# Genetic testing for inherited cardiovascular diseases. A position statement of the Polish Cardiac Society endorsed by the Polish Society of Human Genetics and Cardiovascular Patient Communities

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## ABSTRACT

According to the latest guidelines of European and American medical societies, genetic testing (GT) is essential in cardiovascular diseases for establishing diagnosis, predicting prognosis, enabling initiation of disease-modifying therapy, and preventing sudden cardiac death. The GT result may be relevant for cascade GT in the patient's relatives, for planning his/her profession and physical activity, and for procreative counseling. This position statement has been prepared due to the scarcity of GT in cardiovascular diseases in Poland and the need to expand its availability.

We give a concise description of the genetic background of cardiomyopathies, channelopathies, aortopathies, familial hypercholesterolemia, pheochromocytomas, and paragangliomas. The article discusses various aspects of GT in specific populations, such as children or athletes, and also presents prenatal genetic diagnostics. We propose recommendations for GT and counselling, which take into account Polish needs and capabilities.

We give an outline of legal regulations, good clinical practice in GT with respect for patient rights, the role of cardiologists and clinical geneticists in GT planning and post-test counseling, and the requirements for laboratories performing genetic tests. The Polish Cardiac Society and Polish Society of Human Genetics experts speak with one voice with cardiovascular patient communities to underline the need for a law on GT and increasing the availability of GT for cardiovascular patients.

**Key words:** cardiomyopathy, channelopathy, familial hypercholesterolemia, genetic testing, thoracic aortic aneurysm

## INTRODUCTION

Over the last 30 years, significant advancements have been made in human genetics. Tedious linkage analysis studies in the 70s led to recognition of genes responsible for familial hypercholesterolemia (FH) in the mid-80s [1]. Then in the 1990s and early 2000s, we witnessed an outburst of discoveries of disease-causing genes. In 1990, *MYH7* (all full names of genes are given in Supplementary material, *Table S1*) became the first gene known for causing hypertrophic cardiomyopathy (HCM) [2], in the following year, *FBN1* became the first known gene responsible for aortic aneurysm formation [3]. Information on genes directly involved in long QT syndrome (LQTS), Brugada syndrome (BrS), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) was published in 1995, 1998, 1999, and 2000 respectively [4–7]. With the advent of next-generation sequencing (NGS), today we have over 100 established genes with definitive or strong associations to hereditary cardiac diseases and hundreds are under investigation [8]. This has improved our understanding of pathomechanisms and allowed the discovery of gene-specific therapies [9] and recognition of new cardiovascular phenotypes [10]. Most cardiac conditions are inherited in an autosomal dominant (AD) fashion and qualify for cardiomyopathies (CMP), arrhythmias, aortopathies, lipid disorders, and congenital heart defects (CHD). These conditions frequently have overlapping phenotypes and can present differently even in one family as the effect of the same pathogenic (P)/likely pathogenic (LP) variant can be modified by common polymorphisms. Apart from strictly monogenic dominant inheritance, some cases are caused by digenic or oligogenic inheritance, with two or more rare variants located in the same or different genes, which is often associated with a more severe phenotype [9, 11]. Taking into account all these complexities, molecular diagnostics requires a comprehensive approach with parallel analysis of a large number of genes with NGS.

Genetic testing (GT) results aid in individualized and more informative counseling in families especially through identification of carriers of asymptomatic pathogenic or likely pathogenic (P/LP) variants, which in many cases enables prevention of sudden cardiac death (SCD). Cardiology guidelines incorporate GT results in recommendations for diagnosis and personalized clinical management [12, 13] although the usefulness of establishing a genetic cause varies between disease entities (Table 1) [14].

GT for inherited cardiac disorders is more effective as a family-based approach since results are most accurately interpreted after integrating genetic and medical test results from multiple family members. The general approach is based on application of a gene panel with the NGS method for the index patient. Identification of P/LP variants or variants of uncertain significance (VUS) following positive segregation analysis leads to recommended clinical evaluations and potential therapeutic and lifestyle change in index patients and affected family members. The absence of a causative variant in the proband's relatives leads to dismissal from further clinical evaluations. Despite the

**Table 1.** The role of genetic testing in nonsyndromic inherited cardiac diseases for the index case in three categories (diagnostic, prognostic, and therapeutic). The relative strength is indicated by the number of + with +++ as the strongest evidence and – as no evidence

| Disease | Diagnostic | Prognostic | Therapeutic | Yield[a] |
|---|---|---|---|---|
| DCM | +++ | ++ | ++ | 30%–70% |
| NDLVC | ++ | ? | + | 20%–25% |
| ARVC | ++ | ++ | ++ | ±60% |
| HCM | +++ | + | + | ±60% |
| RCM[b] | +++ | ++ | + | 40%–60% |
| LQTS | +++ | +++ | +++ | ±60%–70% |
| CPVT | +++ | + | – | ±60% |
| SQTS | + | – | – | ±30% |
| BrS | + | + | + | ±20%–30% |
| fTAAD | +++ | +++ | ++ | ±50% |
| FH | +++ | +++ | +++ | 30%–70% |

[a]The yield of identifying a (putative) pathogenic variant. [b]Providing that a light-chain cardiac amyloidosis was excluded before genetic testing

Modified from Wilde et. al. [14]

Abbreviations: AVRC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; FH, familial hypercholesterolemia; fTAAD, familial thoracic aortic aneurysm and dissection; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy; SQTS, short QT syndrome

continuous increase in knowledge, the yield of GT varies between 20%–75 % depending on the disease. Negative GT results in the proband does not exclude any assumed diagnosis and, in this case, does not exempt the proband's family members from routine evaluations. In the case of negative GT for patients with clear clinical phenotypes, experts encourage establishing cooperation with scientific laboratories looking out for novel disease-causing variants, but it is also possible to consider clinical exome or whole exome or genome sequencing [15]. Negative NGS results should be also periodically reanalyzed in light of expanding knowledge on genotype-phenotype correlation [16, 17]. Reporting VUS to patients is debatable, and some experts do not recommend disclosing those variants to patients [16, 18, 19].

It is of utmost importance that clinical GT should be ordered by cardiologists or clinical geneticists who understand the principles of cardiovascular genetics and can recognize patients who might have an underlying genetic condition. Results should be assembled by a team of cardiologists, laboratory, and clinical geneticists to take into account as many data as possible and ensure making best decisions regarding further management.

## ROLE OF GENETIC TESTING AND RECOMMENDATIONS FOR GENETIC TESTING AND COUNSELING IN CARDIOVASCULAR DISEASES

### *Cardiomyopathies*

When evaluating a patient with CMP, the recommended approach includes: (1) obtaining a family history of at least 3 generations; (2) clinical screening for CMP in first-degree relatives; (3) patients with CMP at initial evaluation should be referred to expert centers, and (4) genetic counseling should be recommended for all CMP patients and their family members.

### Dilated cardiomyopathy

DCM is defined as the presence of left ventricular (LV) enlargement accompanied by LV systolic dysfunction unexplained by abnormal loading condition or coronary artery disease (CAD) [19]. Recently a phenotype of DCM with decreased ejection fraction (EF) without dilatation (non-dilated left ventricular cardiomyopathy [NDLVC]), was discerned as a separate clinical condition which in some cases can progress to DCM.

The prevalence of DCM was estimated at 36 per 100 000 and is the highest in Europe and North America; however, more recent studies estimate its prevalence from 1 in 250 to 1 in 500 in these populations [19]. DCM is frequently diagnosed in young adults and is the leading cause of heart failure (HF) in this group.

Echocardiographic diagnostic criteria for DCM, include an LV end-diastolic diameter of >58 mm in males and >52 mm in females and an LV end-diastolic volume index of ≥75 ml/m$^2$ in males and ≥62 ml/m$^2$ in females accompanied by LVEF <50%. Contrast-enhanced cardiac magnetic resonance (CMR) is recommended with evaluation of late gadolinium enhancement in all DCM patients at initial evaluation. Left and/or right ventricle endomyocardial biopsy should be considered in selected patients with suspicion of myocarditis, storage diseases, or in situations when diagnosis cannot be established by other investigations [19].

**Recommendations for genetic testing and counseling in CMP**

**Recommendations for GT**

GT for CMP should be ordered by a cardiologist experienced in cardiomyopathy or a clinical geneticist, performed in a tertiary center, and interpreted by a multidisciplinary expert team specialized in cardiomyopathy

- NGS panel test encompassing genes listed in Tables 2–5 is recommended in probands
- Variant-specific testing is recommended for first-degree family members and appropriate relatives following the identification of the P/LP variant in the proband
- Variant-specific testing in patients with VUS to determine if the variant segregates with the CMP phenotype should be undertaken, first of all in an affected relative and/or in parents. It should be underlined that in some cases results may have informative rather than therapeutic impact

**GT is recommended in:**

**Patients**

- Patients fulfilling diagnostic criteria for CMP when it may affect diagnosis, prognosis, risk stratification, therapy, or reproductive management of the patient
- Patients with cardiomyopathy when it enables cascade genetic evaluation of their relatives
- Patients with a borderline phenotype of CMP to establish diagnosis in a tertiary center, after clinical screening of the proband's relatives
- Patients with identified P/LP variant but without overt clinical CMP phenotype should be closely monitored
- Patients with suspected causative variants should be considered to undergo CMR to exclude myocardial scarring

**Pediatric population**

- Children regardless of age, fulfilling diagnostic criteria for CMP in cases where it enables diagnosis, prognostication, therapeutic stratification
- Children with CMP when it enables cascade genetic evaluation of their relatives
- Children with a borderline phenotype not fulfilling meeting diagnostic criteria for CMP to establish a diagnosis

**Family members**

- Adult relatives if a P/LP variant has been identified in a CMP patient starting with symptomatic relatives, then first-degree relatives, and cascading out sequentially
- Pediatric relatives if a P/LP variant has been identified in a CMP patient, considering clinical and legal consequences, starting with symptomatic relatives, then first-degree relatives, and cascading out sequentially
- In relatives of the patient with VUS to determine if the variant segregates with the CMP phenotype, first of all in an affected relative and/or in parents. It should be underlined that in some cases results may have informative rather than the therapeutic impact

***Post-mortem* genetic testing**[a]

- In a deceased individual with identified CMP, if a diagnosis would have an impact on management of relatives

**Recommendations for genetic counseling in CMP**

- Pre- and post-test genetic counseling, provided by an appropriately trained healthcare professional, is recommended for all individuals undergoing genetic testing for CMP
- For families with a genetic diagnosis of CMP, genetic counseling should include a discussion of genetic testing results also in terms of decisions related to procreation

[a]Currently, there are no legal regulations regarding post-mortem genetic testing in Poland

Abbreviations: CMP, cardiomyopathy; CMR, cardiac magnetic resonance; GT, genetic testing; NGS, next-generation sequencing; P/LP, pathogenic/likely pathogenic; SCD, sudden cardiac death; VUS, variant of uncertain significance

**Table 2.** Genes most frequently associated with dilated cardiomyopathy

| Gene | Protein[a] | Gene ontology | Evidence for causality | Additional comments |
|---|---|---|---|---|
| ACTC1 | Actin, alpha cardiac muscle 1 | Sarcomere | Moderate | 1%; frequently ASD |
| ACTN2 | Alpha-actinin-2 | Z-disc | Moderate | <1% |
| BAG3 | BAG family molecular chaperone regulator 3 | Co-chaperone | Definitive | ~2% |
| DES[b] | Desmin | Cytoskeleton | Definitive | <1% |
| DSP | Desmoplakin | Desmosome | Definitive | 2%; high SCD risk |
| FLNC[b] | Filamin-C | Cytoskeleton | Definitive | 1%, high SCD risk |
| JPH2 | Junctophilin-2 | Junctional membrane | Moderate | <1% |
| LMNA | Prelamin-A/C | Nuclear lamina | Definitive | ~6%; high SCD risk |
| MYH7 | Myosin-7 | Sarcomere | Definitive | ~3%; peripheral myopathy |
| MYPN | Myoapalladin | Sarcomere | Moderate | ~1% |
| NEXN | Nexilin | Z-disc | Moderate | <1% |
| PLN[b] | Cardiac phospholamban | Sarcoplasmic reticulum | Definitive | ~1%; high SCD risk |
| RBM20[b] | RNA-binding protein 20 | RNA binding | Definitive | ~2%; high SCD risk |
| RYR2 | Ryanodine receptor 2 | Ion channel | Moderate | CPVT |
| SCN5A | Sodium channel protein type 5 subunit alpha | Ion channel | Definitive | 1%–2%; BrS, SSS, LQTS3, AF, VT/VF, AV-block |
| TMEM43[b] | Transmembrane protein 43 | Inner nuclear membrane | Sporadic cases | NDLVC phenotype in most cases |
| TNNC1 | Troponin C, slow skeletal and cardiac muscles | Sarcomere | Definitive | <1% |
| TNNI3 | Troponin I, cardiac muscle | Sarcomere | Moderate | <1% |
| TNNT2 | Troponin T, cardiac muscle | Sarcomere | Definitive | 1%–3% |
| TPM1 | Tropomyosin alpha-1 chain | Sarcomere | Moderate | 1%–2% |
| TTN | Titin | Sarcomere | Definitive | ~20%; mainly truncating variants |
| VCL | Vinculin | Cytoskeleton | Moderate | <1% |

[a]Protein names are given according to the UniProt database (https://www.uniprot.org/uniprotkb). [b]Also associated with NDLVC phenotype

Abbreviations: AF, atrial fibrillation; ASD, atrial septal defect; AV-block, atrioventricular block; SCD, sudden cardiac death; SSS, sick sinus syndrome; VT/VF, ventricular tachycardia/ventricular fibrillation; other — see Table 1

DCM can have a monogenic cause or be a result of a complex interplay between genetic and environmental causes. In particular, DCM phenotype may be a result of myocarditis, autoimmune diseases, toxins and medications, endocrinology diseases, tachycardia-induced, nutritional deficits as well as neuromuscular diseases and genetic syndromes [20].

