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STATE OF THE ART REVIEW
Arrhythmias

Genetic testing in early-onset atrial fibrillation

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Abstract

Atrial fibrillation (AF) is a globally prevalent cardiac arrhythmia with significant genetic underpinnings, as highlighted by recent large-scale genetic studies. A prominent clinical and genetic overlap exists between AF, heritable ventricular cardiomyopathies, and arrhythmia syndromes, underlining the potential of AF as an early indicator of severe ventricular disease in younger individuals. Indeed, several recent studies have demonstrated meaningful yields of rare pathogenic variants among early-onset AF patients (~4%–11%), most notably for cardiomyopathy genes in which rare variants are considered clinically actionable. Genetic testing thus presents a promising opportunity to identify monogenetic defects linked to AF and inherited cardiac conditions, such as cardiomyopathy, and may contribute to prognosis and management in early-onset AF patients. A first step towards recognizing this monogenic contribution was taken with the Class IIb recommendation for genetic testing in AF patients aged 45 years or younger by the 2023 American College of Cardiology/American Heart Association guidelines for AF. By identifying pathogenic genetic variants known to underlie inherited cardiomyopathies and arrhythmia syndromes, a personalized care pathway can be developed, encompassing more tailored screening, cascade testing, and potentially genotype-informed prognosis and preventive measures. However, this can only be ensured by frameworks that are developed and supported by all stakeholders. Ambiguity in test results such as variants of uncertain significance remain a major challenge and as many as ~60% of people with early-onset AF might carry such variants. Patient education (including pretest counselling), training of genetic teams, selection of high-confidence genes, and careful reporting are strategies to mitigate this. Further challenges to implementation include financial

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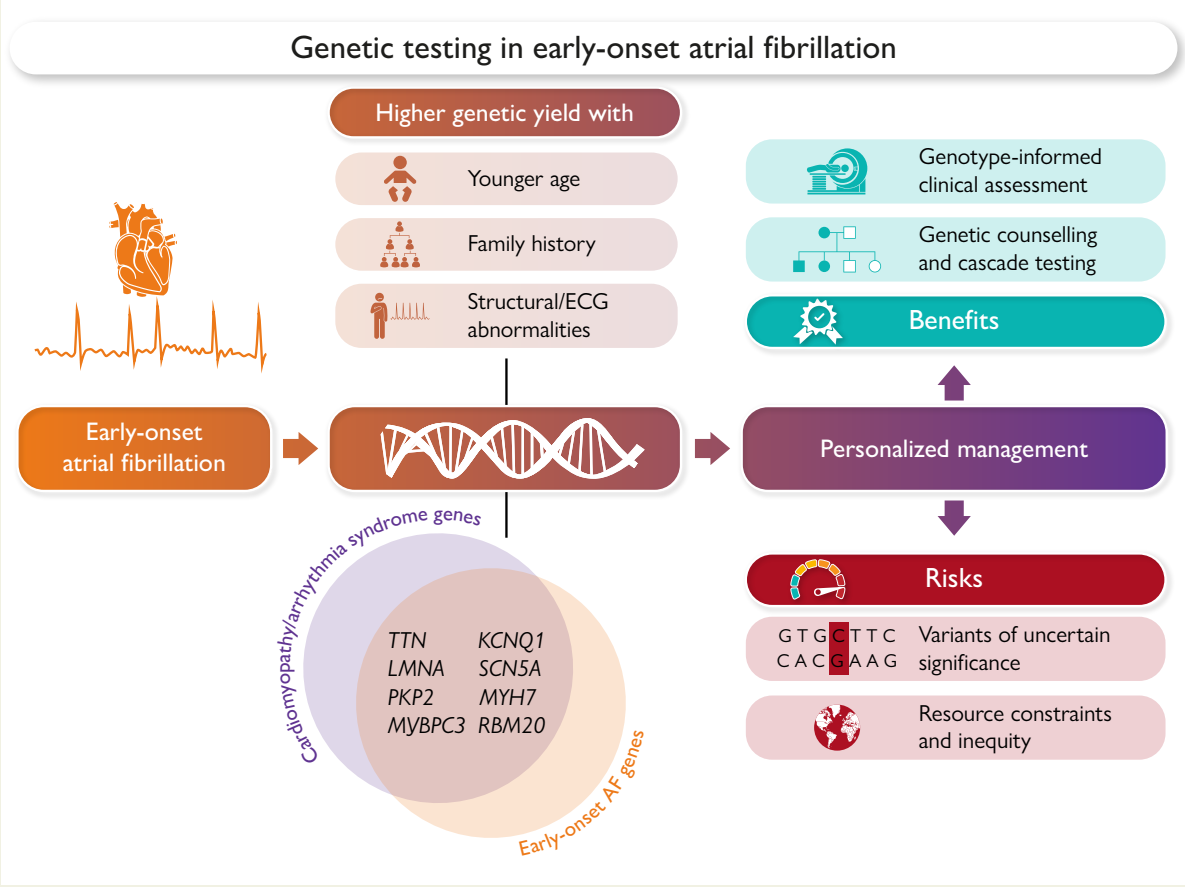
barriers, insurability issues, workforce limitations, and the need for standardized definitions in a fast-moving field. Moreover, the prevailing genetic evidence largely rests on European descent populations, underscoring the need for diverse research cohorts and international collaboration. Embracing these challenges and the potential of genetic testing may improve AF care. However, further research—mechanistic, translational, and clinical—is urgently needed.

Graphical Abstract



In people with early-onset atrial fibrillation (AF), an enrichment in pathogenic or likely pathogenic variants in cardiomyopathy and or/arrhythmia syndrome-associated genes is observed (see Figure 2 for more details). The diagnostic yield of capturing people with variants in these genes is higher with younger age, family history, structural or electrocardiogram (ECG) abnormalities (see Figure 1 for more details). Uncovering these high-risk individuals for heart failure enables personalized management that will need to comprehensively assess potential risks and benefits of genetic testing results. Some benefits include genotype-informed clinical assessment such as reinterpretation of borderline left ventricular hypertrophy in the setting of hypertrophic cardiomyopathy variants as well as genetic counselling and cascade testing of family members. Potential risks include the high likelihood of variants of uncertain significance that may lead to anxiety without informing healthcare decisions. Resource constraints in clinical settings might lead to further inequity for people without access to academic centres with the necessary infrastructure to offer such genetic testing services or genetic counselling (see Figure 3 for more details).

Keywords Genetic testing • Atrial fibrillation • Cardiomyopathy • Rare variants • Cascade testing

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia, affecting millions of individuals globally.[1] With an aging population, AF poses a significant socioeconomic burden, leading to considerable healthcare costs, disability, and reduced quality of life.[2,3] Despite advances in diagnosis and management, personalized treatment options remain elusive. While current guidelines stress the importance of individualized risk factor management, the integration of genetic data into clinical practice is still an unrealized potential.

