Family screening in hypertrophic cardiomyopathy: time for a change or should we tread cautiously?

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Hypertrophic cardiomyopathy (HCM) is primarily a disease of the cardiac sarcomere and genetic testing identifies disease-causing variants in up to 40% of index patients[1]. Sarcomeric variants are inherited in an autosomal dominant fashion but with incomplete and age-related penetrance. Recent studies have shown that the penetrance of sarcomeric disease is higher than previously reported, with up to 50% of genotype positive individuals developing a phenotype of HCM over 15 year follow up independent of the age of screening[2]. Family screening to identify affected relatives is therefore a key aspect of clinical care, allowing appropriate therapies to be instigated early and an opportunity to prevent disease-related complications. This forms the basis of current class I recommendations for family screening in international clinical practice guidelines[3, 4]. The question now is not whether we should screen family members, but who will benefit most and when and how we should screen. In particular, while previous studies have described a higher yield of family screening for index patients with a confirmed sarcomeric variant, family history of disease, younger proband age and male sex[2, 5-8], the benefit and clinical yield of family screening for index HCM patients who are genotype elusive is largely unknown.

The study by Nielen and colleagues in this issue of the *Journal* provides important and timely data on this issue. In a large, multi-centre cohort study of 751 relatives (270 index patients), 34 (5%) met diagnostic criteria for HCM at baseline and a further 2 relatives developed a phenotype during a median follow up of 6 years. Of note, 12 of the 34 relatives were diagnosed prior to family screening due to symptoms, ECG abnormalities or abnormal clinical examination, thereby reducing the yield of clinical screening in this cohort to 3%. Importantly, however, whilst the overall yield of screening at an individual patient level was low, a diagnosis was made as a result of family screening in over 10% of families, which is not insignificant. Relatives with a diagnosis were older at the time of screening and had a

higher prevalence of hypertension. Given the low incidence of major cardiovascular events at follow up, including sudden cardiac death and stroke, the authors suggest that a modified strategy for family screening might be appropriate for gene-elusive HCM families. There are a number of limitations, including a relatively short follow up period and a lack of cardiac magnetic resonance (CMR) imaging data, which in previous studies of family screening in sarcomeric HCM has been shown to have a higher diagnostic yield than echocardiography alone[2]. Furthermore, although the incidence of stroke was low, 22% of affected relatives developed atrial fibrillation, raising the possibility that, had these individuals not been diagnosed through family screening, they would not have been anticoagulated and may therefore have had a higher prevalence of stroke.

In addition, the lower yield of screening in genotype-elusive patients reported in this study is perhaps not unexpected. Historically, patients with genotype-negative HCM have been described to be older, less likely to have a family history, and more likely to have cardiovascular comorbidities including hypertension and obesity than patients with a confirmed sarcomeric variant[7, 9]. Recent studies have suggested a polygenic inheritance in HCM with common genetic variants contributing significantly to both the risk of developing, and overall HCM phenotype, particularly for genotype-negative individuals[10, 11]. Indeed, diastolic blood pressure has been identified as the key modifiable factor associated with the development of sarcomere negative HCM[11] and as such could offer an important intervention to reduce the likelihood of developing HCM in family members. This study provides further evidence in support of polygenic inheritance and a different natural history of genotype-elusive HCM and, as such, further strengthens the argument for genetic testing to be offered to all patients with a diagnosis of HCM, irrespective of the age of onset. Both the AHA HCM guidelines and the new 2023 ESC guidelines for the management of cardiomyopathies

recommend that first degree relatives of these patients should undergo clinical and genetic screening[4]. Genotype-negative family members can be discharged from long-term cardiology follow up, improving the cost-benefit of family screening[12], whilst genotype positive individuals should receive long-term, serial follow up.

Whether such a strategy should be applied to genotype-negative families remains unresolved. It may be considered premature to remove the recommendation for family screening in gene elusive families, particularly given the finding that a diagnosis was still made in 12% of families, suggesting that family screening is still important for this patient group, but further work is needed to identify which individuals will truly benefit. In this study, three quarters of relatives diagnosed with HCM had an abnormal ECG compared to 0.5% of unaffected relatives suggesting it could be used as an initial screening tool. Similar findings have been reported in gene positive cohorts where an abnormal ECG was identified as a strong risk predictor for developing HCM over follow up[2]. Additionally, 94% of affected relatives in this study had a phenotype at first evaluation with rare phenotype conversion over follow-up. This is in contrast to sarcomere-related disease, and could support the practice of offering a single cardiac assessment for first degree relatives of genotype negative patients rather than life-long screening. This nuance is reflected in the new ESC guidelines, which recommend that in genotype-negative families, cascade clinical screening should be performed but if no additional relatives are identified, early termination of clinical screening might be appropriate.

Another unresolved question is whether the findings of this study can be extrapolated to younger genotype-negative patients. Historically, HCM has been considered a disease of adolescence or adulthood leading to previous guidelines recommending commencing screening later in childhood. However, more recent studies have shown a high yield of

clinical screening during childhood with the majority of diagnoses made in pre-adolescence[6, 8]. As a result, the new ESC guidelines and the 2020 AHA/ACC HCM guidelines have removed the age-cut off for starting screening childhood relatives[4]. It is unclear how many probands in this study were under the age of 18 years at the time of diagnosis. A family history of childhood onset disease is associated with a higher yield of clinical screening in genotype-positive families so it is possible that the yield of screening could be higher than reported for relatives of younger index cases. Paediatric studies have suggested a similar yield of genetic testing in childhood as seen in adulthood[13, 14], but it is unknown if the phenotype and natural history of this group of patients differs to adult genotype elusive patients given the polygenic nature of sarcomere negative disease and absence of comorbidities associated with the development of a phenotype in adulthood. Further studies are needed to characterise this group of childhood patients and determine the yield of clinical screening in paediatric relatives.

The study by Neilan and colleagues is a significant addition to our existing knowledge and provides further support to the notion that one size does not fit all for family screening in HCM and that the optimal timing and intervals of clinical screening should be tailored to the individual index patient. Genetic testing is essential to identify families who will benefit most, as well as to enable those not at risk to be reassured and discharged. Genotype elusive families can be counselled that the yield of screening is lower but not negligible, and that normal baseline investigations (ECG and imaging), in adulthood at least, appear to identify the lowest risk group.

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