Conservatively, it is estimated that GT can identify the cause of DCM in families with apparent AD inheritance in approximately 40% of cases, whereas in sporadic cases, the yield of testing is estimated at 10%–15% [21]. DCM can have a highly diverse genetic architecture.

Recently, the international DCM Gene Curation Expert Panel summarized existing evidence on GT in DCM [22]. Definitive or moderate evidence for causality in DCM is present for genes coding: (1) sarcomere proteins (definitive — *MYH7*, *TNNC1*, *TNNT2*, *TTN*, moderate – *ACTC1*, *ACTN2*, *NEXN*, *TNNI3*, *TPM1*); (2) nuclear envelope proteins (definitive — *LMNA*); (3) cytoskeleton proteins (definitive — *DES*, *FLNC*; moderate — *VCL*); (4) desmosome proteins (definitive — *DSP*); (5) sarcoplasmic reticulum proteins (definitive — *PLN*); (6) co-chaperone/heat shock protein (definitive — *BAG3*); (7) RNA binding proteins (definitive — *RBM20*), and (8) sodium ion channel proteins (definitive — *SCN5A*); (8) junctional membrane proteins (moderate — *JPH2*). DCM-associated genes are presented in Table 2. Syndromic forms are presented in the Supplementary material, *Table S2*.

Due to diverse genetic architecture of DCM, there is substantial overlap for arrhythmic diseases (like *SCN5A* involved in LQT3 and BrS) or other CMP especially regarding sarcomeric proteins and HCM (Table 3).

At present, it seems reasonable to recommend GT in DCM for genes that have definitive and moderate evidence for causality [23]. At the same time, numerous commercially available genetic panels test for genes classified as limited, disputed, or without any associations with DCM phenotype.

## Non-dilated left ventricular cardiomyopathy

NDLVC is a new phenotype that can be defined in two ways: (1) the presence of non-ischemic LV scarring or fatty replacement (in place of lost cardiomyocytes); the absence of LV dilatation, or (2) isolated global LV hypokinesia without scarring. The threshold for EF is below 50% to confirm LV systolic dysfunction. Diagnostic work-up is similar to DCM. Although GT is recommended in NDLVC, yet exact genes have not been clearly curated for associations with this phenotype. At present, we recommend testing the same gene panel as in DCM (Table 2).

## Arrhythmogenic right ventricular cardiomyopathy

ARVC is a cardiac muscle disorder characterized by progressive replacement of the myocardium with fibrous and fatty tissue, caused by the damage of desmosomes leading to

**Table 3.** Genes most frequently associated with hypertrophic cardiomyopathy with moderate to strong evidence of causality

| Gene | Protein[a] | Frequency | Additional comments |
|---|---|---|---|
| **Genes encoding sarcomeric proteins** | | | |
| *ACTC1* | Actin, alpha cardiac muscle 1 | 1% | Variable clinical picture depending on the location of the P/LP variant |
| *ACTN2* | Alpha-actinin-2 | <1% | May be associated with myopathy |
| *MYBPC3* | Myosin-binding protein C, cardiac-type | 40%–50% | Usually a milder course than in the case of P/LP variants in the MYH7 gene. Often manifests in adulthood |
| *MYH7* | Myosin-7 | 35% | Higher risk of SCD than in patients with a variant in the MYBPC3 gene, which may be accompanied by muscle weakness |
| *MYL2* | Myosin regulatory light chain 2, ventricular/cardiac muscle isoform | ~2% | Often has a milder clinical course |
| *MYL3* | Myosin Light Chain 3 | ~2% | Lower penetration than variants in other genes encoding sarcomere proteins |
| *TNNC1* | Troponin C, slow skeletal and cardiac muscles | <1% | Increased risk of arrhythmias and HF |
| *TNNI3* | Troponin I, cardiac muscle | 5% | |
| *TNNT2* | Troponin T, cardiac muscle | 5% | |
| *TPM1* | Tropomyosin alpha-1 chain | 2% | Often has a milder clinical course |
| **Genes encoding proteins that are not directly a part of the sarcomere** | | | |
| *ALPK3* | Alpha-protein kinase 3 | ~1.5% | The phenotype may manifest at a later age |
| *BAG3* | BAG family molecular chaperone regulator 3 | <1% | May also lead to progressive skeletal myopathy, rapid progression to HF More often causes the DCM phenotype |
| *CAV3* | Caveolin-3 | <1% | Additionally, frequent cardiac rhythm disturbances, myopathy may occur, LQTS |
| *COX15* | Cytochrome c oxidase assembly protein COX15 homolog | <1% | Early manifestation, lethal cases <1 year of age have been described |
| *CSRP3* | Glycine-rich protein 3 | <1% | May be accompanied by myopathy |
| *DES* | Desmin | <1% | Often accompanied by myopathy, more often causes DCM |
| *FHL1* | Four and a half LIM domains protein 1 | <1% | Mainly affects men. myopathy, high risk of arrhythmias |
| *FLNC* | Filamin-C | <1% | Frequent arrhythmias, rapid progression to HF |
| *JPH2* | Junctophilin-2 | <1% | |
| *PLN* | Cardiac phospholamban | <1% | |
| *TRIM63* | E3 ubiquitin-protein ligase TRIM63 | <1% | Mainly AR inheritance |

[a]Protein names are given according to the UniProt database (https://www.uniprot.org/uniprotkb)

Abbreviations: AR, autosomal recessive; CMP, cardiomyopathy; EP, electrophysiology; HF, heart failure; LQTS, long QT syndrome, P/LP, pathogenic/likely pathogenic

**Table 4.** Genes most frequently associated with arrhythmogenic right ventricular cardiomyopathy

| Gene | Protein[a] | Gene ontology | Evidence for causality | Additional comments |
|---|---|---|---|---|
| *DES* | Desmin | Cytoskeleton | Moderate | Common conduction system abnormalities. Skeletal myopathy possible |
| *DSC2* | Desmocolin-2 | Desmosome | Strong | Classic ARVC |
| *DSG2* | Desmoglein-2 | Desmosome | Strong | Frequent LV involvement |
| *DSP* | Desmoplakin | Desmosome | Strong | Frequent LV involvement. Myocarditis-like episodes |
| *FLNC* | Filamin-C | Cytoskeleton | Disputable | Atypical |
| *JUP* | Junctophilin-1 | Desmosome | Definitive moderate | Naxos disease, AR AD, rare |
| *PKP2* | Plakophilin-2 | Desmosome | Definitive | Classic ARVC, most common - up to~ 50% |
| *PLN* | Cardiac phospholamban | Sarcoplasmic reticulum | Moderate | Frequent LV involvement. |
| *TMEM43* | Transmembrane protein 43 | Inner nuclear membrane | Strong | Extremely SCD risk in males |

[a]Protein names are given according to the UniProt database (https://www.uniprot.org/uniprotkb)

Abbreviations: AD, autosomal dominant; LV, left ventricular; other — see Tables 1–3

cardiac myocyte detachment and death. Progressive fibrosis of the cardiac muscle creates a substrate for arrhythmias; it also results in initially regional and later global systolic dysfunction of both left and right ventricles.

The estimated prevalence of ARVC is 1 per 1290, accounting for 0.078% of the population [19]. ARVC is associated with increased risk of life-threatening ventricular arrhythmias, which can occur even in the early stages of the disease. It is considered one of the most common causes of SCD in young individuals and athletes. The risk of sudden cardiac arrest in ARVC is estimated to be 11%, with the mean age of the event being 25 years [24]. In athletes, ARVC increases the risk of SCD four-fold [25]. Sports participation, especially endurance training, is associated with the earlier

presentation of symptoms, increased arrhythmic risk, and acceleration of structural progression [26].

Treatment is based on implantation of implantable cardioverter defibrillators (ICD) in high-risk patients, administration of anti-arrhythmic drugs, and catheter ablation of ventricular tachycardia (VT) in selected cases. Cardiac transplantation remains the only therapeutic option for patients with end-stage HF [27].

The genetic basis is identified in approximately 60% of ARVC patients (Table 4). The classical form of the disease, characterized by monomorphic VT, right ventricular regional wall motion abnormalities, and mild LV involvement, is typically associated with P/LP variants in desmosomal genes: *PKP2*, *DSG2*, *DSC2*, *DSP*, *JUP*, and *TMEM43*, involved in myocardial fibrosis. Inheritance of ARVC is usually AD with variable, age-dependent penetrance. However, autosomal recessive (AR) cardiocutaneous syndromes are observed, such as Naxos disease — a severe form of ARVC with palmoplantar keratoderma and woolly hair, which occurs endemically on Naxos Island. Approximately 50% of patients with isolated ARVC are found to have a P/LP variant in *PKP2* [28, 29].

Atypical presentations of the disease may be associated with P/LP variants in genes encoding structural and regulatory proteins, such as phospholamban (*PLN*), desmin (*DES*), or filamin C (*FLNC*). Additionally, associations of ARVC with variants in genes encoding lamin A/C (*LMNA*), titin (*TTN*), transforming growth factor beta-3 (TGFB3), alpha-T-catenin (*CTNNA3*), N-cadherin (*CDH2*), and tight junction protein 1 (*TJP1*) have been described [19, 30, 31].

GT is of great importance in ARVC patients as the identification of a P/LP variant is one of the major diagnostic criteria according to the International Task Force consensus [27]. In the case of a typical clinical presentation, identification of the P/LP variant confirms the diagnosis, while in borderline cases, it holds high diagnostic value. The unavailability of GT results in the failure to accurately diagnose ARVC in approximately 5% of probands and 4% of relatives, concurrently leading to a delay in diagnosis for 10% of ARVC patients [32]. Identifying more than one P/LP variant is linked to a worse prognosis and increased risk of SCD ("gene dosage effect"). It should be noted that the arvrisk.com calculator most accurately assesses the arrhythmic risk in patients with desmosomal gene variants [33]. Given the established negative impact of sports on disease progression, it is recommended that all ARVC patients avoid engaging in intense physical activities; they are allowed only moderate recreational exercise [19, 26, 34]. This recommendation also applies to asymptomatic carriers of the P/LP variant. Therefore, GT is of great significance for determining the lifestyle and developmental pathways of children in ARVC-affected families. Genetic family screening is also crucial for distinguishing asymptomatic carriers, who require regular check-ups, from individuals without P/LP variants who can be released from observation [19].

## Hypertrophic cardiomyopathy

HCM is characterized by primary heart wall thickening or increased muscle mass, not due to factors like heart defects or hypertension [35]. Adult HCM diagnosis requires ≥15 mm of wall thickness. A 13 mm threshold applies to first-degree adult relatives of HCM patients [19]. This condition usually affects the left ventricle, but ~30% of cases show right ventricular hypertrophy in CMR [36]. HCM involves myocyte hypertrophy, disarray, and increased fibrosis, leading to rhythm disorders and HF. It can be familial, sporadic, or part of congenital malformation syndromes or caused by inborn errors of metabolism [19, 35, 36].