Genome-wide association studies (GWAS) have now identified hundreds of common variant loci for AF.[4] Such GWAS loci encompass transcription factors (*PITX2* and *ZFHX3*), ion channel components (*KCNN3* and *SCN5A*), and myocardial structural genes (*TTN* and *MYH6*), among many others,[4] highlighting the complex, polygenic architecture of the disease. Polygenic risk scores (PRS), derived by summing

small individual contributions of common GWAS-derived variants across the genome to overall risk, are showing promise in identifying patients susceptible to AF, but their clinical utility has yet to be determined.[5]

Contrasting the individually small contributions of common genetic variants, with the possible exception of variants on chromosome 4q25, more recent large-scale whole exome (WES) and genome sequencing (WGS) studies have started to unravel the role of rarer genetic variants with larger effects. While genetic testing has not played a role in the clinical workup of AF, the detection of such rare variants by sequencing may open an avenue for precision medicine and improved AF care.

For the first time in any guidelines, the most recent 2023 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on management of AF provide a Class IIb recommendation on genetic testing in individuals with AF before the age of 45 years and no obvious risk factors, which reflects the growing evidence of genetics in AF.[6]

This review aims to summarize current data on genetic testing in AF, how cardiomyopathy and channelopathy genes overlap with AF as a clinical manifestation, which genetic tests are available, and how to interpret and potentially integrate these findings into clinical practice. This review follows the most recent European Society of Cardiology (ESC) guidelines on cardiomyopathies in nomenclature, and therefore uses the term arrhythmogenic right ventricular cardiomyopathy (ARVC) throughout this work.[7]

Atrial fibrillation and inherited cardiac disease

There is a growing body of evidence highlighting the overlap between AF and cardiomyopathy in the clinical setting.[8] The term 'atrial myopathy', which refers to structural changes in the atria such as fibrosis and dilation, is an emerging concept in understanding the connections between these conditions.[9] While genetic variants have been described for primary atrial myopathy,[10] AF is the most common sustained arrhythmia diagnosed in heritable ventricular cardiomyopathies [e.g. hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and ARVC]. Likewise, AF is a frequent comorbidity of the heritable arrhythmia syndromes, including Brugada syndrome, long QT syndrome (LQTS), short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia.[11–13]

The presence of AF in patients with a cardiomyopathy significantly increases the risk of stroke, heart failure (HF), and death.[7] Recent studies show a varying prevalence of AF depending on the specific cardiomyopathy, from about 10% to as high as 50% in restrictive physiology, with an annual occurrence rate of up to 12%.[14–16] Atrial fibrillation can both worsen symptoms and negatively affect left ventricular function[8,17] further exacerbating a coexisting cardiomyopathy. An emerging body of studies indicates that AF can be an early sign of cardiomyopathy, especially in younger individuals without other significant comorbidities.[18]

Panel testing, next-generation sequencing, and polygenic risk scores

With recent advances in genomic sequencing, the availability of genetic testing has increased in both clinical and research settings. While panel testing usually refers to the targeted sequencing and analysis of a select list of genes, many newer available tests utilize WES or WGS.[19] In panel and WES, the coding and flanking intronic regions (exons) of the DNA are analysed, while in WGS expanded non-coding regions can be interrogated as well. In terms of post-sequencing analysis and reporting, a specific panel of genes can be interrogated using data from either WES or WGS. The genetic data available can be re-interrogated for other genes, or when other indications for genetic testing arise. Whole genome sequencing data additionally encompass the non-coding regions of the genome, which rarely contain causative monogenic variants. Analyses of the non-coding regions of the genome may be of interest if a non-pathogenic or likely pathogenic (P/LP) coding variant is identified, particularly for exploring deep intronic splice variants, which can now be more readily assessed with newer algorithms.[20] Furthermore, WGS data enable calculation of PRS, which summarize the effects of many common variants of small effects across the genome.[21] While PRS are currently only utilized in secondary research applications, such data may in future be incorporated in risk models to provide more nuanced counselling. Since WGS is becoming increasingly affordable, it is anticipated that most testing labs will employ this technique in the future.

Rare variant determinants of early-onset atrial fibrillation

Consistent with the strong link between AF and cardiomyopathy, recent rare variant analyses have implicated myocardial structural genes in AF. The gene *TTN*, which encodes the sarcomere protein titin, has been robustly associated with AF across studies and datasets. For instance, in one Danish study, truncating variants in *TTN (TTNtv*) were found in 16% of patients with familial AF and 4.7% of patients with an onset of AF before 40 years of age.[22] In another study of 2781 participants with an AF onset at <66 years of age, the proportion of *TTN*tv carriers increased with younger age and reached over 6.5% in patients with AF onset before 30 years of age.[23]

Further large-scale WGS/WES studies have helped identify additional genes associated with large effect sizes for AF. Jurgens *et al.* studied over 50 000 cases of AF with available sequencing data. In addition to *TTN*, they reported and replicated rare variants associated with AF in a range of well-known Mendelian cardiomyopathy genes (*MYBPC3*, *LMNA*, and *PKP2*), previously reported cardiomyopathy genes with currently unclear significance (*CTNNA3*), and novel genes for cardiovascular pathology (*KDM5B*).[24] Again, an inverse relationship between age of onset and rare variant yield was found. Rare high-impact variants (largely truncating and large deletions) in a select group of associated genes were reported in 6%–7% of AF cases with onset before 35 years of age.

In another study using a cohort of early-onset AF patients from Denmark and AF cases from the UK Biobank, the authors found that truncating variants in the cardiomyopathy gene *RBM20* were associated with early-onset AF and larger atrial volumes.[25] Rare genetic forms of primary atrial myopathy and early-onset AF have also been described for rare variants in the atrial-specific gene *MYL4*.[10,26] In HCM and DCM, sarcomere gene and *TTN* variants were associated with larger atrial size and worse atrial function,[27] and *MYH7* variants in particular have been associated with higher AF incidence in HCM.[28]

Many rare variants associated with AF are functionally consistent with those that are known to cause ventricular cardiomyopathy and would be considered P/LP for these conditions. For instance, the following variants were associated with AF: (i) truncating variants in *MYBPC3*, known to underlie HCM, (ii) truncating variants in *LMNA* and *TTN* (cardiac exons), known to underlie DCM, and (iii) truncating

variants in *PKP2*, known to underlie ARVC.[24] These variant classes were all enriched in early-onset AF, and these same variant classes are considered P/LP and reportable due to their potential ventricular cardiomyopathy manifestations.[29] Interestingly, these rare variants were associated with AF even when accounting for known cardiomyopathy, HF, or left ventricular dysfunction, pointing to risk that is not captured simply by prevalent cardiomyopathy.

