

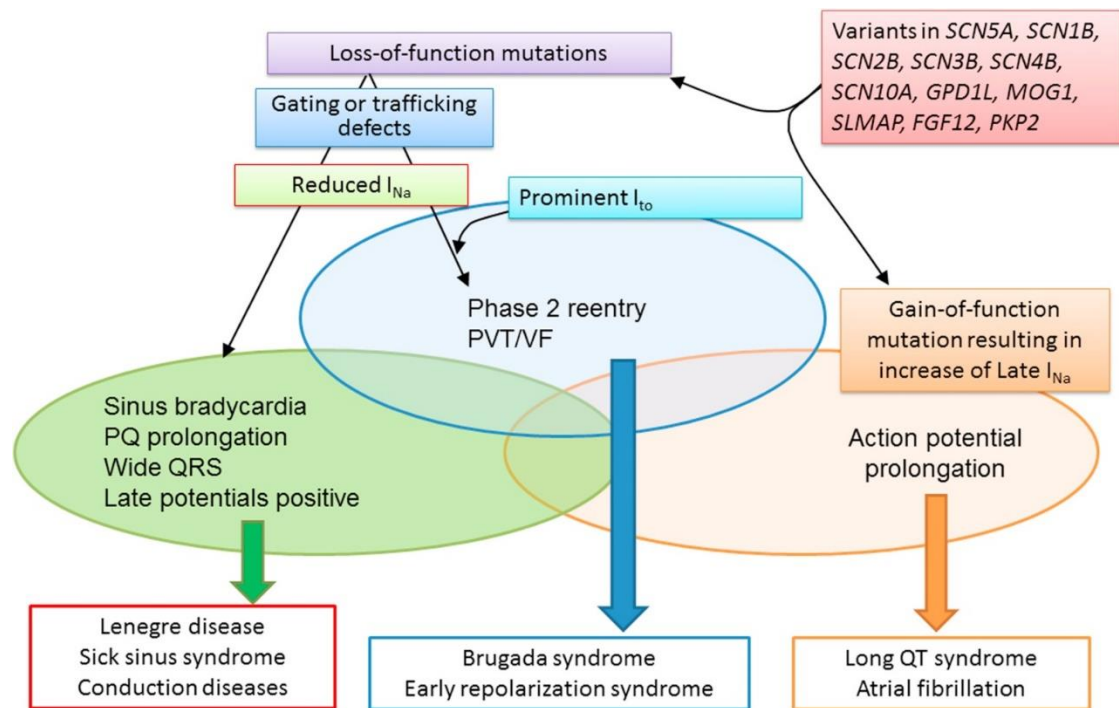


Figure 1. Schematic showing overlap syndromes resulting from genetic defects resulting in loss of function of sodium channel current (I_{Na}) or gain of function in Late I_{Na} .

In the absence of prominent I_{to} or I_{K-ATP} , loss-of-function mutations in the inward currents result in various manifestations of conduction disease. In the presence of prominent I_{to} or I_{K-ATP} , loss-of-function mutations in inward currents cause conduction disease as well as the J-wave syndromes (Brugada and early repolarization syndromes). Early repolarization syndrome is believed to be caused by loss-of-function mutations of inward current in the presence of prominent I_{to} in certain regions of the left ventricle, particularly the inferior wall of the left ventricle. The genetic defects that contribute to Brugada syndrome and early repolarization syndrome can also contribute to the development of long QT and conduction system disease, in some cases causing multiple expressions of these overlap syndromes. In some cases, structural defects contribute to the phenotype.

PVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation.

**Table 1. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing.
Impact of genetic testing for the proband**

Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	-	+	-
Atrial fibrillation	-	+	-
Early repolarization syndrome	-	-	-
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic cardiomyopathy	+++	++	++
Left ventricular non-compaction	+	+	-
Restrictive cardiomyopathy	+	+	+
Congenital heart disease			
Syndromic CHD	+++	+	-
Non-syndromic CHD	+	-	-
Familial CHD	++	-	-

+++ : is recommended/is indicated or useful.

++ : can be recommended/can be useful.

+ : may be considered/may be useful.

- : is not recommended/is not indicated nor useful.

Table 2. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Different methods of genetic testing.