The frequency is about 1/500. Mitochondrial diseases, congenital malformation syndromes, and inborn errors of metabolism with cardiac manifestation in the form of HCM are rare or ultra-rare diseases. Those forms of HCM should be, however, primarily suspected in the pediatric population (*Table S3*). Therefore, they are described in the section on GT in children with cardiovascular diseases.

Most HCM cases are linked to P/LP variants in sarcomere protein genes, found in 40%–55% of patients [37] (Table 3). Inheritance is usually AD, sometimes AR or X-linked. Common variants affect genes encoding the myosin heavy chain and *MYBPC3* gene (70%) and less often myosin light chain proteins (5%–20%) [37]. Therefore, since the proteins forming myosin chains occur in complexes consisting of two chains, variants P/LP in genes coding for those proteins often disrupt sarcomere function by forming abnormal complexes with proteins coded by normal gene copy (dominant-negative effect). P/LP variants in the *MYBPC3* gene lead to reduced levels of the myosin-binding protein (haploinsuficency) [38]. Other important HCM-related variants are in genes coding for thin filament proteins like actin, troponins (*TNNT2*, *TNNI3*, less documented *TNNC1*), and tropomyosin. It is less certain whether P/LP variants in Z-disk genes, titin, filamin C, crosslinking actin filaments with Z-disc and sarcolemma, protein kinases, and ion channels are associated with HCM [39].

P/LP variants in the *MYH7* are associated with a worse prognosis compared to P/LP variants in *MYBPC3* (although there are exceptions) [40]. Generally, P/LP variants in genes associated with thin filament proteins are linked to a lesser degree of LV hypertrophy and less frequent occurrence of LV outflow tract obstruction, but worse prognosis due to life-threatening arrhythmias [41]. Patients in whom a monogenic cause cannot be established generally have a better prognosis than patients with an identified P/LP variant [42]. Information on genotype-phenotype correlations is presented in Table 3. A calculator for the SCD risk stratification of HCM based on clinical parameters is available [43]. In patients with low (<4%) and intermediate risk (4%–6%) of SCD, additional risk factors might be considered: apical aneurysms, cardiac fibrosis on CMR >15%, and reduced EF <50% [19]. Including GT results in SCD risk stratification is currently not recommended [19].

Studies show that the penetration of P/LP variants associated with sarcomere proteins is on average 57% [44]. It is lowest for variants in the *MYL3* gene (32%) and highest for variants in the *MYH7* gene (65%) [44]. Currently, there are no data on whether early introduction of drugs affecting the renin-angiotensin-aldosterone system or beta-blockers can have an impact on delaying HCM phenotype development [19]. An individual approach to monitoring genotype--positive phenotype-negative patients is recommended, and clinical assessment every 1–3 years seems reasonable but should be tailored individually.

### Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a heterogeneous group of disorders with persistent restrictive pathophysiology, biatrial enlargement, and nondilated ventricles, regardless of ventricular wall thickness and systolic functions [45]. Cardiac amyloidosis (mainly light-chain amyloidosis) remains the most common cause and a prototype of RCM. Transthyretin amyloidosis associated with pathogenic gene variants is recognized more frequently nowadays thanks to improvements in cardiac imaging and availability of disease-modifying therapies. Recently a position statement of the Polish Cardiac Society on diagnosis and treatment of ATTR cardiomyopathy was published [46]. RCM occurs with an incidence of 2% of all CMP [47]. Primary RCM with a genetic background makes up 30% of cases (up to 60% of patients with RCM and light-chain amyloidosis excluded). RCM-associated genes are presented in Table 5. [48]. They are localized on autosomes and encode sarcomere, cytoskeleton, and Z-disc protein. There is genetic overlap between RCM and HCM (e.g. *MYH7*, *MYBPC3, TNNI3*, *MYL2*, *MYL3*) and RCM and myofibrillar myopathy (*DES*, *CRYAB*, *FLNC*, *LMNA*, *BAG3*). The prognosis for RCM of genetic origin remains poor, with 5-year survival c.a. 56%. Delaying the onset of HF and pulmonary hypertension as well as primary prevention of SCD is a challenge. Besides cardiac biomarkers, echocardiography parameters, and myocardial fibrosis revealed on CMR or endomyocardial biopsy GT is of utmost importance as it helps to identify P/LP variants associated with the risk of rapidly progressive HF or malignant arrhythmias. Considering the rare occurrence and poor prognosis of RCM and its relatively common genetic background, it seems justified to recommend GT in every RCM patient after excluding light-chain amyloidosis and other diseases that may mimic RCM, such as systemic sclerosis or sarcoidosis. Moreover, every patient with ATTR amyloidosis should undergo GT, as it has a prognostic significance and influences the choice of treatment [46].

## *Channelopathies*

Cardiac channelopathies are inherited cardiac diseases caused by loss of function or gain of function variants in genes encoding cardiac ion channels or proteins involved in their regulation, predisposing to life-threatening arrhythmias. The main channelopathies are LQTS, catecholaminergic polymorphic VT (CPVT), BrS, and short QT syndrome (SQTS) (see Table 6).

### Long QT syndrome

LQTS is the most common channelopathy with a prevalence of 1:2500. Prolongation of the QT interval on the electrocardiogram (ECG) usually with abnormal T-wave, reflects the prolongation of action potential that causes early afterdepolarisation. This leads to VT, typically torsade de pointes. Clinical diagnosis is based on a scoring system (modified Schwartz score), but there are a lot of borderline cases [49, 50]. Clinical manifestations are syncope and cardiac arrest occurring frequently after specific triggers such as swimming, unexpected noise, or emotional stress. P/LP variants in 3 major genes underline the disorder in 75%–90% of patients: LQT1 (*KCNQ1,* OMIM #19250), LQT2 (*KCNH2*, OMIM #613688), and LQT3 (*SCN5A*, OMIM #603830) [51]. Usually inherited as an AD disorder. Variants in other genes responsible for LQTS account for 1% of cases with strong evidence for variants in *CALM 1*, *CALM 2*, *CALM 3* (LQT14, LQT15, LQT16), and *TRDN* (LQT17) (Table 6). *CALM* gene P/LP variants result in a functional atrioventricular block and a high predisposition to cardiac arrest in the first 1.5 years of life [52]. Homozygosity for P/LP variants in *TRDN* is responsible for Triadin Knockout Syndrome characterized by QT prolongation extensive T-wave inversion and exercise-induced cardiac arrest. Syndromic LQTS forms encompass Jervell Lang-Nielsen syndrome (JLN; OMIM #220400) caused by homozygous or compound heterozygous P/LP variants in *KCNQ1* or *KCNE1*. JLN syndrome is characterized by deafness and very high arrhythmic risk. Timothy syndrome (LQT8; #OMIM 618447) caused by P/LP variants in *CACNA1C* presents also with webbing of fingers and toes, congenital heart defects, immune deficiency, hypoglycemia, cognitive abnormalities, and autism spectrum disorder. Andresen Tawil syndrome (ATS, LQT7; #OMIM 170390) caused by P/LP variants in the *KCNJ2* gene presents with facial dysmorphism, hypo- or normokalemic periodic paralysis, and characteristic ventricular bidirectional rhythm [53]. Up to 20% of clinically diagnosed LQTS patients are genotype-negative [51].

### Catecholaminergic polymorphic ventricular tachycardia

CPVT presents as adrenergic-triggered polymorphic VT, typically bidirectional tachycardia which may degenerate into ventricular fibrillation.

The resting ECG recording is normal with a tendency towards bradycardia. CPVT is the most common genetic cause of SCD in young people (1–35 years old) with normal heart anatomy. Thus CPVT should be expected in young persons with normal heart anatomy, normal resting ECG, and exercise or emotional stress-induced syncope or seizure. Causative variants in the *RYR2* gene account for 60% of cases with AD inheritance (CPVT1; OMIM #604772). About 1%–2% of individuals with clinical diagnosis have AR form with a P/LP variant in *CASQ2* (CPVT2; OMIM #611938). Overlapping features of LQTS and CPVT are found in patients

**Table 5.** Genes associated with primary restrictive cardiomyopathy

| Gene | Protein[a] | Gene ontology | Additional comments |
|---|---|---|---|
| *ACTC1* | Actin, alpha cardiac muscle 1 | Sarcomere | |
| *ACTN2* | Alfa-actinin 2 | Sarcomere, Z-disc | May be associated with skeletal myopathy |
| *BAG3* | BAG family molecular chaperone regulator 3 | Co-chaperone | May be associated with myofibrillar myopathy |
| *CRYAB* | Alfa-beta-crystallin | Intermediate filament-associated protein, Z-disc, Sarcomere | May be associated with skeletal myopathy |
| *DCBLD2* | Discoidin CUB and LCCL domain-containing protein 2 | Membrane | RCM with AF, tachycardia, developmental delay, and dysmorphic features |
| *DES* | Desmin | Cytoskeleton | |
| *FLNC* | Filamin-C | Cytoskeleton | |
| *LMNA* | Prelamin-A/C | Nuclear lamina | |
| *MYBPC3* | Myosin binding protein C, cardiac-type | Sarcomere | HCM-associated gene |
| *MYH7* | Myosin-7 | Sarcomere | Strong evidence, for causality. Main HCM-associated gene |
| *MYL2* | Myosin regulatory light chain 2, ventricular/cardiac muscle isoform | Z-disc, Sarcomere | |
| *MYL3* | Myosin light chain 3 | Sarcomere | |
| *MYPN* | Myopalladin | Sarcomere | |
| *TMEM87B* | Transmembrane protein 87 B | Membrane | |
| *TNNC1* | Troponin C, slow skeletal and cardiac muscles | Sarcomere | |
| *TNNI3* | Troponin I, cardiac muscle | Sarcomere | Strong evidence for causality. First described, the most common, poor prognosis |
| *TNNT2* | Troponin T, cardiac muscle | Sarcomere | |
| *TPM1* | Tropomyosin alpha-1 chain | Sarcomere | |
| *TTN* | Titin | Sarcomere | |

[a]Protein names are given according to the UniProt database (https://www.uniprot.org/uniprotkb)

Modified from Brodehl et al. [48]

Abbreviations: HCM, hypertrophic cardiomyopathy; other — see Tables 1 and 2

with P/LP variants in *KCNJ2*, *CALM1*, *CALM2*, *CALM3,* and *TRDN* [54], see Table 6.

## Brugada syndrome

BrS is an inherited arrhythmogenic disease characterized by a coved-type ST-segment elevation of ≥2 mm with T-wave inversion in the right precordial leads and malignant ventricular arrhythmias, although conduction disease and atrial arrhythmias may also occur [55]. The prevalence of BrS is estimated to be 1 in 2000. BrS may account for up to 28% of unexplained SCD. Symptomatic patients are typically young to middle-aged males, although patient sex does not appear to impact prognosis. Most BrS cases are not associated with a single causative gene variant, as disease-causing variants in *SCN5A* are found only in ~20% of patients [56]. Other genes reported to be associated with BrS have disputed validity.

Asymptomatic patients with typical ECG features not meeting other clinical criteria have the so-called Brugada ECG pattern [55]. BrS phenocopies due to electrolyte disturbances, drug intoxications, and myocardial ischemia, should also be excluded [57]. Drug-induced and fever-induced Brugada ECG pattern is not considered a BrS phenocopy, thus GT of *SCN5A* may be considered in such cases. GT should be offered to family members regardless of age when a P/LP *SCN5A* variant is found in the index patient [12].

BrS in the absence of P/LP *SCN5A* variants is considered to be polygenic. Interestingly, positive provocative drug challenge tests in non-carriers of the *SCN5A* variant in families with pathogenic *SCN5A* variants support this concept of polygenic inheritance of BrS [56]. The presence of multiple common variants may account for the majority of BrS cases and may affect the phenotypic expression of BrS within families [58].

GT results in BrS impact prognosis and treatment. Although the presence of *SCN5A* P/LP variants does not imply prophylactic ICD implantation, due to the risk of conduction disturbances associated with *SCN5A* variants, it affects the choice of a type of implantable device [12, 59]

## Short QT syndrome

SQTS is a very rare inherited arrhythmogenic disorder characterized by a short QT interval on ECG and an increased risk of premature atrial fibrillation and ventricular fibrillation in patients with normal hearts [59]. The disease is associated with high mortality across all age groups [60]. Two cut-off thresholds were proposed: (1) ≤320 ms alone, and (2) ≤360 ms in patients with no heart disease and a presence of a family history of SQTS, aborted cardiac arrest, or a P/LP variant in disease-causing genes [59].