In addition to cardiomyopathy genes, variants in ion-channel genes have been implicated in early-onset AF. Gain-of-function variants in *SCN5A*, associated with LQTS, have been found in early-onset AF kindreds and cohorts,[30,31] while atrial arrhythmia is also common in *SCN5A*-related Brugada syndrome.[11,32] Both gain-of-function and loss-of-function variants in *KCNQ1* have been found to co-segregate with early-onset AF in several kindreds, further associating with QT abnormalities (including short QT syndrome and LQTS) and sudden cardiac death (SCD) in some cases.[33,34] Rare variants in the atrial-specific ion-channel gene *KCNA5* have been shown to co-segregate with early-onset lone AF in a handful of families.[35–37] While many other ion-channel genes have been proposed for monogenic and/or early-onset AF,[38] existing data rely on small families and/or small candidate gene approaches, and lack replication in larger studies. Indeed, contemporary studies suggest that the yield of potentially causative variants in arrhythmia genes, other than *SCN5A* and *KCNQ1*, is small in early-onset AF.[18,39]

Genetic yield in early-onset atrial fibrillation

Genetic testing assessing a panel of disease-associated genes is a standard part of cardiovascular medicine in many areas, including the evaluation of the cardiomyopathies, arrhythmia syndromes, channelopathies, dyslipidemias, and others.[7,40] A similar approach may be useful in certain people with AF as first outlined in the recent consensus document of professional societies on genetic testing in cardiac diseases.[41] Preferably, either WES or WGS could be employed for assessing genetic information to enable re-interrogation of the data for other indications or changes in the investigated panel, if needed.

A recent study assessed the potential diagnostic yield of P/LP variants among 1293 early-onset AF patients. Using a broad cardiomyopathy and arrhythmia panel, and applying American College of Medical Genetics and Genomics (ACMG) criteria, the authors identified P/LP variants in ~10% of early-onset AF patients, defined as AF before the age of 65.[39] The highest yield was found for variants in *TTN* (3% of early-onset AF cases), followed by *MYH7*, *MYH6*, *LMNA*, and *KCNQ1*. Earlier age of onset was correlated with a higher genetic yield, in which a cut-off of 45 years gave a yield of ~10%, with up to 16% yield in individuals diagnosed before 30 years. In subsequent work, the same group demonstrated an increased risk of death (hazard ratio 1.5; 95% confidence interval 1.0–2.1) in variant carriers vs. non-carriers over a follow-up of almost 10 years,[42] which was largely driven by known ventricular cardiomyopathy genes. Notably, those with early-onset AF and P/LP variants were at increased risk for cardiomyopathy-related death and SCD.[42] It should be noted that these studies included several genes with less clear roles in ventricular cardiomyopathy and/or inherited arrhythmia syndromes. Nonetheless, ~7% of early-onset AF cases carried causative variants in high-confidence genes for these conditions, and 4% carried P/LP truncating variants in genes where such variants are considered readily reportable by ACMG guidelines (e.g. *TTN*, *LMNA*, *MYBPC3*, *KCNQ1*, *DSP*, and *SCN5A*). A recent study by Kandola *et al.* reported a prevalence of P/LP variants using cardiomyopathy and arrhythmia genes at around 4.2% for people with AF onset younger than age 45. However, due to the lack of use of ACMG criteria, comparisons with other work are challenging.[43]

Several smaller studies have reported clinically relevant genetic yield among independent early-onset AF cohorts (*Table 1*). In a study of 25 patients with early-onset AF (mean age ~27 years) without significant comorbidities presenting to an inherited cardiovascular disease clinic, six patients (24%) carried P/LP variants (five in cardiomyopathy genes *TTN* and *RBM20*, and one in *KCNQ1*).[18] In another study from Canada, among 200 AF patients with onset <60 years and without any risk factors at diagnosis, 4% were found to carry P/LP variants (2.5% in *TTN*).[44] In a Latvian study of 54 patients with AF <66 years without relevant risk factors, 13 (24%) carried P/LP variants in cardiomyopathy genes (9 *TTNtv*).[45]

Genetic testing in non-European populations—an ongoing issue to address

Populations of non-European ancestry are still underrepresented in genetic studies, which leads to downstream consequences when applying genetic testing in routine care. This issue has been well-known in the genomics community and leads to disparities and inequities, as previously reviewed.[47,48] Data on genetic testing in AF within non-European populations are sparse. In one study from Chicago investigating 60 candidate AF genes among 227 ethnic minorities (Black or Hispanic individuals) with AF onset <66 years, 7% carried P/LP variants (mostly *TTNtv*).[46] The same group later investigated the prevalence of 22 candidate cardiomyopathy genes in 305 AF patients recruited from the same centre. In this older cohort (mean age 60 years), the prevalence of P/LP cardiomyopathy variants was 3.9%.[49] The lack of genetic diversity in research studies also hinders pathogenicity assessment. In a study of variant classification in cardiomyopathy genes extracted from ClinVar (between 2011 and 2021), variants with higher minor allele frequency were more likely to be classified as P/LP in non-European populations compared with European populations, highlighting the diagnostic uncertainty associated with lack of diverse genetic studies.[50]

Temporality of atrial fibrillation and ventricular cardiomyopathy in rare variant carriers

Considering the potential yield of cardiomyopathy variants in early-onset AF, it is important to understand the temporal relation between the atrial and ventricular manifestations among P/LP variant carriers. Recent studies have suggested that AF is not solely a manifestation of an overt ventricular cardiomyopathy in all carriers. In many studies, individuals with AF and risk factors at the time of diagnosis, including HF or cardiomyopathy, were deliberately excluded.[18,44,45] Notably, in the Latvian study, 5 out of 13 early-onset AF patients carrying P/LP variants in cardiomyopathy genes, who initially exhibited normal left ventricular findings on echocardiography, later showed signs of ventricular chamber enlargement indicative of ventricular cardiomyopathy on cardiac magnetic resonance imaging (MRI).[45]

Consistently, a comprehensive analysis of *TTN*tv carriers from the UK Biobank revealed that AF may precede ventricular cardiomyopathy in ~50% of individuals who eventually develop both conditions.[51] Likewise, AF is common in carriers of *LMNA* variants, with AF and atrial

Table 1 Studies that used American College of Medical Genetics and Genomics–AMP criteria to report yields of rare genetic variants among early-onset atrial fibrillation cases

