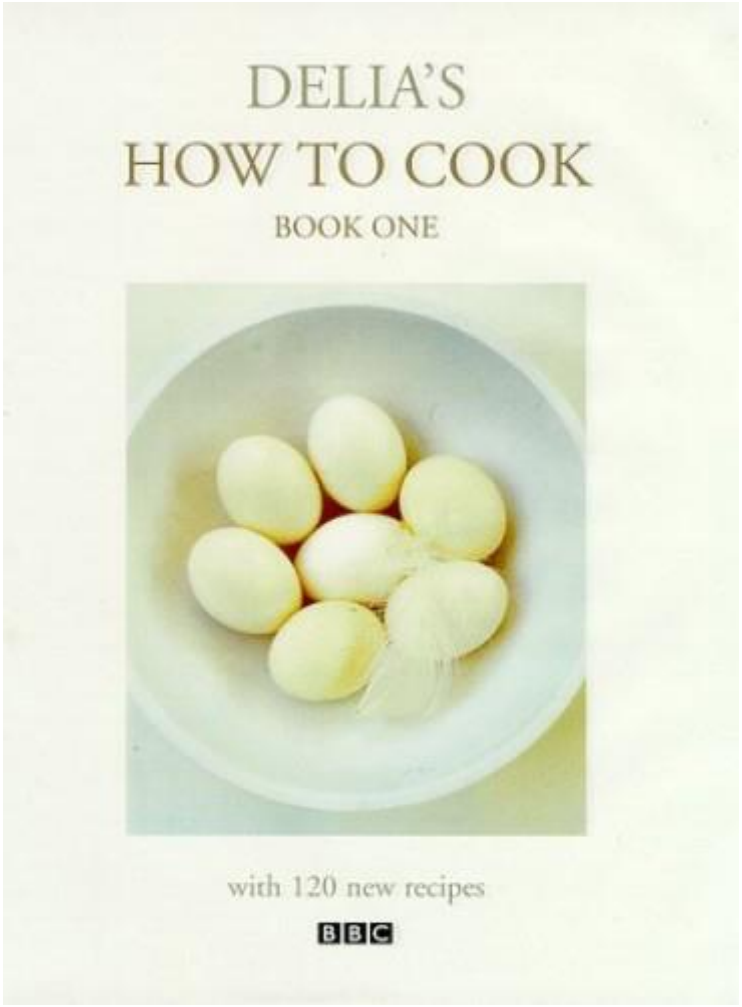
Possible results

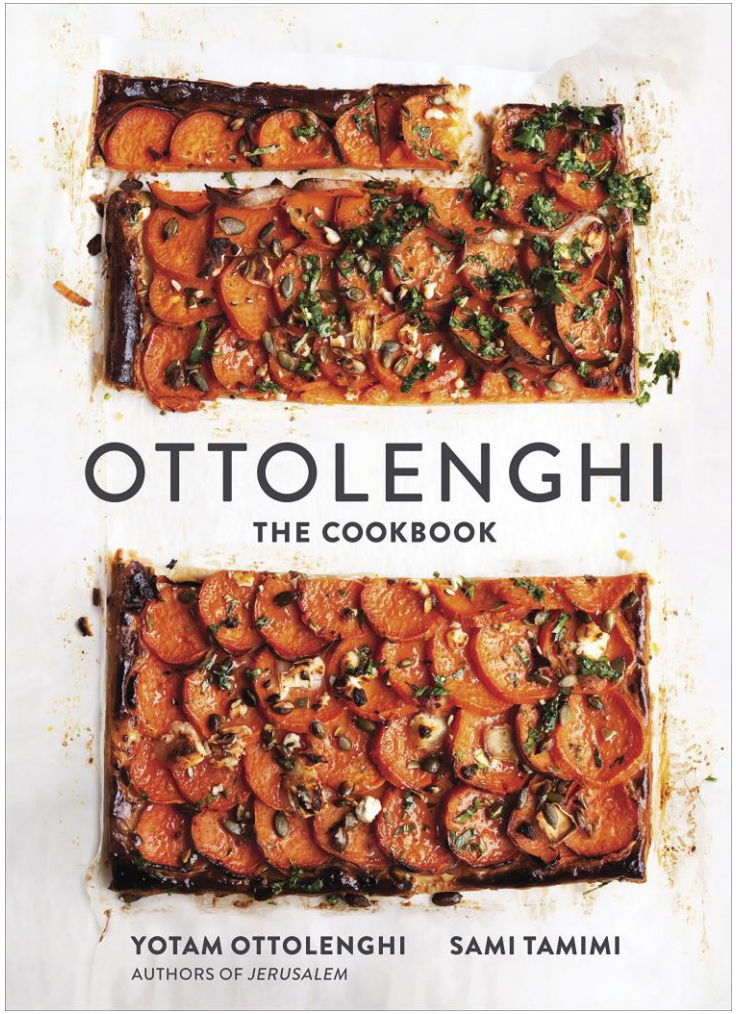
Pathogenic mutation (predictive test)