QTc assessment should be performed on 12-lead ECG and at exercise test [61].

Three potassium channel genes, *KCNH2*, *KCNQ1*, *KCNJ2,* and anion exchanger *SLC4A3* have been identified as SQTS-susceptibility genes [12]. However, only *KCNH2* and *KCNQ1* have a definite or strong disease association, thus in index patients genetic screening for two potassium channel genes (*KCNQ1* and *KCNH2*) is recommended, and

**Table 6.** Genes associated with channelopathies

| Gene | Protein[a] | Frequency | Additional comments | Inheritance |
|---|---|---|---|---|
| **LQTS (major genes)** | | | | |
| *KCNQ1* | Potassium voltage-gated channel subfamily KQT member 1 | 35% | LQTS1 (#192500) — typical VA trigger – exercise, emotional stress<br>JLNS type 1 — (#220400) — congenital deafness, QT interval prolongation, syncopal attacks, VA, high risk of SCD | AD<br>AR |
| *KCNH2* | Potassium voltage-gated channel subfamily H member 2 | 30% | LQTS2 (#613688) — typical VA trigger — emotional stress, sudden loud noises | AD |
| *SCN5A (LQT3)* | Protein Sodium channel protein type 5 subunit alpha | 10% | LQTS3 (#603830) — typically VA during sleep or rest | AD |
| LQTS (minor genes): *AKAP9, ANK2, CACNA1C, CALM1, CALM2, CALM3, CAV3, KCNE1, KCNE2, KCNJ2, KCNJ5, SCN4B, SNTA1* | | | | |
| **CPVT** | | | | |
| *RYR2* (CPVT1) | Ryanodine receptor 2 | 50% | CPVT1 (#604772) | AD |
| *CASQ2* | Calsequestrin 2 | 1-2% | CPVT2 (#611938) | AR |
| CPVT (minor genes) *KCNJ2, CALM1, TRDN* | | | | |
| **BrS (major genes)** | | | | |
| *SCN5A* | Protein Sodium channel protein type 5 subunit alpha | 25% | BrS1 (#601144) | AD |
| BrS (minor genes): *CACNA1C, CACNA2D1, CACNB2, DLG1, GPD1L, HCN4, KCND3, KCNE3, KCNE5, KCNJ8, RANGRF, SCN1B, SCN3B, SLMAP* | | | | |
| **Short QT syndrome (major genes)** | | | | |
| KCNH2 | Potassium voltage-gated channel subfamily H member 2 | 15% | SQTS1 (#609620) | AD |
| KCNQ1 | Potassium voltage-gated channel subfamily KQT member 1 | 5% | SQTS2 (#609621) | AD |
| KCNJ2 | Inward rectifier potassium channel 2 | 3% | SQTS3 (#600681) | AD |
| SQTS (minor genes): *CACNA1C, CACNA2D1, CACNB2, SLC22A5, SLC4A3, SCN5A* | | | | |

[a]Protein names are given according to the UniProt database (https://www.uniprot.org/uniprotkb)

Abbreviations: JLNS, Jervell, and Lange-Nielsen syndrome; VA, ventricular arrhythmia; other — see Tables 1 and 3

for *KCNJ2* and *SLC4A3* genes may be considered [12, 62]. In the case of phenotypes overlapping with BrS, mutations in L-type calcium channel-related genes may underlie the phenotype [63]. It is recommended that in patients with a high probability of SQTS, other genes are screened but only in experienced centers that perform thorough variant adjudication [12].

There are some genotype-based differences e.g. atrial fibrillation occurs more frequently in patients with *KCNH2* mutations [64]. Although implantation of an ICD is recommended for high-risk patients independent of genetic status [59], in patients with P/LP variants of *KCNH2* treatment with hydroquinidine prolongs QTc and is very effective in preventing cardiac events [65].

## *Thoracic aortic aneurysms and dissections*

Thoracic aortic aneurysms (TAA) occur in 5 to 10 per 100 000 person years [13]. TAA are a major cause of cardiovascular mortality due to acute aortic dissection (AAD). In the United States, the incidence of AAD is estimated between 5 and 30 cases per million people per year, and AAD more commonly affects males [13].

Thoracic aortic aneurysms and dissections (TAAD) may present as familial or sporadic, isolated or syndromic [66]. Familial TAAD are observed in 20% of patients, and approximately 30% can be explained by monogenic defects in more than 30 genes [66]. Syndromic TAAD are often caused by mutations involving extracellular matrix proteins or involved in transforming the growth factor-β pathway [13, 67], see Table 7A. Patients with P/LP variants in these genes are predisposed to developing aneurysms of the root and ascending aorta at an early age, and have a faster rate of aortic growth than those with sporadic aneurysms.

Of the syndromic forms of TAAD, Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), and vascular Ehlers-Danlos syndrome (vEDS) require major attention.

**MFS** (OMIM#154700) is an AD, highly penetrant connective tissue disorder caused by pathogenic variants in the *FBN1* gene coding for fibrillin-1 [3, 68, 69]. Its prevalence is estimated as 1 in 3000–5000 in the general population, and MFS is responsible for 6%–9% of AAD cases. MFS causes AAD in 50% of patients <40 years of age. The modified Ghent criteria for MFS diagnosis (Ghent II nosology) at first ask about family history, and later, apart from aneurysms involving the aortic root comprise either ectopia lentis, the systemic score, or positive GT [69]. MFS patients are at risk of life-threatening AAD, and prophylactic aortic root replacement for aneurysm disease improves survival in MFS. GT in MFS is helpful in diagnosis, whenever patients present with Marfanoid habitus not meeting strictly the

**Recommendations for genetic testing and counseling in channelopathies**

**Recommendations for genetic testing**

- Genetic testing for channelopathy should be ordered by a cardiologist experienced in channelopathy or a clinical geneticist. It should be performed in a tertiary center and interpreted by a multidisciplinary expert team specialized in arrhythmias of genetic origin.

**Genetic testing is recommended in:**

**Patients**

- NGS panel encompassing genes associated with channelopathies listed in Table 6 is recommended in probands
- Probands with a clinical diagnosis of channelopathy to confirm diagnosis and to determine prognosis and in selected channelopathies for directing therapy
- Patients with moderate to high probability of channelopathy to confirm diagnosis
- In selected cardiac arrest survivors, genetic testing target for channelopathy may be considered

**Family members**

- Variant-specific testing is recommended for first-degree family members and appropriate relatives following the identification of the P/LP variant in the proband
- Variant-specific testing in patients with VUS to determine if the variant segregates with the channelopathy phenotype, first of all in an affected relative and/or in parents. It should be underlined that in some cases results may have informative rather than therapeutic impact.

**Pediatric population**

- Regardless of age, when it can affect diagnosis, prognosis, risk stratification, or therapy

***Post-mortem* genetic testing**[a]

- When SCD remains unexplained despite extensive investigation (autopsy and toxicology) and/or family history, circumstances of death suggest arrhythmic disease, GT targeting for channelopathy is recommended

**Recommendations for genetic counseling in channelopathies**

- Pre- and post-test genetic counseling, provided by an appropriately trained healthcare professional, is recommended in all individuals undergoing genetic testing for channelopathy
- For families with a genetic diagnosis of channelopathy, genetic counseling should include a discussion of genetic testing results also in terms of decisions related to procreation.

[a]Currently there are no legal regulations regarding post-mortem genetic testing in Poland

Abbreviations: GT, genetic testing; NGS, next-generation sequencing; VUS, variant of uncertain significance

**Recommendations for genetic diagnostics in thoracic aortic aneurysms and dissections**

**NGS panel including genes listed in Tables 7A and 7B should be performed in patients with:**

- Familial TAAD, defined as >1 person with TAAD ascertained clinically or sudden unexplained death in the family<50 years of age
- Marfanoid habitus (5 or more systemic points) and thoracic aortic aneurysm (z score ≥2.0; in children ≥3.0)
- Acute aortic dissection <60 years of age

**Family members**

- Variant-specific testing is recommended for first-degree family members and appropriate relatives following the identification of a P/LP variant in the proband (cascade testing)
- Variant-specific testing in patients with VUS to determine if the variant segregates with the TAAD phenotype, first of all in the affected relative and/or in parents. It should be underlined that in some cases, results may have informative rather than therapeutic impact.

Abbreviations: NGS, next-generation sequencing; TAAD, thoracic aortic aneurysms and dissections

Ghent criteria [69]. The majority of MFS patients have parents with the syndrome, however, one-fourth may have *de novo* mutation. Variants in the exons 24–32 are associated with rapid progression of MFS [69].

**LDS** is a connective tissue disorder inherited in an AD manner with a prevalence of 1:50000-200 000 in the general population [10, 70]. Phenotypic features in the cardiovascular system (aortic and branch vessel aneurysm, arterial tortuosity, mitral valve prolapse, and not infrequently CHD, e.g., bicuspid aortic valve, atrial septal defect), skeletal features similar to MFS, unique craniofacial and cutaneous features may be present. GT is necessary to establish the diagnosis. Causative variants in genes coding for transforming growth factor β pathway are responsible for LDS types 1–5, namely *TGFBR1* (type 1; OMIM #609192), *TGFBR2* (type 2; OMIM #190182), *SMAD3* (type 3; OMIM #603109), *TGFB2* (type 4; OMIM #190220), *TGFB3* (type 5; OMIM #190230). All LDS types confer a risk for AAD, some variants in particular in the *TGFBR1* and *TGFBR2* genes may cause earlier onset of TAA, and AAD may occur at relatively smaller aortic diameters when related to P/LP variants in *TGFBR1* and *TGFBR2* [71, 72]. This led to a recommendation for earlier prophylactic aortic surgery than in MFS (4.5 cm, while in MFS 5 cm) [13, 68]. As in MFS, prophylactic aortic root replacement for aneurysm disease prevents AAD type A and improves survival. Despite prophylactic surgery, after AAD, progressive aneurysmal dilatation of another part of the aorta takes place, and these patients are likely to have multiple operative interventions.

**vEDS** (OMIM #130050) is due to P/LP variants in *COL3A1* coding for the pro-alpha1 chains of type III collagen that is found in extensible tissues — artery wall, uterus, or gastrointestinal tract. It affects 1 in 50 000–100 000 individuals [68, 73]. vEDS may cause spontaneous aortic and arterial dissections, aneurysms, and rupture; it often affects middle-sized arteries, ruptures of the hollow organs including bowel and uterus rupture, pneumothorax; involvement of the skin, joints; fistulas may also occur. Notably, the aorta and arterial branches in that syndrome may rupture even without dilation. Therefore, genetic diagnosis is very important.

**Nonsyndromic familial TAAD** refers to a genetic predisposition, to dissections of the aorta, and is most commonly associated with P/LP variants in the *ACTA2*, *MYH11*, *MYLK*, *LOX,* and *PRKG1* genes, with AD inheritance (see Table 7B). There are no systemic features that can aid in diagnosis, therefore, genetic diagnosis is vital for at-risk family members. Of particular interest are patients with *ACTA2* P/LP variants that often present with type A or type B AAD, who have aneurysmal disease involving the root and ascending aorta, and some of them have occlusive vascular disease, either coronary artery or cerebrovascular disease [74]. Patients with *ACTA2* pathogenic variants may have AAD at aortic diameters <4.5 cm, and, therefore, earlier consideration of prophylactic surgery is warranted [74, 75].

Other syndromic and nonsyndromic forms of TAAD are presented in Tables 7A and 7B [13, 68, 72].