Study	*N*	Ancestry/race of participants	Case definition	Gene panel used	Variant assessment criteria	*N* P/LP variants/*N* P/LP in ACMG genes/*N* P/LP in *TTN*	*N* with VUS only
Goodyer et al.[18]	25	68% self-reported white; 16% Hispanic; 8% African American; 8% Asian	AF onset <45 or onset <60 with first-degree relative with AF <45; no structural heart disease on initial echocardiogram; no classical AF risk factors (including heart failure)	Various broad inherited arrhythmia and cardiomyopathy panels	Genomic testing laboratories classified according to 'contemporary gene- and disease-specific classification approaches' (supposedly ACMG–AMP criteria)	6 (24%)/ 6 (24%)/ 4 (16%)	18 (72%)
Yoneda et al.[39]	1293	Largely European ancestry (95.7% self-reported white); 3.7% self-reported black	AF onset <66; no specific exclusion for co-morbidities	Combined broad cardiomyopathy and arrhythmia panels from various providers	Automated AI-based process (Franklin) integrating ACMG–AMP criteria; manual re-review of VUS/LP/P using ACMG–AMP criteria	130 (10.1%)/ 85 (6.6%)/ 38 (2.9%)	812 (62.8%)
Chalazan et al.[46]	227	All self-reported African American (65.2%) or Hispanic (34.8%)	AF onset ≤66; no surgery-related AF	60 AF candidate genes	ACMG–AMP criteria	16 (7.0%)/ 12 (5.3%)/ 8 (3.5%)	NA
Chalazan et al.[44]	200	Primarily self-reported European ancestry (82.1%); 15.3% Asian ancestry; 2.6% First Nations	AF onset ≤60; no classical cardiovascular risk factors or overt heart disease (including heart failure or cardiomyopathy); no structural heart disease echocardiography	8 genes curated by authors as being strongly implicated in AF+ 17 genes with high evidence of association with ventricular cardiomyopathies (as determined by existing ClinGen curation)	ACMG–AMP criteria, taking into account phenotype-specific curation	8 (4.0%)/ 7 (3.5%)/ 5 (2.5%)	NA
Rudaka et al.[45]	54	All European ancestry	AF onset <65; no abnormalities on initial echocardiogram; no classical AF risk factors (including heart failure or cardiomyopathy)	Broad panel of 349 genes previously associated with inherited cardiac disorders (including arrhythmia and cardiomyopathies)	ACMG–AMP criteria, and cardiodb for *TTN* variants	13 (24%)/ 12 (22%)/ 9 (17%)	NA

ACMG, American College of Medical Genetics and Genomics; AF, atrial fibrillation; P/LP, pathogenic or likely pathogenic variant; VUS, variants of unknown significance.

myopathy often preceding ventricular manifestations.[52–54] In a study of over 18 000 people with MRI, ECG, and WES in the UK Biobank, arrhythmia and conduction abnormalities were the most common early DCM features among variant carriers with no clinical diagnosis.[55] Nevertheless, the temporal relationship remains less clear for many genes, necessitating further research to unravel the phenotypic cascades on a per-gene (and per-variant) basis. Furthermore, for some genes implicated in AF, no ventricular phenotype may be expected (e.g. for variants in *KCNA5*).

Polygenic risk and rare variants

While rare variants and polygenic risk from common variants are distinct in allele frequency, there is an important interplay between mono- and polygenic risks. For example, in the 2020 work by Choi *et al.* on ∼44 000 people in the UK Biobank, the penetrance for AF in carriers of *TTNtv* carriers was significantly modified by polygenic risk: carriers in the lowest tertile of polygenic risk saw a 6.7% prevalence, while 21.5% of carriers in the highest tertile had AF.[56] A similar risk modification has been described for PRS in carriers of P/LP variants for inherited breast-cancer, colon-cancer, and hypercholesterolaemia.[57] This stratification of polygenic risk among rare variant carriers was shown for a similar analysis of HCM variant carriers in the UK Biobank. Those in the highest centile of a PRS for HCM had 14-fold increased risk compared with those in the median of PRS. This work also showed that the penetrance in P/LP carriers is much higher in those with a PRS in the highest quintile, as compared with the median or lowest quintile of PRS (odds ratio 3.69 and 9.56, respectively).[58] Nevertheless, it currently remains uncertain how PRS should be incorporated with rare variants for more nuanced counselling in the cardiovascular space, including in early-onset AF.

Current guidelines on genetic testing in atrial fibrillation

Current ESC guidelines on AF do not provide a recommendation for genetic testing in young individuals without comorbidities.[59] As outlined earlier, 2023 ACC/AHA guidelines provide a Class IIb recommendation for genetic testing in people with AF younger than 45 years. At the same time, for those <30 years with unexplained AF, an electrophysiological study to assess and treat supraventricular tachycardia (which can trigger AF) may be considered (Class IIb recommendation).[6] The consensus document of European, US American, Latin American, and Asian-Pacific Societies provided an initial consideration for genetic testing in people with familial AF under the age of 60.[41] Contrasting the current consensus on genetic testing in AF, in DCM and other cardiomyopathies, genetic testing is a Class IB recommendation in current ESC guidelines.[7] Interestingly, the diagnostic yield may be comparable between non-familial DCM and early-onset AF; in non-familial DCM the genetic yield is ∼10% (as compared with 50% in familial DCM and an average around 19%).[60,61]

When to consider genetic testing

Knowledge on the genetic causes of AF continues to expand and evolve. Therefore, genetic testing for early-onset AF is best integrated into clinical care by an interdisciplinary team involving cardiologists with expertise in AF, cardiologists with expertise in cardiomyopathies, specialist nurses, cardiovascular geneticists, and genetic counsellors. The ACMG currently recommends reporting of secondary findings for many of the genes found to underlie early-onset AF (including *TTN*, *LMNA*, *MYBPC3*, *KCNQ1*, *PKP2*, and more)[29] independent of the primary indication for genetic testing. However, when testing is done for the specific indication of early-onset AF, comprehensive integration of all factors supporting and opposing the decision for testing should be considered (*Figure 1*). Factors in favour of testing include a very early-onset of disease (<45 years) or familial aggregation of AF or cardiomyopathy in those under the age of 65 years.[6,41] Similarly, signs suggestive of ventricular cardiomyopathy in echocardiography or MRI such as elevated volumetric indices or even slightly reduced contractile function may be suggestive of underlying pathology. Clinical presentation that is suggestive of a specific monogenic defect, such as early-onset AF with conduction disease or ventricular arrhythmias (*LMNA*), or early-onset AF[62] with QT abnormalities in (*KCNQ1*), may raise suspicion of genetic causes. The ECG provides valuable information that may point to underlying cardiomyopathy, including but not limited to bundle branch block,[63] atrioventricular block, T-wave inversion, or QRS abnormalities.[64]