Negative result (further testing-research, clinical screen)

Variant of unknown clinical significance (family studies or further testing-research, clinical screen)

The changing times…..





Changes in the genetic testing landscape

Genomics england

Over 100,000 whole genome sequences now available for approved researchers

Posted on July 31, 2019 at 2:14 pm

Genomes	**101,162 genomes** • 26,488 Cancer • 74,674 Rare Disease	**Primary clinical data**	**90,643 participants** • 17,682 Cancer • 72,961 Rare Disease
Secondary data	• NHSD - Hospital Episode Statistics (HES) • NHSD - Diagnostic Imaging Dataset (DID) • NHSD - Patient Reported Outcome Measures (PROMs) • NHSD - Mental Health Services Data Set (MHSDS) • NHSD - Office for National Statistics (ONS) • PHE - Systemic Anti-Cancer Therapy Data Set (SACT)		
Clinically interpreted data & QC	• **30,157 families** with Tier 1, 2 and 3 variants from interpretation pipeline • **8,227 families** with GMC exit questionnaires • **54,216** tiered and quality checked rare disease genomes; **24,568** quality checked cancer genomes	**New Datasets**	• **Exomiser output table** • PHE - National Radiotherapy Dataset (**RTDS**) • PHE - Cancer Registration (**AV**) tables • PHE - Cancer waiting times (**CWT**) • PHE - Lung Cancer Data Audit (**LUCADA**) • PHE - Diagnostic Imaging Dataset (**DID**)

Changes in our understanding of ICCs

Circulation

IN DEPTH

Beyond the One Gene–One Disease Paradigm

Complex Genetics and Pleiotropy in Inheritable Cardiac Disorders

Marina Cerrone, MD
Carol Ann Remme, MD, PhD
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Connie R. Bezzina, PhD*
Mario Delmar, MD, PhD*