Technology	Strengths	Limitations	Example diagnostic application
Sequencing approaches			
Sanger sequencing	○ Accuracy ○ Low cost per reaction	○ Not scalable ○ Insensitive to large SVs	○ Single gene test ○ Single variant testing—for a pre-specified variant during cascade family evaluation
Panel sequencing	○ Balances reasonably comprehensive coverage (e.g. all genes associated with a particular phenotype) against cost ○ Often highly optimized for complete and uniform capture of region of interest	○ Usually exonic only ○ Needs updating as knowledge changes (e.g. new gene-disease associations discovered)	First line diagnostic test for proband
WES	○ Comprehensive coverage of all genes ○ Off-the-shelf design ○ Can run a single wet-lab workflow, and introduce specificity at analysis stage ○ Can update analysis to incorporate new knowledge without regenerating data—adaptable ○ Enables analyses for secondary findings	○ Larger target requires more sequencing (c.f. panels) ○ May be less optimized than more focused panel ○ More costly and complex to store and process data (c. 10–100× more data than panel) ○ Will not detect non-coding variants ○ May not detect all variant classes	○ Diagnosis in proband for very heterogeneous conditions (e.g. paediatric and syndromic cardiomyopathies) ○ Second line test if panel negative in specific circumstances, for example with informative family structure
WGS	○ Comprehensive genetic characterization—all genes, all elements, all variant types ○ Will also detect common variants for PRS, pharmacogenetics and other applications ○ Enables analyses for secondary findings	More costly and complex to store and process data (~100× more data than WES)	○ Diagnosis in proband for very heterogeneous conditions ○ Second line test if panel negative ○ Definitive and future-proof genetic characterization if funds permit—e.g. hold data in medical record for iterative targeted interpretation according to clinical needs
Non-sequencing approaches			
Allele-specific PCR	Quick, cheap, accurate	Pre-specified variants only	Testing a single variant in a large family (more likely Sanger sequencing now)
Array comparative genomic hybridization	○ Cheap screening for SVs/CNVs ○ High-resolution (compared with cytogenetic approaches)	Insensitive to other variant classes	Screening for structural variants, including aneuploidy, e.g. in structural congenital heart disease
Droplet digital PCR	Low cost, high-sensitivity, detection of genome dose for SV/CNV detection at a pre-specified locus	Scalability limited by multiplexing of pre-specified PCR amplicons targeting regions of interest	Confirmation of putative CNVs detected in high-throughput sequence data
DNA SNP arrays	○ Genome wide ○ Relatively cheap	○ Pre-specified variants only ○ Accuracy poor for many rarer variants	○ Recreational ancestry analysis ○ Polygenic risk ○ Pharmacogenetics

CNV, copy number variant; PCR, polymerase chain reaction; PRS, polygenic risk score; SNP, single-nucleotide polymorphism; SV, structural variant; WES, whole-exome sequencing; WGS, whole-genome sequencing.

Table 3. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Indications for Genetic Testing.

Should do

Genetic testing in patients with a potential cardiogenetic condition is performed only with appropriate genetic counselling.

In patients with a clear specific phenotype, it is appropriate to perform genetic testing analysing genes with definite or strong evidence supporting disease causation.

Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multidisciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists.

Variant interpretation is best performed using standard guidelines for interpretation and can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration.

In families where a LP/P variant has been identified, detailed genetic counselling and guidance regarding inheritance patterns, variant penetrance, and risk should be offered, and cascade testing facilitated.

In patients with a high probability of a specific inherited cardiac disease and a molecular screening performed in a pre-NGS era or with an incomplete NGS panel, repetition of the testing should be considered.

May do

In patients with a clear specific phenotype, it may be appropriate to analyse genes with moderate evidence supporting disease causation.

In selected cases with a definite phenotype and no genetic diagnosis after testing of the genes with definite or strong evidence supporting disease causation, broader genetic testing may be considered. Such selected cases may include familial cases, those with atypical features, such as extracardiac manifestations and those with unusual early disease onset.

Reported Variants of Uncertain Clinical Significance (VUS) may be reclassified, i.e. ‘upgraded’ [Likely Pathogenic/Pathogenic (LP/P)] or ‘downgraded’ (Likely Benign/Benign), in multidisciplinary clinics with access to molecular genetics laboratories, according to robustness of clinical phenotype and/or familial segregation evidence.

Do not do

Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting.