Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular diseases, with a prevalence of at least 1 in 500 in the general population. HCM is characterized by left ventricular hypertrophy, in the absence of other loading conditions, such as hypertension. The hallmark feature of HCM is significant clinical heterogeneity in presentation, ranging from asymptomatic patients to those who have the most serious outcomes of heart failure and sudden cardiac death. Over 1500 mutations in at least 15 sarcomere-encoding genes have been identified. The significance of cardiac genetic testing in clinical practice is 2-fold. For the proband, identification of the underlying genetic cause in some cases can clarify the cause of hypertrophy, for example, clarifying phenocopies, such as PRKAG2-glycogen storage disease and Fabry disease. The greatest utility, however, is in cascade genetic testing of asymptomatic relatives, with clear benefits either for confirming a borderline clinical diagnosis, or suspicious clinical changes suggestive of early disease, or most importantly ruling out the disease in those who test gene-negative. Identification of a silent gene carrier will guide cascade testing of additional family members, in effect clarifying their risk status. Of most benefit, a negative genetic result can reassure offspring that they are not at risk of HCM.

The escalation in our understanding of the genetic basis of HCM has been catalyzed by the implementation of next generation sequencing technologies. In response to faster and more affordable testing, commercial genetic testing for HCM now often comprises vast cardiac gene chips (ie, 50–200 or more genes). This approach, although comprehensive, also draws into sharp focus the limitations of our current knowledge. The challenges of cardiac genetic testing are increasingly documented, such as identification of variants of uncertain significance (VUS), incidental genetic findings, reclassification of variants, increased need for pretest genetic counseling, and appropriate initiation of treatments in gene carriers.

Despite the challenges, the benefit of knowing with some certainty that a family member does not carry the family mutation and can be released from clinical surveillance and worry cannot be underestimated. What, on the other hand, does it mean for the asymptomatic relative who is told they are a gene carrier? Are we presented with a unique opportunity to detect early preclinical disease, allowing therapeutic intervention to prevent the worst outcomes? Or are we inflicting unnecessary harm and worry on an individual who would never have developed clinically significant disease? In our eagerness to prevent and treat disease early, are we overlooking the increasing burden on healthcare resources and costs? The impact of cascade genetic testing measured by benefits and harms remains largely unknown (Figure 1), but should be a key component in guiding the most effective and appropriate use of this technology.

The overuse of diagnostic tests and subsequent overdiagnosis is increasingly recognized as a major side effect of technological advances. This spans all medical disciplines and is frequently seen in the setting of new emerging technologies, such as new imaging modalities for cancer detection, or the inappropriate use of population screening tests, such as prostate-specific antigen testing in early detection of prostate cancer. In 2011, it is estimated that between $158 billion and $226 billion was spent on unnecessary low-value healthcare in the United States. Initiatives such as Choosing Wisely challenge clinicians and patients to question whether the test or procedure ordered is supported by evidence, free from harm, and truly necessary.

This review aims to provide a basis for the importance of assessing benefits and harms of new technologies and to outline the evidence for the application of HCM genetic testing as a predictive tool for asymptomatic family members. There is no doubt genetic testing when used appropriately provides a powerful tool for diagnosis and management. Adequate consideration of potential harms, however, will ensure we continue to use this technology in an effective and sustainable way. We suggest practical measures that may minimize potential harms and allow the positive aspects of a genetic diagnosis to be realized.

New Genetic Testing Technologies and Complexity of Genetic Data

Throughout the history of medicine, there have been key discoveries that have revolutionized the care of patients. This...
includes the application of new technologies offering earlier and more accurate disease detection, from the discovery of the diagnostic ultrasound to cardiac magnetic resonance imaging, allowing visualization of cardiac structures in far greater detail than one could have previously imagined. The ability to more accurately diagnose structural heart disease means appropriate management strategies can be initiated with overall improved treatment of the patient. Although this is the ideal scenario, not all new technologies afford the same overall benefits, and indeed, some introduce unnecessary harms. Assessment of new technologies before their widespread integration into clinical practice is essential for a sustainable health system, with a view to defining how these might be used judiciously, taking advantage of the benefits while minimizing potential harms.