Circulation. 2019;140:595–610. DOI: 10.1161/CIRCULATIONAHA.118.035954

Complex genetics: from monogenic to polygenic

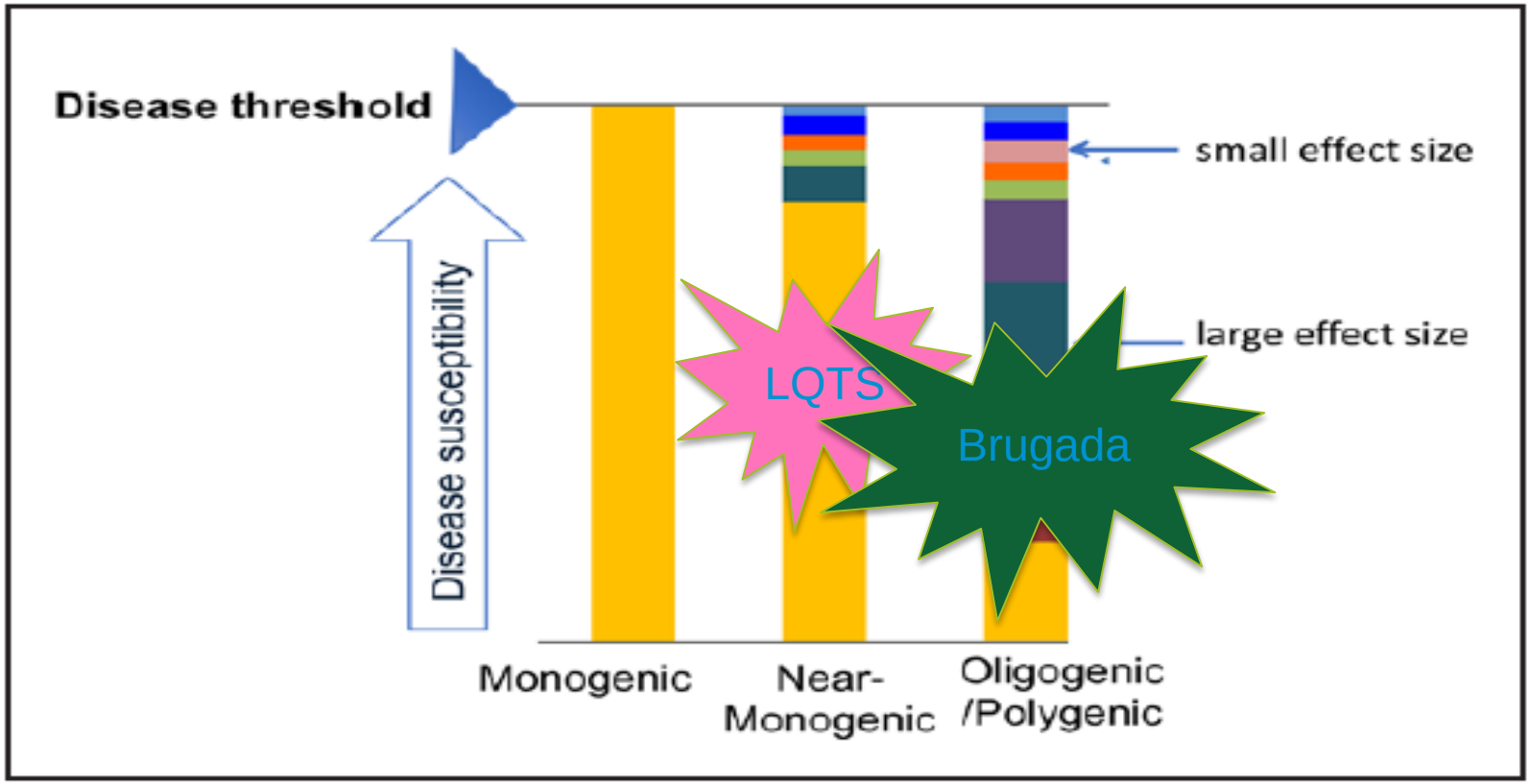

Figure 1. Evolving model of genetic architecture of inherited arrhythmias and cardiomyopathies.