GT panels of the heritable TAAD include the following genes confirmed to confer a highly penetrant risk of TAAD: *FBN1*,

**Table 7A.** Genes associated with monogenic thoracic aortic aneurysms and genotype-phenotype correlations

| Gene | Protein | Frequency | Syndrome | Inheritance |
|---|---|---|---|---|
| *ACTA2* | Actin, aortic smooth muscle | | Smooth muscle dysfunction syndrome (#613834) Asymptomatic TAA, occlusive vessel disease: moyamoya-like cerebrovascular disease, pulmonary hypertension, hypoperistalsis, hypotonic bladder congenital mydriasis | AD |
| *ADAMTS2* | A disintegrin and metalloproteinase with thrombospondin motifs 2 | | Dermatosparaxis EDS (#225410) extreme skin fragility, excess loose skin, and severe bruising Asymptomatic TAA, AAA, AAD, arterial rupture less frequent than in vEDS | AR |
| *BGN* | Biglycan | <1:50 000 | Meester-Loeys syndrome (#300989) Asymptomatic TAA, AAD, MFS-like and LDS-like features | XLD |
| *COL3A1* | Collagen alpha-1(III) chain | ~1:50 000–1:200 000 | Ehlers-Danlos syndrome vascular type (#130050) | AD |
| *COL1A1 (rare)* | Collagen alpha-1(I) chain | <1:50 000 | Asymptomatic TAA, AAA, AAD, arterial rupture, carotid-cavernous fistula, intracranial aneurysm, MVP, bowel and gravid uterine rupture, pneumothorax, joint hypermobility, fragile and extensible skin, easy bruising, dystrophic scars | |
| *COL5A1* | Collagen alpha-1(V) chain | 1:20 000 | Ehlers-Danlos syndrome classical type (#130000) | AD |
| *COL5A2* | Collagen alpha-2(V) chain | | Loose jointedness and fragile, bruisable skin, asymptomatic TAA, AAA, AAD, arterial rupture less frequent than in vEDS | |
| *COL1A1 (rare)* | Collagen alpha-1(I) chain | | | |
| *FBN1* | Fibrillin-1 | 1:2500 | Marfan syndrome (#154700) Asymptomatic TAA, especially related to the aortic root, possible extension, MVP, Ghent II nosology: systemic features, ectopia lentis | AD |
| *FLNA* | Filamin-A | <1:50 000 | PVNH (#300049) Asymptomatic TAA, BAV, MVP, PDA, VSD, seizures, periventricular nodular heterotopia, gastrointestinal obstruction, joint hypermobility | XLD |
| *LOX* | Protein-lysine 6-oxidase | <1:50 000 | LOX- related TAA (#153455) Asymptomatic TAA, BAV, MFS-like features, aortic dissection | |
| *PLOD1* | Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1 | <1:50 000 | Kyphoscoliotic EDS (#225400 ; #614505) | AR |
| *FKBP14* | Peptidyl-prolyl cis-trans isomerase FKBP14 | | Congenital muscle hypotonia, joint hypermobility, progressive scoliosis, Asymptomatic TAA, AAA, AAD, and arterial rupture less frequent than in vEDS | |
| *SKI* | Ski oncogene | <1:50 000 | Shprintzen-Goldberg syndrome (#182212) Asymptomatic TAA, MVP, MFS-like and LDS-like systemic features, developmental delay, craniosynostosis | AD |
| *SLC2A10* | GLUT-10 (Glucose transporter type 10) | <1:50 000 | Arterial tortuosity syndrome (#208050) Tortuosity of large and medium-sized arteries, aortic dilatation craniofacial, skin, and skeletal abnormalities? | AR |
| *TGFBR1* | TGF-beta receptor type-1 | <1:50 000 | Loeys-Dietz syndrome types 1–5 (#609192, #610168, #610168, #614816, #615582) Asymptomatic TAA, especially related to the aortic root, possible extension, MVP, arterial tortuosity, craniofacial features including craniosynostosis, hypertelorism, blue sclera, bifid/broad uvula, club feet, translucent skin, premature osteoarthritis, scoliosis, pectus deformity, joint laxity, allergic/inflammatory features | AD |
| *TGFBR2* | TGF-beta receptor type-2g | | | |
| *SMAD3* | Mothers against decapentaplegic homolog 3 | | | |
| *TGFB2,* | Transforming growth factor beta-2 proprotein | | | |
| *TGFB3* | Transforming growth factor beta-3 proprotein | | | |

Abbreviations: AAA, abdominal aortic aneurysm; AAD, aortic aneurysm dissection; BAV, bicuspid aortic valve; EDS, Ehlers-Danlos syndrome; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; PVH, periventricular nodular heterotopia; TAA, thoracic aortic aneurysm; vEDS, vascular EDS; VSD, ventricular septal defect; XLD, X-linked dominant

*LOX*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *ACTA2*, *MYH11*, *MYLK*, *PRKG1*. The remaining most important genes involved in the pathogenesis of TAAD are as follows: *TGFB3*, *SKI*, *SLC2A10*, *FLNA*, *BGN*, *MAT2A*, *MFAP5*, *FOXE3*, and *THSD4* [13].

## *Familial hypercholesterolemia and other dyslipidemias*

FH is a single-gene, AD entity that results in the premature development of atherosclerotic cardiovascular disease (ASCVD) as a result of long-term exposure to elevated levels of low-density lipoprotein cholesterol (LDL-C). Heterozygous FH is the most common genetically determined disease leading to ASCVD. Its prevalence is estimated at 1:217–1:313. However, in the population with CAD, the frequency is much higher (1:31), especially in patients with premature CAD (1:15) and in the population with severe hypercholesterolemia (1:14). An untreated male subject with FH has a 50% risk of fatal or non-fatal myocardial infarction by the age of 50, and an untreated female subject a 30% risk by the age of 60 [76–79].

**Table 7B.** Genes associated with nonsyndromic thoracic aortic aneurysms. All are ultra-rare diseases

| Gene | Protein[a] | Gene ontology | Additional comments |
|---|---|---|---|
| *ACTA2* | Actin, aortic smooth muscle | Smooth muscle contraction fiber | Asymptomatic TAA, involving both the root and the ascending aorta, tubular shape, premature CAD, moyamoya-like cerebrovascular disease, most common genetic contributor to nonsyndromic TAAD |
| *MYH11* | Myosin-11 | Smooth muscle contraction | Asymptomatic TAA, AAD, and PDA, probably the most common genetic contributors to TAAD |
| *MYLK* | MYLK | Regulation of smooth muscle contraction | AAD, without dilatation of the aorta |
| *PRKG1* | cGMP-dependent protein kinase 1 | Regulation of smooth muscle relaxation | AAD at young ages, without dilatation of the aorta |
| *MAT2A* | Methionine adenosyltransferase 2 | Methionine adenosyltransferase activity | Asymptomatic TAA, AAD, BAV |
| *MFAP5* | Microfibrillar-associated protein | Microfibril organization | Asymptomatic TAA, AAD, mild MFS-like systemic features |
| *FOXE3* | Forkhead box protein E3 | Cell differentiation | Asymptomatic TAA, AAD |
| *THSD4* | Thrombospondin type-1 domain-containing protein 4 | Cell adhesion and extracellular matrix organization | Asymptomatic TAA, AAD |

[a]Protein names are given according to the UniProt database (https://www.uniprot.org/uniprotkb)

Abbreviations: CAD, coronary artery disease; other — see Table 7A

Genetic causes of FH are single-gene loss-of-function variants in the *LDLR* or *APOB* genes or gain-of-function mutations in the *PCSK9* gene. In rare cases, a similar phenotype can be a result of P/LP variants in the *LDLRAP1* gene with AR mode of inheritance. *LDLR* mutations are predominant (>1700 different mutations have been described), followed by *APOB* variants, while gain-of-function mutations in the *PSCK9* gene account for only a few percent of all FH cases. Premature ASCVD with dyslipidemia can also be a result of other inherited lipid disorders such as sitosterolemia (*ABCG5*, *ABCG8*). The presence of *APOE* ε4 risk allele for CAD and Alzheimer's disease, polygenic inheritance, like in familial combined dyslipidemia, or elevated lipoprotein(a) levels contribute to premature ASCVD [76–78].

GT for FH is justified by , among others, the following facts [76–78]:

- The diagnosis of FH can be based only on the clinical presentation using various criteria including the Dutch Lipid Clinic Network Diagnostic Criteria (DLCNC) – these criteria without taking into account GT have low sensitivity, with relatively high specificity;
- Not all individuals with FH are characterized by significantly elevated LDL-C concentrations, but at any level of LDL-C concentration, individuals with P/LP FH variants have a higher risk of developing ASCVD than those with the same LDL-C concentration without the presence of causative FH variants;
- Widespread use of statins leads to a less frequent occurrence of the "classic" FH phenotype, which includes the presence of tendon xanthomas and corneal arcus;
- Type of pathogenic FH variant translates into the risk of developing ASCVD – the risk is higher in those with *LDLR* null variants than in those with non-null *LDLR* variants as well as with *APOB* and *PCSK9* pathogenic variants;
- FH is an AD disease so finding the pathogenic variant enables effective cascade diagnosis;
- Last but not least, GT positively influences the initiation of lipid-lowering treatment, its effectiveness, and adherence to therapy.

Homozygous FH is a rare disease (1:250000 to 1:360000) with a poor prognosis — if untreated, the vast majority of people die before the age of 30. Critical to the survival of patients with homozygous FH remains early genetic diagnosis (including cascade testing of relatives) and early intensive lipid-lowering therapy [77, 80].

An approach to GT for FH includes a gene panel encompassing *LDLR*, *APOB*, *PCSK9,* and *LDLRAP1* as well as multiplex ligation-dependent probe amplification analysis of the *LDLR* gene. An updated *LDLR* variant database is available [81]. Consensus guidelines for *LDLR* variant classification have been created [78, 82, 83]. The recommendations for GT in FH are provided in the recommendation table below [79]. When other causes of dyslipidemia are suspected a larger, more inclusive, gene panel might be carried out including, additionally, the *ABCG5*, *ABCG8* genes (sitosterolemia OMIM #210250, #618666), *APOA1*, *ABCA1* (OMIM #107680, Tangier disease, OMIM #205400), *LCAT* (LCAT deficiency OMIM#245900), *LPL*, *APOCII* (familial chylomicronemia syndrome OMIM #238600), and *APOE* variants.

For inherited cardiovascular diseases that are not rare, such as FH, a basic NGS panel should be possible to carry out by a cardiologist in the setting of an outpatient center. For FH, these will be the centers that run the PCSK9 inhibitor drug program. In patients at high risk of FH but without a P/LP variant found on a baseline evaluation, further diagnosis in a specialized cardiology center in collaboration with a geneticist is indicated.

## *Pheochromocytomas and paragangliomas*

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors. PPGLs can lead to cardiovascular symptoms ranging from mild ones like hypertension or tachycardia to severe ones, including arrhythmias, takotsubo syndrome, and death from cardiovascular causes. Up

to 40% of patients with PPGLs carry germline mutations in one of the 25 or more known susceptibility genes. It is recommended to consider GT for any patient diagnosed with PPGL with the use of targeted NGS, which enables testing of all relevant genes in a single panel. Genetic screening for the same mutation should be offered to family members at risk of the mutation [84, 85].

## *Genetic testing in children with cardiovascular diseases*

### Cardiomyopathies in children

In children presenting with CMP, 30% of patients have an underlying metabolic, syndromic, or neuromuscular condition making the etiologies more complex as compared to adults (Supplementary material, *Tables S2–S4*).

Recent guidelines have emphasized specific issues to consider when counseling children with CMP and their families. The guiding principle remains that any testing, clinical or genetic, should be in the best interests of the child and have an impact on management, lifestyle, and/or ongoing clinical testing. With appropriate multidisciplinary support in the pediatric setting, psychosocial outcomes in children undergoing clinical screening and cascade GT are no different than those of the adult population [19]. Recommendations for genetic counseling and testing in CMP, including the pediatric population, are presented in the recommendation table below.

### Dilated cardiomyopathy

In the pediatric population, DCM is the most common form of CMP, especially in children under one year of age. In childhood, reversible causes (i.e., hypocalcemia vitamin D-dependent rickets), congenital heart diseases, and viral myocarditis might be responsible for DCM phenotype and should be excluded [19, 86]. According to the current ESC guidelines, GT is recommended in children fulfilling diagnostic criteria for DCM at any age when it may affect diagnosis, prognosis, risk stratification, and therapy and enables cascade genetic evaluation of their relatives [19].