Harms can arise where a diagnostic test is performed without evidence of benefit (overuse), leading to healthy people being labeled as at risk or diseased (overdiagnosis), and more being treated unnecessarily (overtreatment). The net effect is considerable healthcare expenditure for little or no health benefit. In a climate of tightening healthcare spending, these scenarios are in agreement and support a deleterious role. In some cases, incidental findings from testing may also arise, that is findings not associated with the specific disease but often requiring further investigation. Although there is potential for harms as a result of many new diagnostic tests, awareness and strict guidelines around appropriate use are critical.

In HCM, next-generation sequencing technologies have transformed our understanding of the genetic basis of disease and the options available to our patients. The basis of the technology, massively parallel sequencing, has significantly reduced the time and costs required to perform genetic tests. Although the application of these technologies to clinical-based cardiac genetic testing panels has progressed rapidly, our ability to interpret the variant data generated is lagging because of a basic lack of understanding of the biological mechanisms underpinning the disease genes and genetic variants identified. Over 80 million genetic variants have already been reported in the human genome (www.1000genomes.org). In one healthy person, over 200 rare potentially disease-causing variants and between 12 and 20 reportable variants might be identified. Interpreting variant information for clinical use is, therefore, problematic. Among the core HCM genes, there is a low tolerance for genetic variation, and thus, the number of variants identified per sample is generally small; however, this is not necessarily true for many other cardiac expressed genes included in large panels. The probabilistic nature of variant interpretation is well described, where genetic results are considered along a continuum from benign to VUS, likely pathogenic, and pathogenic rather than a binary (yes/no) outcome (Table). Conveying this result to the family can be a challenge, and pretest genetic counseling is vital to ensure the consequences, and potential outcomes of genetic tests are understood before testing is ordered.

Most recently, the American College of Medical Genetics and Genomics has devised guidelines for determining pathogenicity of sequence variants in Mendelian disease. Evidence for causation is based around many factors, including rarity in population databases, identification in multiple unrelated patients with matching phenotypes, cosegregation with clinical disease, agreement between in silico models and conservation scores of an interruption to the protein function, and others. A move to more stringent variant classification has highlighted the need for collaborative efforts to centralize variant data and maximize the prospect of assigning causation, information that is clinically relevant to the family. The National Institutes of Health–funded Clinical Genome Resource (ClinGen) provides a platform to achieve this on a global scale, with a key goal to share data and knowledge about genetic variants via the publicly available ClinVar site (www.clinvar.com).

### Early Genetic Diagnosis and Potential for Disease Prevention

**Case 1:** A healthy 10-year-old female suffers a cardiac arrest while running to catch a train. She is successfully resuscitated and on cardiac investigation is found to have HCM with asymmetric left ventricular hypertrophy of 22 mm. Her family is informed that they have a 50% inheritance risk and undergo clinical surveillance. Her father is found to be affected, whereas her mother and brothers show no evidence of disease. Genetic testing is performed, and a gene variant MYBPC3 NM_000256.3:c.1484G>A, p.Arg495Gln is identified. This variant has been reported previously in several unrelated HCM patients and is seen at a low frequency in the Exome Aggregation Consortium database (ExAC, http://exac.broadinstitute.org) and in silico prediction models/conservation scores are in agreement and support a deleterious role. Furthermore, sequence changes of Arg495Gly and Arg495Trp have also been reported in HCM patients. Based on this evidence, the variant was classified as likely pathogenic, and cascade genetic testing was offered to family members. After careful pretest genetic counseling, her 16-year-old brother, a
competitive basketball player, is identified as a gene carrier despite normal clinical investigations.

Disease prevention remains a cornerstone of medicine and the intense focus of public health efforts. Early detection of disease, particularly in the preclinical asymptomatic phase, affords the opportunity to intervene with prevention strategies or treatments to reduce overall disease morbidity and mortality. In 1968, Wilson and Jungner wrote, “The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease, and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes may appear deceptively easy”.25 Intuitively, early detection of disease is likely to improve health outcomes. For example, early detection of high cholesterol and subsequent lifestyle modification and pharmacological therapy has been shown to reduce both cardiovascular morbidity and mortality. However, several recent examples, such as prostate-specific antigen screening in prostate cancer, have challenged the generalizability of such approaches. Without evidence of benefit, there is growing recognition that we may be creating new healthy patient populations, that is, the worried well or patients in waiting.