Pleiotropy

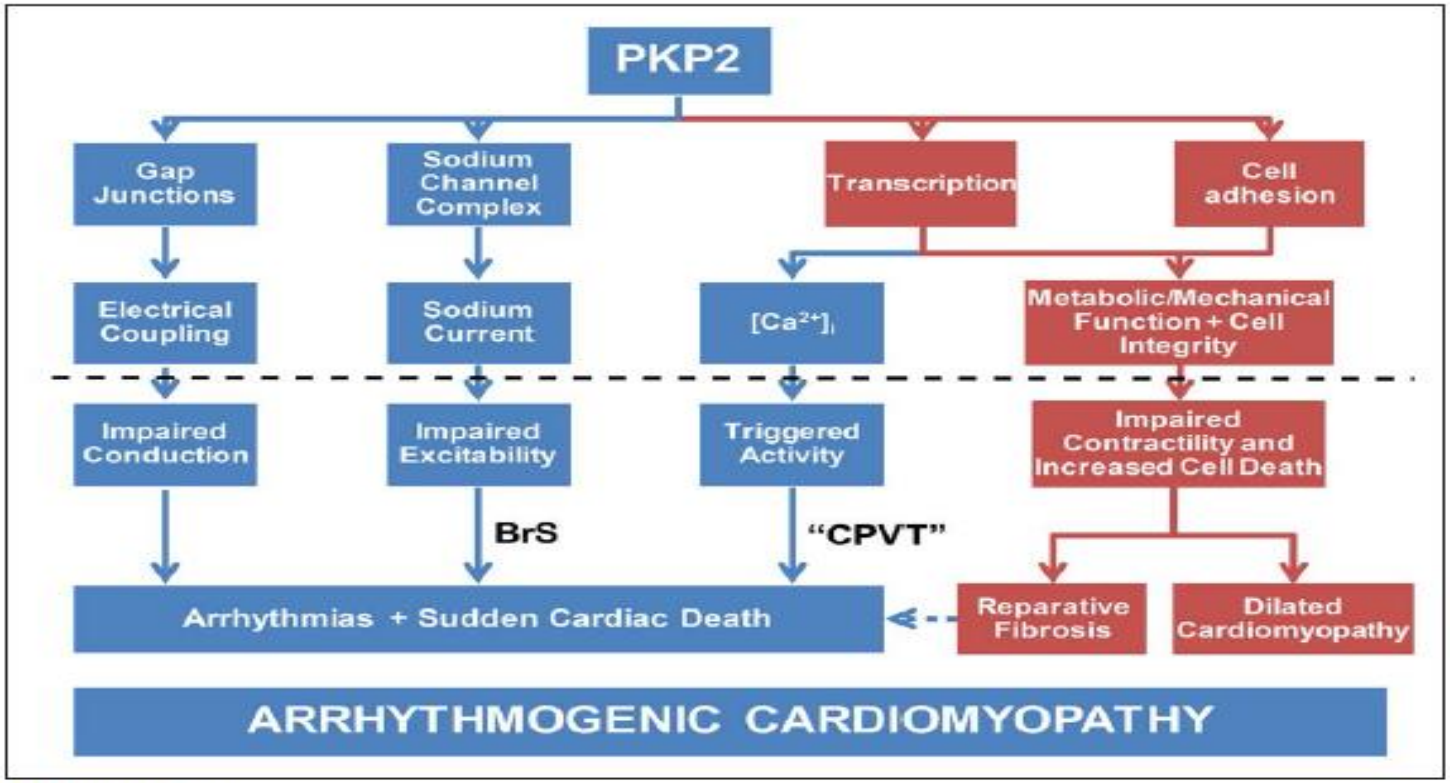

Figure 6. PKP2 as a pleiotropic gene.
Deficiencies in PKP2 have been associated with at least 4 downstream effects: integrity of gap junctions and, hence, electrical coupling; function of the sodium channel complex and, consequently, sodium current properties; cell adhesion to maintain mechanical integrity, and regulation of transcription that affects both metabolic/mechanical function, and the regulation of intracellular calcium concentration, $[Ca^{2+}]_i$, as well. If disturbed (dotted line), each of the 4 arms can lead to either an electrical or a structural phenotype. A dysfunction along all 4 arms would yield the complete arrhythmogenic cardiomyopathy phenotype. But not all arms have to be affected in all cases and, as such, a walk downstream of the sodium channel complex arm would lead to a BrS-like phenotype; downstream of transcription $[Ca^{2+}]_i$ would yield a phenotype resembling CPVT, whereas a mechanical phenotype of dilated cardiomyopathy would also be possible. As such, a pleiotropic gene can result in one or more of multiple, seemingly unrelated phenotypes. BrS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; and PKP2, plakophilin-2. Reproduced from Cerrone et al[76] with permission.