Conversely, typical features associated with more common forms of AF include those triggered by known risk factors such as obesity,[65] diabetes, hypertension, sedentary lifestyle,[66] sleep apnoea, or smoking.[67] The strongest marker that favours a non-genetic cause is age and many of the mentioned factors are often found in older individuals. However, several risk factors for AF are either age-independent such as height or often found in younger individuals such as endurance sports.[68] Toxicities including alcohol,[69] drugs, or hormonal abnormalities (hyperthyroidism) are possible AF triggers in younger people and may be considered. Finally, as the 2023 ACC/AHA guidelines outline, the possibility of supraventricular tachycardia inducing AF may be considered, particularly in younger individuals in whom an electrophysiology study could be diagnostic and therapeutic.[70]

Gene selection for testing

The main goal of genetic testing in early-onset AF is to identify carriers of P/LP variants known to underlie inherited cardiomyopathies and/or inherited arrhythmia syndromes. In terms of panel testing, cardiomyopathy and arrhythmia gene panels may be considered for early-onset AF, with a strong focus on including genes that have a high confidence for inherited cardiomyopathies and/or inherited arrhythmia syndromes (in particular, genes where P/LP variants are considered actionable by the ACMG.[29]) As the phenotypic presentation is variable, a standard 'arrhythmias and cardiomyopathy panel' that is regularly updated is used in many centres. *Figure 2* offers an overview of genes that are often included in such panels and have robust evidence for a role in (early-onset) AF, as well as genes considered high confidence for cardiomyopathy and/or Mendelian arrhythmia syndromes. For a more comprehensive dataset containing curation of evidence and actionability as defined by ACMG for an extended list of (potential) AF genes, see Supplementary data online, *Table S1*. While not all genes have yet gone through a full expert consensus-driven approach tailored to AF, such as conducted by ClinGen Expert Panels, it may contribute to ongoing efforts.

Implication of testing results for care

The identification of rare pathogenic variants in cardiomyopathy or channelopathy genes in these settings has a number of important implications. First, it would lead to more detailed clinical evaluation to identify early signs of cardiomyopathy, such as ECG abnormalities or

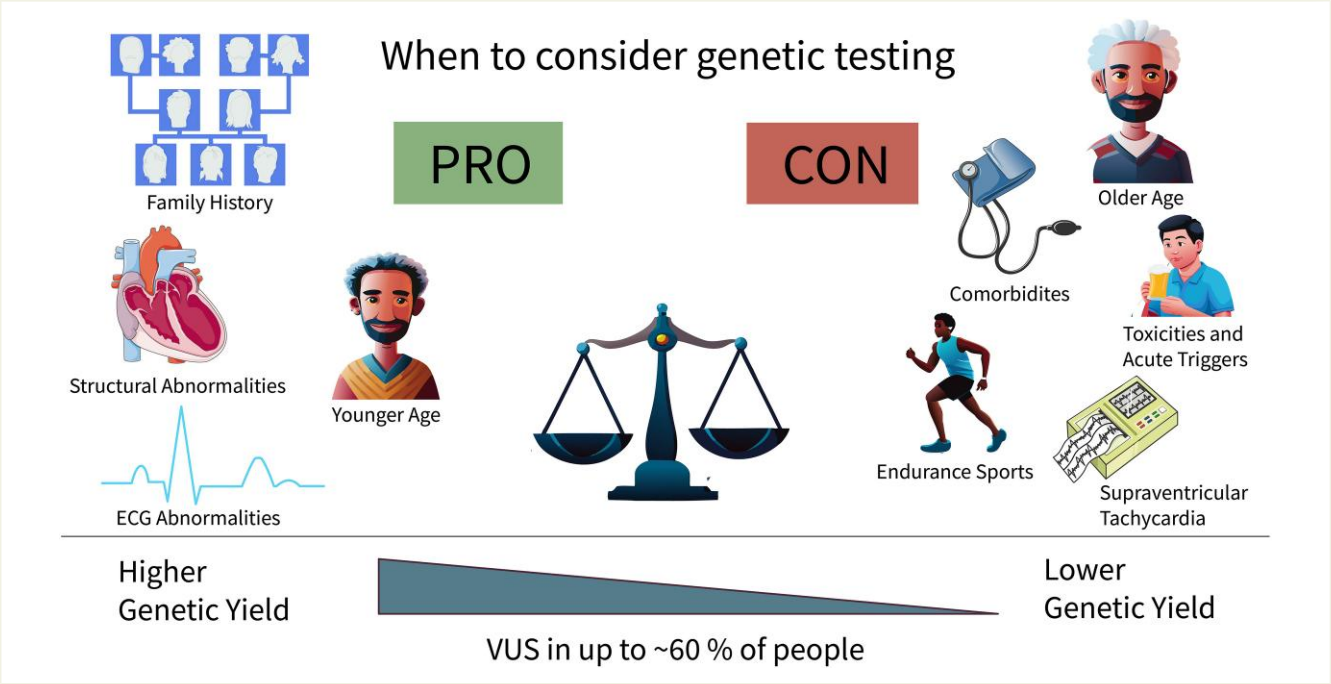


Figure 1 Overview of when to consider genetic testing and expected diagnostic yield in rare variant testing in early-onset atrial fibrillation across lifetime. This figure uses medical images from Servier Medical Art under the Creative Commons 3.0 license. VUS, variants of unknown significance