### Hypertrophic cardiomyopathy

In children, HCM diagnosis is defined as an LV wall thickness greater than 2 standard deviations above the body surface area-corrected population mean (z score ≥2) that could not be explained solely by abnormal loading conditions such as congenital heart defects or arterial hypertension [87]. In infants with HCM, reversible causes of myocardial hypertrophy (maternal diabetes, twin–twin syndrome, corticosteroid use) should be excluded. HCM diagnosed in neonates and infants should always raise the suspicion of RASopathies or inborn error of metabolism [88]. RASopathies are to be suspected when, apart from HCM congenital heart defect, characteristic dysmorphic features are present. Noonan syndrome is the most common RASopathy with nearly 50% of cases caused by pathogenic variants in the *PTPN11* gene [89]. The most cost-effective approach is doing a panel test encompassing all genes implicated in RASopathies to identify rarer forms such as Costello or cardiofaciocutaneous syndrome. Abnormal results of laboratory analyses can also point toward inborn errors of metabolism (glycogen storage disorders such as Pompe or Danon disease, lysosomal diseases, fatty acid oxidation defects, and mitochondrial disorders). In particular, hypoglycemia with hypertransaminasemia may indicate glycogen storage diseases. Hypoketotic hypoglycemia is typical for β-oxidation disorders. Neuromuscular diseases, such as Friedreich's ataxia, may develop in patients >1 year of age when pathogenic variants resulting in premature termination of frataxin protein translation are present. However, symptoms of Friedrich's ataxia usually occur in the second decade of life. Intellectual disability accompanies Danon disease [90] and some RASopathies [91]. However, recent data have shown that in most children with HCM (excluding neonates and infants), like in adults, the disease is caused by P/LP variants in genes encoding cardiac sarcomere proteins, inherited as an AD trait [92]. Additionally, rapidly progressive isolated HCM in infancy might arise from homozygous or compound heterozygous pathogenic variants in HCM-related genes [19]. Current evidence suggests that clinical and genetic cascade screening should be offered to all children fulfilling diagnostic criteria for HCM or with a first-degree relative with HCM, regardless of their age [19, 93]. This might be also true for syndromic cases of HCM especially with regard to Noonan syndrome as there

**Recommendations for genetic counseling and testing in familial hypercholesterolemia (FH). Based on [78] with modifications**

**Recommendations for genetic testing**

- GT for FH should be ordered, performed, and interpreted in the setting of lipid disorder/cardiology/genetics outpatient center

**GT for FH is recommended in:**

- Children with LDL-C levels ≥160 mg/dl and adults with LDL-C levels ≥190 mg/dl with at least 1 first-degree relative similarly affected or with premature CAD or where a family history is not available
- Children with LDL-C levels ≥190 mg/dl or adults with LDL-C levels ≥250 mg/dl in the absence of a positive family history
- Patients with clinical suspicion of FH based on physical examination — tendon xanthomas at any age or corneal arcus under the age of 45 years

**GT for FH should be considered in:**

- Children with LDL-C levels ≥160 mg/dl and adults with LDL-C level ≥190 mg/dl especially when at least 1 first degree relative had a family history of hypercholesterolemia or premature CAD
- Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD
- Adults with LDL-C levels ≥160 mg/dl in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD

**Cascade GT for the specific variant(s) identified in the FH proband:**

- Should be offered to all first-degree relatives of the proband
- If first-degree relatives are unavailable or do not wish to undergo testing, testing should be offered to second-degree relatives
- Testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified

Abbreviations: CAD, coronary artery disease; GT, genetic testing; LDL-C, low-density lipoprotein cholesterol

are cases with mild clinical manifestations that remain unrecognized. Importantly, HCM diagnosis may change the clinical course in examined children, including starting medication and proceeding to surgery or an implantable cardiac device [94]. In infants with HCM in the setting of Pompe disease, enzyme replacement therapy has been shown to reduce the degree of LV hypertrophy. Similarly, there is some promise in MEK inhibitors that modify ventricular hypertrophy in infants with P/LP variants in the RAS/MAPK cell signaling pathway [95].

### Left ventricular noncompaction (hypertrabeculation)

The current ESC guidelines do not consider left ventricular hypertrabeculation as a distinct form of CMP, nonetheless, left ventricular noncompaction phenotype (LVNC) occurs in 9% of CMP in the pediatric population [96]. The genetic cause is identified in 44%–52% of children [97, 98, 99, 100]. The current ESC guidelines indicate that the decision to perform GT is guided by the coexistence of another CMP phenotype, family history of CMP, or presence of symptoms [101, 102]. GT is not recommended when LV hypertrabeculation is identified in asymptomatic individuals with otherwise normal cardiovascular phenotype, as in some cases it might be considered as the norm. Mitochondrial diseases, metabolic causes of LV hypertrabeculation, and genetic syndromes should be tested following the suspected underlying disorder according to the cardiovascular phenotype and additional extracardiac clinical features of the individual [23, 103, 104].

### Arrhythmogenic right ventricular cardiomyopathy

Patients with childhood-onset ARVC showed more frequent biventricular involvement and HF necessitating heart transplantation [105]. Except for rare AR cardiocutaneous syndromes such as Naxos disease or Carvajal syndrome, which usually present in childhood, ARVC has traditionally been considered a disease that affects young adults. Recent studies [106] highlight that classical ARVC can be present in young children, often with a very severe phenotype, and provide an argument for considering genetic screening for children younger than 10–12 years.

### Restrictive cardiomyopathy

RCM is the rarest form of CMP, accounting for 2%–5% of pediatric CMP cases, but a mixed RCM/HCM phenotype is more frequently encountered. In children, RCM often presents with severe HF, and heart transplant is the only long-term treatment option. The main benefit of GT in childhood RCM is diagnosis and cascade testing in their family members. In line with the current ESC guidelines, GT should be considered for children in whom a cardiologist has established a clinical diagnosis of RCM. Cascade testing should be performed following the identification of the disease-causative variant [19].

### Aortopathies

Young children with TAA are more likely to have a genetic syndromic cause of disease. Diagnostic panels including genes associated with both syndromic and nonsyndromic TAA are preferred. *FBN1*-specific testing for Marfan syndrome may be considered in children who fulfill the diagnostic criteria for the disease. GT is important even in individuals fulfilling clinical criteria for connective tissue disorders because gene-specific management guidelines exist. Negative GT in TAA provides useful risk stratification information [13, 107]. Diagnostic GT should be initiated at the time of diagnosis of TAA or in individuals with suspicious connective tissue disorder features. Current guidelines recommend cardiac screening in first-degree relatives of TAA patients. If a P/LP variant is identified in the proband, risk-predictive GT should be offered to relatives [13].

### Congenital heart defects

CHD are the most common form of birth disorders, affecting nearly 1% of all live births. Syndromic forms of CHD have a well-established genetic cause and methods for GT but make up only 20% to 30% of CHD cases. The genetic etiology of nonsyndromic (isolated) CHD is more complex. The combination of inherent variable expressivity and the difficulties in identifying syndromic features in newborns/infants further support the need for more standardized clinical and GT assessments. Whom to test, when, and with what modality remain contentious issues, especially in infants with apparently isolated nonsyndromic CHD [108]. In general, clinical phenotype drives the choice of GT modalities. Recent evidence suggests that 10% of syndromic and nonsyndromic CHD cases may be attributed to *de novo* variants in the coding genome, with a similar proportion potentially attributable to *de novo* variants in noncoding areas of the genome [109]. Cytogenetic GT (e.g., karyotype, fluorescence *in situ* hybridization, and microarrays) or gene panel testing should be used for diagnostic GT in infants and children in whom syndromic CHD is suspected. If there is a family history of isolated congenital heart defect (CHD), a gene panel might be of value. In sporadic nonsyndromic cases, exome and genome sequencing or microarray analysis to detect copy number variants may yield diagnostic results in about 20% of cases [110]. Given that the distinction between syndromic and isolated CHD is often subtle, a high level of suspicion and careful prospective evaluation are warranted in cases of presumed isolated CHD for extracardiac anomalies or neurodevelopmental features [108, 109].

## *Genetic testing for cardiovascular diseases in the fetus*

Fetal cardiology as a subspecialty of pediatric cardiology has been rapidly advancing, especially during the last two decades. It encompasses the management of fetuses with

CHD, fetal arrhythmias, CMP, and HF due to fetal-specific conditions and extracardiac defects [111]. During pregnancy, the main concern of ultrasound examinations are fetal structural congenital anomalies [112].

In Poland, ultrasound screening examinations are performed in the first and the second trimester of pregnancy with a follow-up scan in the third trimester. The first-trimester screening – a combination of fetal ultrasound and maternal blood testing – concentrates on detection of features that may indicate chromosomal abnormalities (such as nuchal translucency) and congenital defects of the fetus. If present, they are the reason for referral for fetal cardiac evaluation [113]. The need for assessment of fetal heart in screening programs was also an important factor in improving the detection rate of cardiac defects. During the second trimester, the main reasons for referral for fetal echocardiography are suspected CHD and fetal arrhythmias diagnosed during obstetric screening examinations [112].

Every diagnosis or even supposition of CHD results in further consultations, including prenatal genetic counseling and decisions concerning invasive procedures. There are several CHD that are associated with specific chromosomal syndromes. In fetal cardiology, there are "simple" lesions or septal defects that have a very high probability of genetic background, and very often the underlying genetic cause is confirmed [114]. According to the current recommendations of the Polish Society of Gynecologists and Obstetricians and the Polish Society of Human Genetics [113], proper genetic counseling should be offered before invasive procedures. We observe a common application of chromosomal microarray analysis (CMA) in the prenatal field, which has become a new standard and should be considered the first-tier genetic diagnostic test in fetuses with suspected or diagnosed congenital anomalies, including heart defects. Due to interpretational problems and the necessity of further GT, each abnormal CMA result must be consulted with a clinical geneticist [113]. In familial cases, with a known P/LP variant, there is a possibility of preimplantation diagnostics when *in vitro* procedure is involved or prenatal diagnosis after genetic counseling, the preferred method is chorionic villus sampling. Due to incomplete penetrance and variable expressivity of cardiovascular diseases, a referral to a specialized multidisciplinary clinical cardiovascular genetics program should be considered when possible. Testing should be evaluated on a case-by-case basis and must include the likelihood of disease onset during childhood, potential morbidity and mortality during childhood, availability of therapies, and the family's preferences [107]. Every patient with an already diagnosed genetic defect or chromosomal aberration (aneuploidy and microdeletion/microduplication syndromes) must be informed about available specialist care, including perinatal palliative care when necessary [113].

According to recent publications, only 20%–30% of CHD patients are syndromic and have a well-established genetic cause which may be diagnosed with routine genetic tests. As new techniques allowing searching for monogenic or polygenic disorders appear and become affordable — genetic counseling (both pre-test and post-test) will be more and more challenging due to genetic heterogeneity and variable expression in isolated CHD [115]. However, in compliance with the recent American College of Obstetricians and Gynecologists/Society for Maternal-Fetal Medicine/European Heart Rhythm Association Committee Opinion, Next Generation Sequencing currently is not recommended for routine use in prenatal diagnosis. Only in select circumstances (syndromic or complex CHD), in which other approaches have been noninformative, whole-exome sequencing (of the affected individual and their parents, if applicable) may be considered as a diagnostic tool [12, 116–118].

The results of prenatal GT allow patients to make fully informed decisions regarding the medical treatment of the fetus and newborn and enable the provision of genetic counseling for the entire family, including planning subsequent pregnancies [119]. There are still many challenges of cardiovascular GT in the antenatal population, and this section summarizes current recommendations, which, undoubtedly, will be improved and expanded in the future, with further advancement and accessibility of new genetic techniques.

**Recommendations for prenatal diagnosis of cardiac disease**

**Recommendations for genetic testing of CHD confirmed by fetal echocardiography examination**

- Comprehensive genetic counseling should be offered before invasive procedures
- Informed consent for invasive diagnostics and planned genetic testing should be obtained from the patient
- A first-tier genetic test in fetuses with suspected or diagnosed congenital anomalies should be CMA
- In conotruncal defects and aortic arch anomalies, CMA is necessary to exclude microdeletion/microduplication syndromes, and routine karyotyping is not recommended
- A post-test genetic counseling should be done by providers with experience in fetal cardiovascular diseases
- In syndromic or complex CHD and cases with hydrops fetalis with normal CMA results, DNA isolation for future NGS testing should be recommended

**Recommendations for routine use of NGS in prenatal CHD diagnosis**

- Currently, NGS is not recommended for routine use in prenatal diagnosis
- After issuing ACOG/SMFM/EHRA Committee Opinion: in select circumstances (syndromic or complex CHDs) in which other approaches have been noninformative, whole-exome sequencing may be considered as a diagnostic tool

**Recommendations for prenatal diagnosis in families with known heritable causes of cardiac disease including CMP and cardiac channelopathies.**

- Similar to the pediatric population, the GT in fetuses should be evaluated on a case-by-case basis and must include the likelihood of disease onset during the neonatal period or infancy, potential morbidity and mortality during childhood, availability of therapies, and the family's preferences
- Due to incomplete penetrance and variable expressivity of cardiovascular diseases a referral to a specialized multidisciplinary clinical cardiovascular genetics program should be considered when possible

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CHD, congenital heart defects; CMA, chromosomal microarray analysis; CMP, cardiomyopathy; EHRA, European Heart Rhythm Association; NGS, next-generation sequencing; SMFM, Society for Maternal-Fetal Medicine

Concerning prenatal consultations, dedicated Fetal Cardiological Expert Centers (FCEC) for inherited cardiovascular disorders (ICVD) should be established. FCEC should have multidisciplinary teams including a pediatric cardiologist, clinical geneticist, and obstetrician or perinatologist, with clinical psychologist support.