Preclinical detection of HCM is routinely performed worldwide as a result of cascade genetic testing of asymptomatic at-risk family members. In a disease with marked clinical heterogeneity that often develops during or after adolescence, the clinical significance of a positive gene result is entirely dependent on the age of the family member. For those identified as children, there is a greater likelihood of the clinical phenotype developing, though currently no therapies to prevent or alter the development of left ventricular hypertrophy exist in clinical practice. For those tested beyond this age, that is, adults, the approach to managing these people has evolved during the last decade, moving from a conservative view that they are part of the spectrum of HCM and should be treated and restricted from high-level exercise to a more contemporary strategy of watchful waiting.

Little is known about the natural history and outcomes of silent gene carriers, and this has created several clinical dilemmas, including frequency of clinical surveillance and whether individuals should be restricted from sports.26 Small retrospective studies suggest silent gene carriers have a benign clinical course, associated with a low risk of sudden cardiac death, and a low probability of developing manifest disease once reaching adulthood.26–28 The largest patient series to date examined 339 silent gene carriers.28 Of those who received follow-up clinical investigations during the study period, 29 of 162 (18%) had developed a phenotype. Overall, the low incidence of serious cardiac events in those without manifest HCM provides a rationale for less frequent clinical evaluation.29 Clinically, the key recommendation for this group is lifelong clinical surveillance, though there is disagreement whether they should participate in high-level competitive sports, and therefore, the recommendation is to consider this on a case-by-case basis.30

The psychological impact of being at risk of HCM has been studied; however, the impact in silent gene carriers is less well understood. Anecdotally, the clinic experience is that provided there is good support and pretest genetic counseling, most patients adjust well to a positive carrier status. In a series of 89 silent gene carriers, self-reported health-related quality of life and psychological well-being (anxiety and depression) were either similar or significantly better than general population normative data.34 Indeed, the strongest indicators of poor physical quality of life was development of manifest disease and perceived negative consequences of gene carriership. The motivation for pursuing cascade genetic testing among family members has also been investigated. Christiaans et al surveyed mutation carriers regarding their experience of undergoing cascade genetic testing, with 90% reporting “because it is hereditary and I wanted to know”; 87%, “because I wanted to know for myself”; and 67%, “because of my children” as reasons for undergoing testing.35 There were 95% of participants who were satisfied with the process of genetic testing in the multidisciplinary cardiac genetic setting, and only 4% indicated that they regretted finding out they are a mutation carrier.

In a disease with no cure that leads to seemingly irreversible hypertrophy, fibrosis, and disarray of cardiomyocytes in the left ventricle, the long-term goal of research has always been focused around disease prevention in HCM. In this setting, effective identification of healthy individuals who are likely to convert to an HCM phenotype are highly sought after with the potential to provide a larger therapeutic window to initiate early prevention strategies. These individuals represent a real opportunity to develop a cure. Studies in animal models of HCM have shown that early treatment