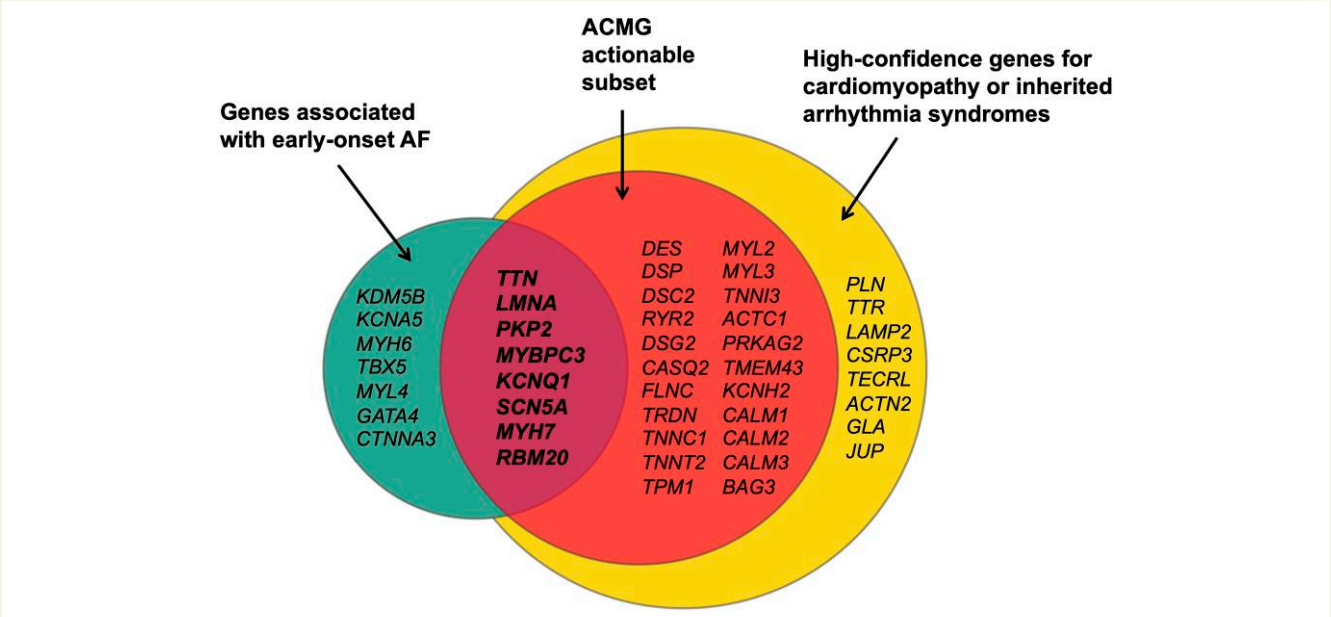


Figure 2 Overview of genes where rare coding variants have been implicated in early-onset atrial fibrillation (turquoise), genes with high confidence for cardiomyopathy or arrhythmia syndromes, and genes in the American College of Medical Genetics and Genomics actionable subset overlapping with the latter (red), or overlapping with the former and latter

structural/contractile dysfunction. Notably, the presence of a cardiomyopathy variant may motivate a decision to perform MRI studies, or may help inform diagnostic considerations in some cases. While it is important to stress that a genetic finding does not constitute a phenotypic diagnosis, an ARVC-associated variant, for instance, may prompt thorough assessments of the right ventricle and task force criteria, while an HCM-associated variant may guide decision of care in case of borderline septal hypertrophy (e.g. between 13 and 15 mm).[7]

Second, a rare variant finding among an AF patient may inform clinical decision-making. For example, in patients with *LMNA* or *FLNC* variants and subclinical ventricular cardiomyopathy, increased surveillance and early consideration of a defibrillator may be in place, as outlined in the recent ESC guidelines for cardiomyopathies.[7] In carriers of ARVC-associated variants, avoidance of competitive high-level exercise may be considered.[71] Specific ion-channel variants might inform consideration of drug choice; in AF patients with variants known to underlie Brugada syndrome (e.g. *SCN5A* loss-of-function variants) and LQTS (e.g. *KCNQ1* and *KCNH2* loss-of-function variants), caution should be taken with sodium channel blockers and potassium channel blockers, respectively.[71]

Third, the identification of a rare cardiomyopathy or arrhythmia syndrome variant enables cascade screening to identify other family members at risk of disease manifestations, including HF and SCD.

Fourth, identifying a potential monogenic cause of AF may represent a critical first step in understanding the underlying pathophysiology, with an eventual goal of developing gene- or even variant-specific therapies.

Variant curation, reporting, and variants of uncertain significance

In genetic diagnostics, implementing careful and systematic variant curation pipelines are essential to limit false genetic diagnoses. The presence of variants of uncertain significance (VUS) in genetic testing poses a challenge for both clinicians and patients. These are genetic variants for which the clinical implications are not yet fully understood, making it difficult to ascertain their role in disease development or progression. Most people with AF that undergo panel testing will carry a VUS [e.g. 812/1293 (63%), in the Yoneda *et al.* study],[39] potentially causing unnecessary stress for patients. This is not uncommon in genetic testing, for reference, VUS are found in ~30% in idiopathic ventricular fibrillation[72] and in ~40% in unexplained cardiac arrest.[73] Further research is crucial to reclassify these variants and the lack of clinical significance of these variants in communicating with patients and other stakeholders. Given the frequency of the VUS finding, it is likely that most are benign or non-contributory.

To identify P/LP variants known to underlie cardiomyopathy or arrhythmia syndromes, strict adherence to the criteria established by the ACMG and ClinGen is imperative, within established frameworks tailored to these heritable conditions. Some guidance has been developed on how to apply evidence-based frameworks for evaluating variants for more common diseases such as AF.[74] Rare variants interpreted as potentially causative for AF, but found in genes with unclear roles in other inherited cardiovascular diseases (diseases with ClinGen/ACMG frameworks), may not reach P/LP classification by current guidelines.[75] Future consortia, potentially in collaboration with ClinGen, may be required to establish AF-specific gene curation and variant classification frameworks.

As an example for variant classification in the context of AF, in absence of other supporting data, *TTN*tv may only be considered as contributing to cardiac disorders (e.g. AF and DCM) if they affect cardiac expressed exons.[29,76] Similarly, truncating variants in many AF-associated genes (e.g. *LMNA*, *MYBPC3*, *PKP2*, and *KCNQ1*) are generally considered P/LP for various heritable cardiac disorders and are considered reportable by the ACMG guidelines, but this is neither universally true for all AF-associated genes, nor for all rare non-predicted loss-of-function (e.g. missense) variants.

Strategies for addressing variants of uncertain significance and ambiguity in variant classification

Due to the high likelihood of finding a VUS in patients with early-onset AF, strategies to address this early on may be beneficial. This may include patient education prior to testing to set boundaries of expectation from the results but can also be mitigated somewhat by careful strategies. For example, an international appraisal study of 17 reported LQTS genes found strong/definitive evidence for only three genes in the context of 'typical' LQTS and for only four genes for 'atypical' presentations.[77] Limiting the gene selection to genes with at least moderate levels of ClinGen evidence might be considered to reduce findings with uncertainty.[78]

Indeed, little to no evidence currently exists to support reporting of VUS and/or variants in genes with uncertain roles in cardiomyopathy/arrhythmia syndromes. Future work is required to assess whether individuals carrying AF-specific rare variants (i.e. those that are causative of AF but not for cardiomyopathy/inherited arrhythmia syndromes) have different outcomes or unexpected additional phenotypic manifestations in early-onset AF.