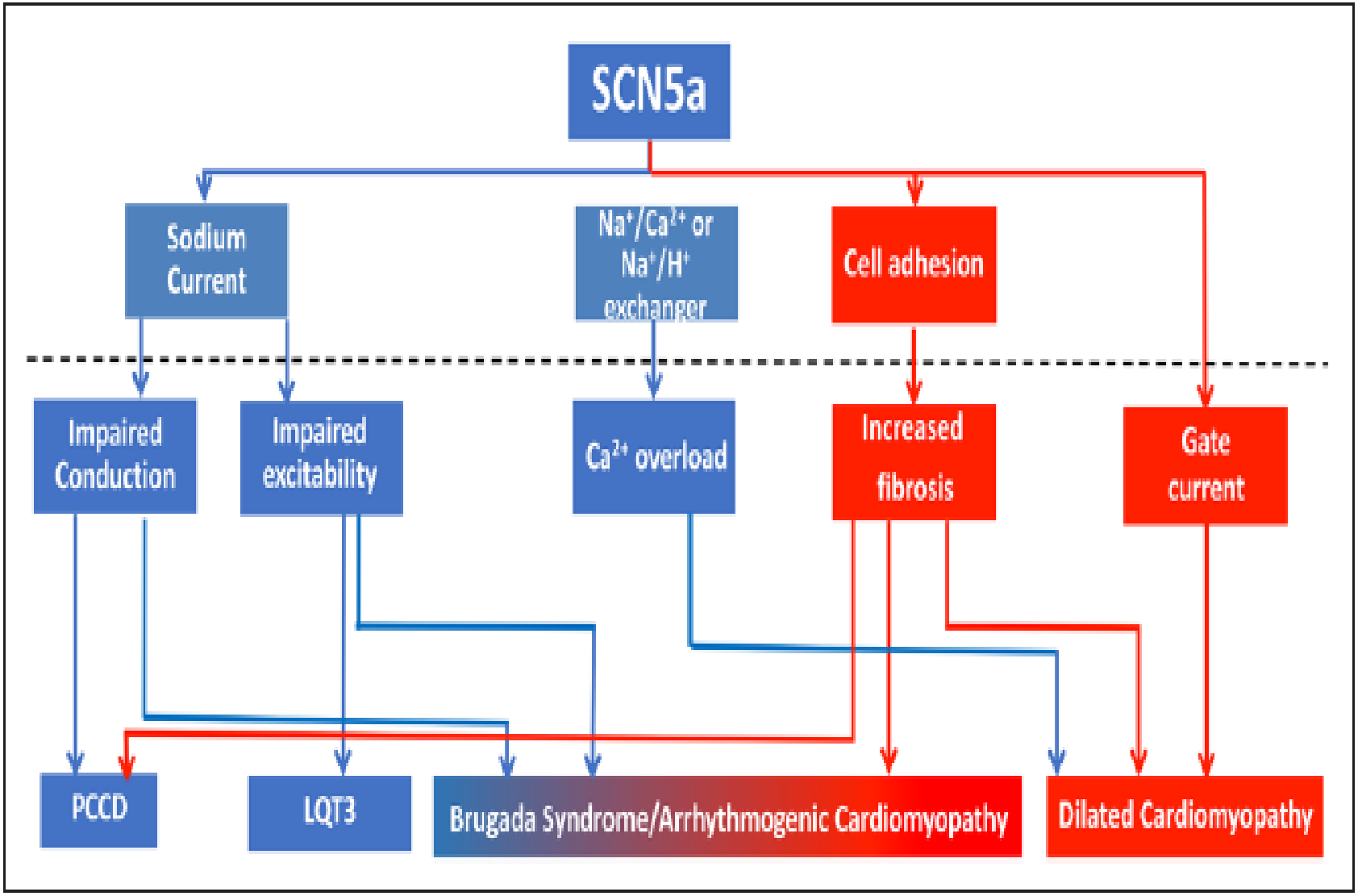

Figure 7. *SCN5A* as a pleiotropic gene.

As in the case of *PKP2* (Figure 6), seemingly unrelated functions related to the expression of the *SCN5A* gene can, if impaired, cause a clinical phenotype consequent to the balance of endophenotypes that were affected by the mutation, ranging from purely electrical (blue) to structural (red) or a combination of both, Brugada syndrome/arrhythmogenic cardiomyopathy. LQT3 indicates long-QT syndrome 3; PCCD, progressive cardiac conduction defect; and *PKP2*, plakophilin-2.

The KHP Model is a team approach

Core ICC Team
& related specialties

South London Genomic Laboratory Hub

NHS Royal Brompton & Harefield NHS Foundation Trust

Cardio Classifier BETA

Patients & families

KING'S College LONDON

Genomics england

EORP

Association for Inherited Cardiac Conditions AICC

Beat Heartbreak Forever

ClinGen Clinical Genome Resource

European Reference Network for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)

Goals:

- Provide equity in access for genetic counselling and testing within the resources of the NHS
- Enable the highest quality of interpretation to support applicability to patient management and care
- Contribute to large-scale datasets & conduct KHP research to enable greater understanding of ICCs
- Ensure comprehensive support and feedback for patients and families

Many changes but core messages remain for genetic testing in ICCs:

- Define the phenotype and inheritance pattern
- Certain criteria must be met before genetic testing can be done/offered
- Genetic testing may not provide a black & white answer-clinical screening is just as important and informative
- Comprehensive genetic counselling & attendance at a specialist ICC clinic is best practice

KING'S HEALTH PARTNERS
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Pioneering better health for all

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