<table>
<thead>
<tr>
<th>Genetic Result</th>
<th>Consequences for the PROBAND</th>
<th>Consequences for the FAMILY</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variants of potential clinical importance identified (benign)</td>
<td>An indeterminate gene result does not exclude HCM, but reassessment of the phenotype should be considered</td>
<td>Cascade genetic testing cannot be offered to the family. At-risk relatives are advised to be clinically assessed according to current guidelines</td>
</tr>
<tr>
<td>Variant of uncertain significance identified (VUS)</td>
<td>Efforts to delineate pathogenicity of the variant are required, including cosegregation studies involving phenotyped family members</td>
<td>Where pathogenicity of a variant is under question, it cannot be used in the family. Cascade genetic testing cannot be offered.</td>
</tr>
<tr>
<td>Pathogenic mutation identified (pathogenic or likely pathogenic)</td>
<td>Confirm clinical diagnosis, limited therapeutic and prognostic application in HCM</td>
<td>Cascade genetic testing of asymptomatic family members is available following genetic counseling</td>
</tr>
<tr>
<td>Incidental or secondary genetic finding</td>
<td>Action regarding incidental findings must be discussed with the proband pretested.</td>
<td>Genetic counseling to determine clinical and genetic impact to family members is available</td>
</tr>
</tbody>
</table>
with pharmacological agents, such as diltiazem and losartan, may prevent the onset of disease or delay progression. Most recently, preliminary studies in silent gene carriers with HCM have shown that preclinical therapy may improve early left ventricular remodeling in HCM, with several other randomized control studies currently in progress (such as HALT [Hypertrophic Regression with N-Acetylcysteine in HCM], LIBERTY [Effect of Eclazoline (GS-6615) on Exercise Capacity in Subjects With Symptomatic HCM], and VANISH [Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM] studies; http://clinicaltrials.gov). The INHERIT (Inhibition of the Renin Angiotensin System with Losartan in Patients with HCM) study, a recent randomized trial of losartan, an angiotensin receptor blocker which has previously shown promising results in transgenic mice, showed no regression of disease; however, it highlighted some important points. First, feasibility of large multicenter trials that were once considered impossible for a relatively rare disease have been successfully demonstrated. Second, the preclinical disease stage is further highlighted as the critical window for effective intervention, and indeed, the VANISH trial is focused on this time point. Rather than using regression of disease as a primary end point, this trial aims to prevent disease onset, which if achieved will be an exciting step forward.

**Benefit of Eliminating Risk and Uncertainty**

**Case 2:** A 42-year-old male who was diagnosed with HCM as a teenager collapsed while exercising and could not be resuscitated. He was a fit man and did not regularly see his cardiologist as he never felt unwell. Because of limited access to genetic testing in 2002, the decedent’s 44-year-old brother attended for ongoing periodic clinical screening. These investigations have not shown evidence of disease, but this does not alleviate his anxiety regarding the risk to his children. Research genetic testing recently identified a known pathogenic variant in MYBPC3 NM_000256.3:c.772G>A, p.Glu258Lys. This variant has been reported in numerous unrelated HCM probands, it is also seen at a frequency of 10% of families; though with more stringent variant classification methods. This may parallel the notion of a false positive, not in the sense of a technical sequencing false positive, but a variant interpretation which initially was conveyed to the patient as a positive result but subsequently found to be false. In HCM, this reclassification has been estimated to occur in at least 10% of families; though with more stringent variant classification criteria in use, this might be expected to be much less frequent in future. Nevertheless, it highlights the importance of periodic re-evaluation (every 1–2 years) of all variants in the setting of rapidly emerging general population data.

**Recategorization of Variants and Impact on Clinical Relevance**

**Case 3:** A 52-year-old man with a longstanding diagnosis of HCM and known family history of disease underwent genetic testing. Two variants were identified, a known pathogenic frameshift in MYBPC3 NM_000256.3: c.2864_2865delICT, p.Pro955Argfs, reported in multiple unrelated HCM probands and causing a premature truncation of the protein, and a deletion in TCAP NM_003673.3: c.37_39delGAG, p.Glu13del, reported at the time as likely pathogenic. The proband’s sister aged 40 years and with no clinical evidence of disease underwent pretest genetic counseling and decided to pursue cascade genetic testing. Given there were 2 variants, there was a 3 in 4 chance she would inherit at least 1 of the variants. She was found to carry only the TCAP deletion, that is, a deletion of a single amino acid, and although it has been previously reported in unrelated HCM probands, it is also seen at a frequency of 2% of the National Heart, Lung, and Blood Institute Exome Sequencing Project and other reported control populations, suggesting a likely benign role. The reclassification of this variant meant the proband’s sister’s carrier status was incorrect and that she and her children were in fact not at risk of disease.

With new knowledge arises change in our understanding of disease causation and pathogenesis. Although variant interpretation and classification systems have been developed and refined, they need to take into account rapidly evolving human genetic databases, such as the ExAC database, 1000 Genomes Project, Exome Variant Server, and most recently, the Genomics England 100 000 Genomes Project. All of these databases have arisen because of the dramatic and rapid advances in genetic technologies. Although once we would be satisfied seeing a potentially pathogenic variant being absent from 200 control alleles, we now often compare to over 50 000 control exomes and genomes. As a result, over time, variant status can change, being downgraded from pathogenic to VUS or benign or, in some instances, upgraded from VUS to pathogenic. This may parallel the notion of a false positive, not in the sense of a technical sequencing false positive, but a variant interpretation which initially was conveyed to the patient as a positive result but subsequently found to be false. In HCM, this reclassification has been estimated to occur in at least 10% of families; though with more stringent variant classification criteria in use, this might be expected to be much less frequent in future. Nevertheless, it highlights the importance of periodic re-evaluation (every 1–2 years) of all variants in the setting of rapidly emerging general population data.
Clinical Implications of Incidental Gene Variant Findings