An important consideration is that variant classification is fluid and therefore variants and genes might be re-classified based on new evidence. In the above-mentioned analysis of variant classification instability in cardiomyopathy genes in ClinVar from 2011 to 2021, 7.3% of cardiomyopathy variants underwent clinically significant pathogenicity re-assignment.[50] Importantly, these changes often include the downgrading of P/LP variants to VUS, which is a considerable challenge for clinical practice and highlights the need to integrate any genetic findings into a comprehensive assessment. How VUS are reported may be decided locally with stakeholders, including patient advocacy groups. Of note, some laboratories provide the option of not reporting VUS while others do so routinely. Additionally, some labs may have sub-tiers of VUS that are usually for internal use, which is not discouraged by current ACMG guidelines.[79]

While there is some hope that VUS will be rarer as our knowledge in pathogenicity of variants increases, several efforts are needed to arrive there as Fowler and Rehm outline.[80] While functional studies can be helpful, variant classification requires comprehensive, systematic, and standardized approaches to reduce variant assessment heterogeneity among different laboratories. The updated ACMG guidance on variant assessment is currently in the works and will provide updated recommendations. In particular, these new sequence variant classification standards will guide the application of VUS sub-tiers, which will make it easier for clinicians to decide which VUS to expend effort on in further investigation given a higher likelihood of reclassification towards pathogenicity.

Framework for clinical integration of genetic data

Integrating results from genetic testing into clinical routine care involves a careful structured pathway that enables informed shared decision-making throughout the patient journey. An example of a theoretical framework on how to handle genetic testing in patient care and communication is provided in *Table 2*. In short, careful patient selection is needed to identify people with early-onset AF that might benefit from genetic testing. A thorough ascertainment of family history should

Table 2 Clinical framework of incorporating genetic testing for atrial fibrillation into care

Step	Description	Key Actions	Examples	Additional Considerations
Initial Patient Assessment	Assess for genetic testing candidacy based on personal and family history.	Evaluate for signs of cardiomyopathy and ventricular arrhythmia; consider age at AF onset.	Prioritize patients with AF onset before age 45, or those with family history.	Consider comprehensive evaluation including imaging such as ECG, echocardiography, and biomarkers such as NT-proBNP.
Risk stratification	Categorize patients by using clinical and family history.	Integrate all available factors to determine likelihood of genetic contribution to disease.	Identify high-risk features like sudden cardiac death or unexplained syncope in the family or ventricular arrhythmia.	Regularly update risk assessment with new clinical information. For instance, drops in left ventricular ejection fraction during follow-up.
Genetic counselling	Provide pretest counselling about the implications of genetic testing.	Discuss potential outcomes, benefits, limitations, and the possibility of incidental findings.	Ensure informed consent and prepare the patient for possible genetic findings and the high likelihood of variants of uncertain significance.	Address psychological impact and family planning considerations.
Selection of genetic testing method	Choose the most appropriate genetic test based on clinical relevance.	Either targeted gene panels or exome/genome sequencing.	Decide on genes based on official recommendations, local expertise, and local arrangements with clinical geneticists.	Consider offering participation in appropriate research trials or cohorts.
Interpretation of results	Collaborate with geneticists for accurate result interpretation.	Classify variants based on established pathogenicity guidelines.	Distinguish between pathogenic, likely pathogenic, and variants of uncertain significance.	Engage in multidisciplinary discussions for complex cases.
Clinical Integration of Genetic Data	Use genetic data to refine diagnosis and inform management strategies.	Incorporate genetic findings into the broader clinical context.	Adjust surveillance and treatment based on findings, such as LV hypertrophy in *MYBPC3* carriers.	Regularly review and update management plans as new genetic information emerges, or clinical characteristics change.
Family Screening and Counselling	Recommend testing and counselling for family members of patients with pathogenic variants.	Identify first-degree relatives at risk and encourage genetic testing.	Discuss the implications of testing for family members, including preventive strategies and lifestyle changes such as endurance sports in *PKP2* carriers.	Tailor counselling based on family dynamics and individual risk.
Regular Follow-Up and Reassessment	Establish protocols for ongoing monitoring based on individual risk profiles.	Schedule regular follow-up appointments and adjust tailored care based on findings.	Use clinical and genetic data to reassess treatment effectiveness and disease progression, consider early specialized heart failure care in cardiomyopathy carriers.	Incorporate new research findings and guidelines into follow-up plans.
Education and Support	Provide ongoing education and psychological support to patients and families.	Address concerns about living with a genetic predisposition to cardiovascular diseases.	Offer resources on disease management, lifestyle modifications, and support groups.	Foster a supportive environment for coping with chronic conditions.

ECG, electrocardiogram.

be ensured to identify family members with early-onset AF or related comorbidities. Clinical assessments may also include cardiac imaging, preferably by cardiac MRI as it has been demonstrated to detect structural abnormalities even when echocardiography results appear normal.[18,81]

Importantly, genetic counselling must be provided to affected patients and family members before any testing to facilitate a comprehensive discussion of the clinical implications, potential risks, the high likelihood of VUS, and available management options. In systems without integrated genetics clinics, referral or cooperation with a specialized centre should be considered. Interpretation of the findings should be considered in collaboration with clinical geneticists and counsellors to integrate into clinical care and inform surveillance, e.g. the early referral to specialized HF programmes when a P/LP cardiomyopathy variant is detected. Rare variants also interact with common modifiable clinical risk factors, as demonstrated by Huang et al.[82] who