FCEC should diagnose and consult more than 200 CHD annually, allowing for precise planning of the perinatal period.

FCEC should have access to fetal magnetic resonance and the ability to perform invasive and non-invasive therapy of fetal cardiovascular diseases in close cooperation with Obstetrics and Gynecology tertiary centers.

### *Genetic testing in athletes, amateur athletes, and patients with cardiovascular diseases*

Regular physical activity is beneficial for well-being; nonetheless, vigorous exercise may lead to myocardial ischemia (infarction) or trigger life-threatening arrhythmias resulting in SCD. It is a well-accepted fact that in individuals who regularly exercise, the heart changes. This so called physiologic remodeling (or athlete's heart), including increased LV size and wall thickness, is occasionally associated with prominent LV trabeculations. Moreover, in athletes longer QT intervals, T-wave inversion, partial or complete right bundle branch block, and early repolarization patterns are frequently observed. Overall, sport is safe and should be encouraged in the general population; however, in people with a certain genetic predisposition to cardiac diseases (i.e., asymptomatic patients with P/LP variants in genes associated with cardiovascular disease), diseases not yet diagnosed or ambiguous phenotype, and patients with diagnosed cardiac diseases vigorous and/or competitive exercise may pose serious life-threatening events. There are certain populations with the highest likelihood of cardiac complications during sport, such as individuals diagnosed with CMP (DCM, HCM, ARVC); patients with channelopathies, such as LQTS, BrS, early repolarization syndromes or CPVT [120], patients with genetic connective tissue disorders, such as MFS, LDS, EDS, TAAD, and CHD or certain genetic syndromes like Turner syndrome [121].

GT are being used more commonly in the setting of sports cardiology [121]. Bearing in mind extensive implications of GT for lives and careers, GT should be used after careful consideration of numerous factors by a multidisciplinary team and after appropriate pre-test counseling. Table 8 summarizes the current approach to GT in sports cardiology.

### *Approach to patients with an identified P/LP variant as secondary finding during whole exome sequencing from other indications*

The increasing number of patients undergoing whole exome sequencing (WES) for a variety of indications presents a challenge as P/LP variants linked to inherited cardiac diseases may be identified in asymptomatic individuals. The American College of Medical Genetics currently recommends reporting P/LP variants in 33 genes associated with CMP, channelopathies, and TAAD [122]. Any patient with a reported P/LP variant should undergo evaluation by a cardiologist specializing in inherited cardiac diseases to identify any symptoms related to the reported variant. Additionally, cascade screening and clinical assessments for variant carriers should be offered to family members, even if the index patient is asymptomatic, due to the possible variable penetrance of the variant within a family member.

### *Recommendations for genetic testing organizations in Poland*

#### Role of cardiologist in genetic testing

Based on the cooperation (the concept of hub and spokes is strongly encouraged) between general cardiologists working in various settings and cardiologists from tertiary centers with special interest in ICVD, referred patients are either diagnosed with ICVD (phenotype) or ICVD diagnosis is ruled out. Dedicated Cardiological Expert Centers for ICVD should be located in large tertiary cardiac and cardiothoracic hospitals and outpatient centers with direct access (on-site) to multimodality cardiac imaging facilities (including advanced transthoracic and transesophageal echocardiography, cardiac computed tomography and CMR, and nuclear medicine), electrocardiographic tools, including novel arrhythmia monitoring devices, functional evaluation (cardiopulmonary test). To provide comprehensive cardiac services for ICVD patients, each center should incorporate the following units: genetics, catheterization and interventional cardiology, electrophysiology and arrhythmia, and cooperate with cardiac surgery departments with active heart transplant and ventricular assist device programs, and a pathology unit or pathology consultant.

Moreover, the centers should also offer the following services: clinical psychological support, telemedicine, and other e-health tools as well as research, teaching, and educational capacity. A professional genetic team consisting of cardiologists specialized in ICVD, and clinical geneticists should be engaged in close cooperation and regularly meet to discuss clinical (phenotype) and genetic (genotype) diagnosis, therapeutic options, and prognosis. Currently, GT for diagnosis and personalized management of the majority of ICVD is recommended by leading scientific societies. It is our opinion that the optimal management of ICVD, including GT, should be undertaken only by multidisciplinary teams including cardiologists experienced in ICVD, clinical geneticists, radiologists nuclear medicine specialists, pathologists, etc. Cardiologists who make the final diagnosis of ICVD and consider genetic data to be relevant for the proband and family members can request GT as a routine investigation, reimbursed by the National Health Fund. We recommends day-to-day cooperation between cardiologists and clinical geneticists, including

**Table 8.** Summary of athletes' characteristics and indications for genetic testing in athletes

| | Left ventricular hypertrophy and T-wave inversion | Ventricular cavity dilatation | Prolonged QT interval | Ventricular arrhythmias (VA) | Aortic dilatation |
|---|---|---|---|---|---|
| Prevalence in athletes | Common<br>Typically < 15 mm<br>LV cavity dilatation | Common | Common<br>QTc ≤470 ms for males and ≤480 ms for females | Common | Larger aortic dimensions |
| Additional clinical features suggesting genetic background | Cardiac symptoms<br>Family history of SCD<br>ECG abnormalities<br>Asymmetric hypertrophy<br>LGE | Conduction abnormalities, in *LMNA*[a] and *SCN5A*[a]<br>Disproportionate arrhythmic burden<br>Cases of SCD in family (*LMNA, SCN5A, FLNC, DSP, BAG3, PLN, TTN, RBM*)[a] | Symptoms<br>Congenital deafness<br>Family history of SCD<br>T-wave notching<br>Documented polymorphic arrhythmias<br>Paradoxical prolongation of QT during exercise<br>T-wave alternans | Polymorphic or bidirectional VA<br>Suspicion of catecholaminergic polymorphic ventricular tachycardia<br>Exercise-induced VA common in DCM and less common in HCM | Aortic root >40 mm associated with:<br>Connective tissue diseases<br>Family history of aortic dissection<br>Bicuspid aortic valve with thoracic aortic aneurysm |
| Indications for genetic testing | HCM diagnosis<br>Highly suggestive but not diagnostic HCM phenotype | Any athlete who has been diagnosed with a familial DCM<br>Healthy athletes with familial DCM | All athletes with a familial diagnosis of LQTS<br>Athletes with a QTc ≥500 (480) ms<br>In athletes with a QTc 440–480 ms only with additional features | Isolated VA with benign features (LBBB, inferior axis) is not an indication for genetic testing | Athlete with aortic dilatation and additional features<br>In athletes with a rapid progression of aortic dilatation (0.3 mm/year) |

[a]Full gene names are presented in the Supplementary material, *Table S1*

Abbreviations: ECG, electrocardiogram; LBBB, left bundle branch block; LGE, late gadolinium enhancement; QTc, corrected QT interval; other — see Tables 1, 2, 5 and 6

selection of the most efficient genetic panel and test, and counseling on implications and uncertainty of GT results (LP/VUS variants). We strongly recommend providing genetic counseling to a patient and family members.

Since FH is not a rare disease, the policy for GT in FH should be developed separately taking into account the availability, cost-effectiveness, and rationale for testing.

## Role and impact of clinical geneticists on genetic testing in cardiology

Clinical geneticists have a key role in diagnosing inherited disorders and birth defects, estimating genetic risks, organizing appropriate genomic or other testing, and providing counseling for individuals who may have or are at risk of a genetic disorder.

However, according to the Genetic Testing Act and the Polish Plan for Rare Diseases, other specialists, including cardiologists, may also refer to GT within their specialty. Cardiologists are qualified to do so while working as part of the clinical team within one of several strictly defined Cardiological Expert Centers with a special interest in inherited cardiovascular disorders (see above — "Role of cardiologist in genetic testing"), which also take care of patients with rare diseases (designated with ORPHA code) and due to this aspect of their activity are part of the Polish Plan for Rare Diseases.

When a referral for GT is done by cardiologists, special importance must be attached to pre- and posttest genetic counseling. Before referral for testing, an obligatory counseling session must end with obtaining informed consent from the patient. A testing sample has to be sent to a laboratory that is certified by the Polish Society of Human Genetics or (in the near future) by the Council for Rare Diseases.

Due to the complexity of posttest counseling, especially after high throughput testing (such as NGS), its course depends on several factors, including classification and interpretation of detected variants based on the clinical picture. The relevant options must appraise differences in recognition of the variant as pathogenic or as LP/VUS. All pathogenic variants have to be verified against the variants listed in population databases. In addition, their significance has to be assessed based on specific predictors, segregation within families as well as available functional data. These data are frequently accessible only to clinical geneticists so in cases of interpretation problems, a consultation with a clinical geneticist, who is a member of the team, is highly advised. However, if the variant is well known and clearly pathogenic, the cardiologist from an Expert Center may complete the posttest counseling with the patient. It has to be completed with a written information card given to the patient.

Special attention and care have to be given to LP/VUS variants. In such cases, the posttest counseling must be undertaken in cooperation with a specialist in clinical genetics since there remains a lot of ambiguity and misperception among other professionals as to how relevant these DNA changes are to the patient's phenotype.

It has to be stressed that more rare and specific instances where a clinical geneticist is necessary for proper care and management include complex clinical pictures involving neurodevelopmental disorders coexisting with inherited cardiovascular disorders as well as specific channelopathies that result in extracardiac phenotypes. In such

cases, a multidisciplinary approach under the guidance of clinical geneticists is the standard of optimal care.

It is widely recognized that the endpoint for all genetic activities in a family is a referral to genetic ambulatory centers where cascade screening and family planning options are thoroughly discussed.

### *Conditions that must be met by a medical diagnostic laboratory performing genetic tests. Legal regulations regarding genetic testing in Poland*

In Poland, the genetics community including both physicians and laboratory diagnosticians with support from patient organizations for years have strongly advocated for a separate legal act on genetic tests to ensure high-quality diagnostics and protection of patient data. The report of the Supreme Audit Office, Safety of Genetic Testing, published in 2018, also draws attention to the need to regulate genetic diagnostics with a separate legal act. The patient's ombudsman has also raised this issue many times. The Ministry of Health, along with a team of experts, prepared a draft of the Genetic Testing Act that precisely defines the principles and conditions for conducting genetic tests in humans for therapeutic purposes as well as for collection and storage of genetic data. The draft was submitted to the Council of Ministers in 2023 and is awaiting legislative proceedings.

Currently, in Poland, there are some legal regulations, which are not equivalent the Genetic Testing Act, which partially regulate proper conduct of genetic diagnostics. The performance of diagnostic tests is regulated by the Act on Laboratory Medicine (Journal of Laws 2022, item 2280). A medical diagnostic laboratory (MDL) performing genetic tests should also meet the conditions specified in several regulations relating to this area. The regulation of the Minister of Health on quality standards for medical diagnostic and microbiological laboratories also sets out detailed rules for performing diagnostic genetic tests from the moment the test is ordered until the report is issued. Moreover, according to Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic (IVD) medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU2017, the laboratory must use diagnostic methods that ensure reliable results. These should be CE-IVD-certified methods following the regulation mentioned above and used following the product manufacturer's protocols, or, in the absence of CE-IVD certified methods, the use of a) CE-IVD certified kits used off-label or modified in the laboratory; b) research use only (RUO) kits; and c) laboratory-developed tests used on a non-industrial scale for the needs of public health institutions are also allowed. The possibility of using these methods depends on meeting the criteria in the above-mentioned European regulation.