Case 4: A family presents to a specialized cardiac genetic clinic after the identification of an incidental genetic finding in AKAP9 NM_005751.4:c.4342A>G, p.Ile1448Val during whole exome sequencing for investigation of benign hereditary chorea. AKAP9 is the gene responsible for LQT1, and the finding of a VUS in a potentially lethal cardiac arrhythmia syndrome precipitates an array of cardiac investigations and segregation studies among the family members. No family members are found to have any clinical evidence of long QT syndrome and were reassured that the AKAP9 variant is unlikely to be of clinical importance. No further investigation was recommended. Three years on, this variant is known to be present in the general population at a frequency of 0.05% in the ExAC database, and the variant has been downgraded to a likely benign status.

Discovery of a clinically actionable finding during investigation for an unrelated problem is not a new concept in medicine. The example of a lung lesion identified during routine imaging of the cardiac structures is well described. An ethical dilemma ensues, where issues may arise regarding the patient’s preferences to receiving the unexpected information, the uncertainty and fear generated, and the medical professional’s flow-on decisions that likely lead the patient down a pathway of additional testing. Our reflex response to such findings is often overwhelming gratitude that disease was detected early and an eagerness to do everything possible to avoid unfavourable outcomes, both by the patient and the clinician. This existential fear of death drives much of the response to an uncertain diagnosis, and for clinicians, there may be additional fear of litigation if they fail to do everything possible. The response to an incidental finding is, therefore, just as much a part of the problem. In our example of an incidental lung lesion identified during routine imaging, although the pathway of investigation that follows is contentious, it is a well-trodden track. Incidental findings in genetic medicine pose much greater uncertainty, with little knowledge about whether the variant is truly capable of causing disease.

Incidental genetic findings are an increasing reality in cardiac genetics and present an ethical challenge. Although a clinical incidental finding may be resolved quickly (eg, a liver lesion detected during a lung computed tomographic scan is quickly resolved as a benign cyst on liver ultrasound imaging), incidental genetic findings may potentially remain unresolved for several years because knowledge about the gene or the specific mutation is poorly understood. In the most extreme circumstances, incidental genetic findings will include reporting of important variants in noncardiac genes (eg, familial cancer genes) and, therefore, result in the patient being given information completely unrelated to the purpose of the genetic test. It is difficult to argue that these are in fact unexpected or incidental results when a whole exome sequencing or whole genome sequencing approach of screening all 22,000 genes is used, and for this reason, there is a move to recognize these as secondary genetic results and highlights the role of pretest genetic counseling and informed consent.

The American College of Medical Genetics and Genomics’s recommendations for the reporting of incidental findings in clinical exome and genome sequencing controversially provide a list of 56 genes in which actionable variants should be reported back to the patient, regardless of the purpose of the test and the patient’s preferences for knowing this information. These reportable variants pose a major clinical challenge, with between 12 and 20 clinically reportable variants identified per healthy individual, and in 3% to 5% of patients referred for investigation of a disease phenotype.

The issue of incidental genetic findings is not just limited to whole exome sequencing/whole genome sequencing approaches. Cardiac gene panel testing can also present the challenges of unexpected findings. More often, probands who have a genetic test for HCM will have variants in other cardiac genes reported, clouding the value of the result. This phenomenon results in confusion for the patient, but also adds complexity to the response of the clinician in investigating these results. For example, an HCM patient who returns a VUS result in the DSP gene may pose a clinical dilemma. DSP is a desmosome gene associated with arrhythmogenic right ventricular cardiomyopathy, a disease clinically distinct to HCM. Thus, a novel, rare missense variant in DSP is unlikely to be the cause of disease in a person with HCM, and indeed, this gene is known to be somewhat tolerant to variation. Despite this, there is a trend to pursue additional cardiac investigations in these families, in search of a phenotype that might explain the uncertain genetic result. Strategies to minimize incidental and uncertain findings (ie, more targeted gene panels) and family management in high-volume specialized clinics with expertise in HCM genetics will certainly minimize downstream delivery of low-value and costly health care.