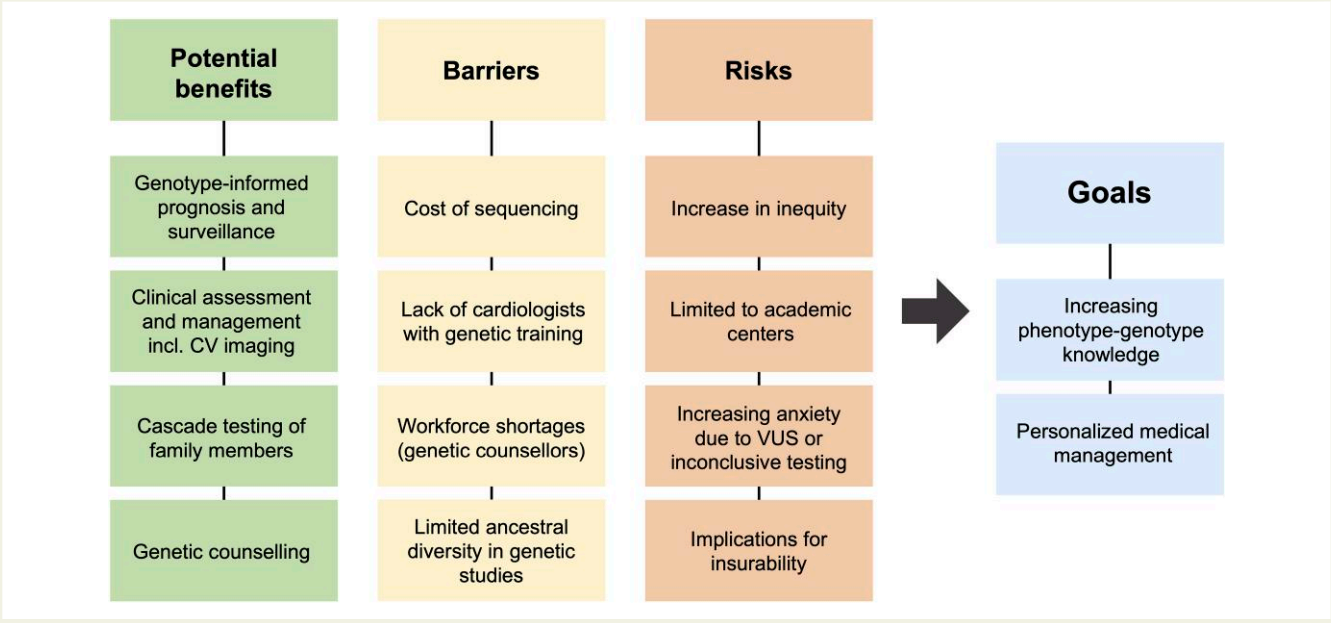


Figure 3 Overview of potential benefits, barriers, and risks associated with increases in genetic testing for atrial fibrillation. CV, cardiovascular; VUS, variants of unknown significance

showed additive increases in the risk of AF in *TTNtv* carriers from hypertension, obesity, diabetes mellitus, and smoking.

Additionally, when appropriate, family counselling and cascade testing should be performed to identify family members at risk as current guidelines outline.[7] The integrated care envisioned would result in tailored and patient-specific follow-up and treatment plans such as early consideration of ICD in *LMNA* carriers with ventricular arrhythmia or the avoidance of endurance sport in *PKP2* carriers. The results may also be constantly reviewed for any changes in variants classification or new evidence from research studies regarding adverse events and treatments.[50] Finally, education and support should be offered to patients and families in a continued manner that ensure stakeholders are fully informed about their care.

Current challenges and barriers, and pathways to overcome them

Despite the existing evidence, several barriers need to be overcome. First, the cost of genetic testing and data analysis must be addressed to make these technologies accessible to a broader patient population (*Figure 3*). Advocacy for insurers and healthcare payers to fund genetic testing in AF needs to be prioritized for implementation into clinical care. To this extent, cost-effectiveness studies are needed to assess the economic burden of genetic testing for a common disease such as AF. Guidelines and recommendations that do not address cost and accessibility of diagnostic tools or treatments have been associated with increasing health inequities.[83,84] Therefore, genetic testing limited to large academic centres or affluent regions may in turn exacerbate health inequities in AF care. Regional networks that offer integrated care for patients in cooperation with specialized centres may reduce inequities to accessing genetic testing.

Second, clinical implementation of genetic testing requires interdisciplinary collaboration among cardiologists, geneticists, genetic counsellors, and bioinformaticians—especially considering the ever-evolving map of AF genes and variant pathogenicity classifications. For a common disease such as AF, workforce shortages, particularly of genetic counsellors and cardiologists with genetic training or knowledge, will be limiting factors to wide-spread implementation.[85] Additionally, patient and provider education will need to be prioritized to set expectations but also prevent over- or misinterpretation of results.

Third, integrating genetic data into clinical practice requires the development of standardized guidelines and definitions of early-onset AF. No standardized definition of what constitutes early-onset AF has been established. Based on current studies, an age cut-off of 45 years confers a diagnostic yield for rare variants of ~8%–10% using a broad panel and ~5% using selected high-confidence genes (mainly, *TTN*).[24,39] This is also the age endorsed by the ACC/AHA guidelines for genetic testing in AF, but future efforts for working groups should be towards establishing standardized definitions for risk groups and enabling comparative research.

Future outlook and what is needed

Little prospective evaluation of genetic testing in early-onset arrhythmias has been conducted thus far. For example, one major unanswered question is the extent to which evidence of ventricular dysfunction is found at the time of detection of a P/LP cardiomyopathy variant or subsequently. Further large-scale studies of the association between rare variants and adverse events are needed, as well as the influence of polygenic modifiers of risk in variant carriers.

Additionally, as discussed previously, the current genetic evidence of rare coding variation for AF and related disorders relies largely on European ancestry data, which might contribute to inequity in medicine. While new biobank platforms that aim to increase genetic and ethnic diversity—such as the *All of Us* program and the Million Veterans Program—represent important developments, additional prospective cohorts/trials of ancestrally diverse early-onset AF patients will be equally critical. Due to the relative rarity of AF in young and very young patients,

international partnerships are needed to design research and trial platforms to achieve a robust evaluation of genetic testing. Early detection of variant carriers and family cascade testing could inform surveillance, help identify individuals at risk for adverse events, and enable tailored treatments, highlighting the need for comprehensive evaluation beyond standard management of sinus rhythm and stroke risk in these patients.

There is also a need for further research studies assessing the role of rare variants in the AF–HF overlap syndrome and the association of adverse events in these individuals. Functional and translational research elucidating how these variants lead to a high co-morbidity of AF and HF are crucial in integrating genetic testing into routine care. For example, high-throughput screens with newer methods such as Perturb-seq or high content imaging–based approaches in cardiomyocytes seem promising to elucidate the effect of variants on structure.[86]

Finally, there is little evidence on how AF patients with cardiomyopathy variants respond to rhythm control therapies such as catheter ablation or anti-arrhythmic drugs.

Conclusion

Rare cardiomyopathy and arrhythmia variants are found in a significant proportion of early-onset AF patients. Genetic testing can identify these individuals and is recommended in those with AF aged 45 years and younger with no obvious risk factors. However, the integration of genetic testing of AF patients in routine care requires careful frameworks that involve all stakeholders. The selection of high-confidence genes as well as patient education are crucial in reporting test results to patients as up to 60% of people may have a variant of uncertain significance (Graphical Abstract). This ambiguity in variant assessment is exacerbated by the lack of genetic data from non-European populations. Critically needed studies include those in patients of non-European ancestry as well as further mechanistic, translational, and large-scale sequencing studies to provide a bridge between basic genetics and clinical practice. The identification of carriers will enable early detection with more precise phenotyping, cascade testing of family members, and personalized follow-up of these patients. While existing barriers to wide-spread clinical application are to be considered, there is immense potential in genetic testing for early-onset AF and it is time to develop a standardized approach for the evaluation of these patients, in research and clinic.

Supplementary Data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for or in support of this paper.

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