One way to recognize an MDL competence is accreditation. Accreditation of MDL following the PN-EN ISO 15189:2022 standard "Medical laboratories — quality and competence requirements" is carried out by the Polish Centre for Accreditation (PCA). The accreditation process of laboratories according to the guidelines of the standard mentioned above is time-consuming and expensive. It is also still not obligatory in Poland, so it is not widespread in Poland. The current list of accredited MDL can be checked on the PCA website.

Certification of MDLs performing genetic diagnostics has been carried out in Poland since 2014 on average every 2–3 years by the Polish Society of Human Genetics (PSHG) in specific scopes. The current list of certified laboratories by the PSHG can be checked on the PSHG website (https://ptgc.pl/).

MDLs should constantly participate in external quality control testing. Currently, some European organizations offer a wide range of programs in the field of genetics, e.g., the European Molecular Genetics Quality Network and Genomic Quality Assessment. The cost of participation in these programs is high and not funded by government. Currently, several treatment options in oncology require an annual European certificate for a particular test. The PCA and the PSHG also require these certificates. Participation in such programs proves that the laboratory performs genetic diagnostics and interprets its results according to current guidelines of scientific societies.

Despite the lack of detailed regulations the genetic laboratory should employ qualified diagnosticians and cooperate closely with medical doctors, clinical genetics specialists (currently about 150 MDs in Poland), and doctors of other specialties. The head of the laboratory should be a specialist in laboratory medical genetics (now about 200 people in Poland), and, according to the recommendations of the PSHG, reports on genetic tests should be by such a specialist. The laboratory staff must have knowledge and skills in simple genetic tests and those requiring detailed bioinformatics analyses, thorough assessment of detected variants, and difficult laboratory interpretation, such as the NGS method.

Genetic laboratories applying for a contract with the National Health Fund must meet the abovementioned criteria.

The Plan for Rare Diseases, adopted on August 24, 2021, is highly important for developing genetic diagnostics, including public financing of high-throughput genomic methods. The plan includes, among other aspects, the creation of Rare Diseases Expert Centers and certification of genetic laboratories. As of May 26, 2022, the Plan for Rare Diseases, together with the establishment of the Rare Diseases Council, is at the implementation stage (the end of this stage is planned for 2024) and will be continued after that.

### *Patients' rights in genetic testing*

In the field of human genetics, patients' rights play a crucial role, involving the treatment of the patient and protection against discrimination. This, in turn, affects employment relationships and the procurement of insurance. These matters are governed by international legal acts such

as the European Convention on Bioethics, the Universal Declaration of Human Rights, the Universal Declaration on the Human Genome and Human Rights, the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, and the GDPR.

In Poland, patient rights are primarily defined by the Constitution of the Republic of Poland, Act on Patients' Rights, and Patients' Ombudsman. However, concerning genetics, we are dealing with particularly sensitive data that requires separate legal regulations. Poland is one of the few European countries lacking such legislation, although a draft law on genetic tests for health purposes, prepared by the PSHG, was submitted to the Ministry of Health in 2012 and again in 2023.

The aforementioned draft law also includes proposals for patient rights in genetic research. This includes the patient's right to full information about the test and its results, as well as the right to consent to the collection of biological material, its storage, the processing of genetic data, and their further disclosure. The expressed consent must be informed, voluntary, and unambiguous. Informed consent occurs when the patient is legally, mentally, and intellectually capable of giving consent and has time to decide after obtaining all necessary information. The person giving consent has the right to withdraw it at any time. In the case of the inability to express written consent, verbal consent in the presence of two witnesses is considered equivalent.

The consent form for the test should include a question about whether, in the case of detecting secondary findings, the patient wants to know about them (the right to know vs. not to know). The patient should also have the option to sign a clause withholding additional genetic information not relevant to the study (opt-out). To understand the potential consequences of such a decision, the patient should have the right to consult with a clinical geneticist or genetic counselor.

Patient rights also include maintaining professional confidentiality by doctors/researchers and protecting data even after the patient's death. The results of the test can be issued to the patient as a medical document, but only delivered to the patient personally or, in the case of a child, to the legal guardian. The premises where genetic tests are conducted should also ensure discretion, dignity for the patient, and the confidentiality of medical data.

According to the Patients' Rights Act, the entity providing healthcare services may provide medical documentation to other institutions for scientific purposes without disclosing the patient's name and other identifying information (anonymization). However, scientific data are not protected in the same way as medical documentation, which belongs to the patient, and it can only be disclosed without the patient's consent by a court order. In the case of genetic data, anonymization may lead to a loss of their scientific value. To ensure legal protection for the patient and the scientific value of the research, the pseudonymization of personal and genetic data is recommended, including the use of data sanitization methods, a kind of informational noise. Scientific entities may conduct genetic tests for health purposes in cases of rare or ultra-rare diseases, provided they obtain the Minister of Health's certificate and fulfill registration obligations.

Patient's rights regarding biological material archived in a biorepository, as part of genetic research conducted for medical purposes, are included in the Polish Society of Human Genetics draft law. However, a separate law on biobanks, which collect this material for scientific purposes, is necessary.

In the modern era, there is a particular threat associated with the proliferation of online services, where information or knowledge about the specific genetic characteristics of humans become a commodity subject to profit and abuse. Services directly targeting consumers, using genetic material sent without the possibility of real identification of the person from whom the material comes, and without signing a bilateral agreement by a representative of the performing entity, should be legally prohibited.

Websites with relevant information and documents are listed in the Supplementary material.

### *Position of cardiovascular patient communities*

Cardiovascular patient communities are constantly monitoring the needs of patients and the options available in modern diagnostics and the treatment of cardiovascular diseases. Collaboration between entities gathered around the Agreement of Patient Organizations has led to the compiling of joint recommendations on GT in cardiology.

Among cardiovascular patients, GT is an absolute requirement in groups of patients with aortic pathologies, congenital connective tissue defects, CMP, valvular defects, dyslipidemias, and ATTR amyloidosis. Cardiovascular patient communities see a huge need for expanding the availability of GT, by shortening and unification of the diagnostic pathway.

For tests performed in laboratories, there should be a standardized way of analyzing results, for example, by comparison to the widest possible databases and registers, with each laboratory having access to the same broad databases to ensure an objective assessment of the result. In addition, if a patient has a test performed independently, its broad interpretation and commentary should be guaranteed as part of the service.

The incidence of heFH (heterozygous FH) in the Polish population is estimated at 1:250, which means that the number of patients in Poland may be 150 000. Unfortunately, due to the low awareness of this disease in society and difficult access to genetic diagnostics, heFH is significantly underdiagnosed. For this reason, only about 5% of heFH patients currently have a diagnosis in our country, and even fewer are obtaining optimum treatment.

Fortunately for patients with HCM, mavacamten therapy is available as part of a drug program reimbursed by the National Health Fund. Identifying patients with

**Table 9.** Relevant papers or guidelines concerning genetic testing in cardiovascular diseases

| Title | Society | First author | Published |
|---|---|---|---|
| 2023 ESC Guidelines for the management of cardiomyopathies | ESC | Arbelo E | Eur Heart J. 2023 [19] |
| European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases | EHRA/HRS/ APHRS/LAHRS | Wilde AAM | Europace. 2022 [12] |
| Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association | AHA | Musunuru K | Circ Genom Precis Med. 2020 [23] |
| European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death | ESHG/ECLM/ ESC/ ERN GUARD-Heart/AECVP | Fellmann F | Eur J Hum Genet. 2019 [120] |
| Indications and utility of cardiac genetic testing in athletes | | Castelletti S | Europace. 2022 [121] |
| International Evidence Based Reappraisal of Genes Associated With Arrhythmogenic Right Ventricular Cardiomyopathy Using the Clinical Genome Resource Framework | | James CA | Circ Genom Precis Med. 2021 [123] |
| European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases | ESC | Charron P | Eur Heart J. 2010 [124] |
| Pediatric Cardiomyopathy Registry Study Group. The genetic architecture of pediatric cardiomyopathy | | Ware SM | Am J Hum Genet. 2022 [92] |
| 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines | ACC/AHA | Isselbacher EM | Circulation. 2022 [13] |
| The use of fetal exome sequencing in prenatal diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG) | ACMG | Monaghan KG | Genet Med. 2020 [125] |
| Genetic Testing for Heritable Cardiovascular Diseases in Pediatric Patients<br>A Scientific Statement From the American Heart Association, ACMG | AHA | Landstrom AP | Circ Genom Precis Med. 2021 [107] |
| ESC Scientific Document Group, 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Pediatric and Congenital Cardiology (AEPC) | ESC/AEPC | Zeppenfeld K | Eur Heart J. 2022 [59] |
| Novel insight into the natural history of short QT syndrome | | Mazzanti A | J Am Coll Cardiol. 2014 [60] |
| SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome | | Probst V | Circ Cardiovasc Genet. 2009 [56] |

CYP2C19 gene alleles that condition a "poor metabolizer" phenotype allows for the adjustment of drug dosing and minimizes the risk of developing contractile dysfunction associated with excessive exposure to mavacamten.

According to information provided by the Marfan Poland Association, based on statistical data there are estimated to be about 30 000 patients with Marfan syndrome and Marfan-like diseases. Cardiovascular patient communities for patients with congenital connective tissue disease also see a need for GT in patients with a positive family history or suspected disease, even if there are no current cardiovascular symptoms.

Cardiovascular patient communities unequivocally propose the abolition of flat-rate limits on genetic tests in genetic counseling clinics.

## CONCLUSIONS

Cardiovascular diseases remain the most common cause of death in the majority of developed countries worldwide. Most CVD have multifactorial etiology where risk alleles of dozens of polymorphisms interplay with environmental and lifestyle factors. On the other side, less frequent monogenic conditions can lead to SCD in young, apparently healthy people if unrecognized early and untreated.

The most common monogenic CVD leading to SCD in young people are CMP, channelopathies, and TAAD. These entities are primarily responsible for SCD among children and athletes. The most frequent monogenic entity, FH, is responsible for premature CAD and may lead to SCD in a mechanism of the unrecognized acute coronary syndrome in the young.

Enormous progress in human genetics and the application of new biomedical technologies allowed us to better understand pathomechanisms of monogenic diseases and improve the diagnostic processes, enabling early risk stratification and application of adequate therapy. GT is recommended by cardiological societies in all developed countries as an obligatory procedure in monogenic cardiac diseases when it may affect diagnosis, prognosis, risk stratification, therapy, or reproductive management of the patient and his family. Access to GT in Poland is limited because of high costs and a lack of clear application rules. This review aimed to formulate recommendations for GT in cardiology, which should be implemented in Poland. The most relevant

references are listed in Table 9. Recommendations include conditions that must be met by an MDL performing GT, legal regulations in Poland, and patients' rights and expectations. Direct-to-consumer genetic tests conducted without prior consultation, as well as polygenic scores for cardiovascular diseases with a genetic basis, are not recommended. Cardiologists, experts in the field of genetic diseases, when considering a genetic background of the CVD, should have the possibility to request the GT as a routine investigation reimbursed by the National Health Fund.

### *Addendum — May 8, 2024*

During the work on "Genetic testing for inherited cardiovascular diseases. A position statement of the Polish Cardiac Society endorsed by Polish Society of Human Genetics and Cardiovascular Patient Communities" the availability of mavacamten therapy for Polish patients has changed. Mavacamten therapy is currently under evaluation for reimbursement by the National Health Fund. The statement placed in the chapter Position of Cardiovascular Patient Communities: "Fortunately for patients with HCM, mavacamten therapy is available as part of a drug program reimbursed by the National Health Fund" is no longer valid.

### *Addendum — June 17, 2024*

From July 1, 2024, mavacamten will be reimbursed under the B.162 therapeutic program: TREATMENT OF PATIENTS WITH CARDIOMYOPATHY (ICD-10: E85, I42.1) in the indication for the treatment of adults with symptomatic New York Heart Association (NYHA) class II–III obstructive hypertrophic cardiomyopathy.

### *Supplementary material*

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

### *Article information*

**Conflict of interest:** EKB received an honorarium for participation in an advisory board of BMS. TO received honoraria for lectures from Amgen and Sanofi-Aventis, and provided consultation for Novartis. ZTB, MK, ALB, IŁ, MMK, RP, JKP, AR, AW, PW, AZK, LZ, RG — none. AP received an honorarium for participation in a clinical trial funded by Amgen. PR and JAS received honoraria for participation in an advisory board of Pfizer and for preparing educational materials on ATTR amyloidosis.

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