A Balanced Approach to HCM Genetic Testing: 6 Key Points

Although there may be a lack of evidence to suggest there is overall benefit for early disease detection in HCM, the purpose of this review is not to dishearten clinicians from the true value of genetic testing in HCM and other inherited cardiac diseases. We hope to have shone a spotlight on the potential limitations, so that this technology can be used in the most effective and appropriate way, with the overall goal to effect some improvement in clinical care. The following 6 points outline the key practical clinical implications that serve as a guide to avoiding some pitfalls of genetic testing and minimizing harms to the patient (Figure 2).

Choose the Appropriate Genetic Test

With the multitude of genetic tests commercially available, there is great importance in choosing the most appropriate test. Confining your analysis to a smaller number of genes (ie, targeted panels over more broad approaches such as clinical exome/imaging sequencing) will reduce the number of uncertain and incidental variants. In the setting of a proband with a confirmed clinical diagnosis of HCM, screening of 10 to 15 genes is entirely adequate. Performing genetic tests that encompass more genes in this instance needs to be questioned, though it is becoming increasingly difficult as laboratories...
Continue to expand the available gene panels. An important exception, however, are families with multiple affected individuals, allowing segregation of uncertain variants to clarify causation, though this approach may be better suited to the research setting.

**Be Confident That the Variant Identified in the Proband Is Actually Disease-Causing**

If there is any doubt regarding the pathogenicity of the variant in the proband, no cascade genetic testing should be undertaken in the family. Such VUS findings require further assessment and re-evaluation and often form the basis of ongoing research studies. For the clinician without expertise in genetics, there are some general aspects of a variant that might act as a red flag for questioning a result. First, the variant being reported should be in a gene previously implicated in HCM. Second, the variant in many cases should have been reported previously in unrelated probands with confirmed HCM, though exceptions to this might occur with radical mutations, leading to loss of function in a gene known to result in disease, for example, MYBPC3. Third, the variant should be exceedingly rare in general population databases, and this can be re-evaluated as new larger data sets are published online. These are not fail safe criteria, but should serve as a guide to questioning a laboratory’s clinical reporting of variants. If we are to realize any of the benefits of HCM genetic testing, basing the cascade genetic testing on incorrect gene variant results must be avoided.

**Not Every Family Member Needs Cascade Genetic Testing**

Cascade genetic testing of at-risk family members needs to be considered on a case-by-case basis. Weighing up the potential benefits with the possibility of causing harm is essential. Key to this decision is the preferences of the family member. How a lay person can understand and make decisions regarding complex genetic information is not well studied, but must become a priority if we hope to facilitate informed choice. For many, they may be content to attend for clinical investigation periodically, knowing that no treatments would be initiated unless there was evidence of clinical disease. Potential for insurance or employment discrimination may also be considered, though will differ between countries; however, legislation, such as the Genetic Information Non-Discrimination Act (GINA), highlights how the United States of America has worked to minimize some of these potential harms. Detailed pretest genetic counseling is essential in facilitating this decision; however, future research to elucidate effective methods to promote informed choice will be needed.

An area where informed choice is problematic is that of testing children. Genetic societies worldwide have acknowledged this, and many have developed strict guidelines on processes around testing children, with the key premise being that there should be some imminent health benefit. In HCM, it can be argued whether a positive genetic result of an asymptomatic child will hold any immediate medical benefit, and for this reason, comprehensive genetic counseling with involvement from a child psychologist if practical is advocated.

**Silent Gene Carriers Are Not Patients**

Silent gene carriers have arisen as a direct result of more widespread genetic testing. As such, in the absence of a clinical phenotype, they should not be seen as patients but rather those under surveillance. Current American Heart Association guidelines suggest clinical follow-up of silent gene carriers every 3 to 5 years after the age of 18 to 21 years and, importantly, do not suggest restriction from competitive sports. How we speak to the asymptomatic family members about the outcomes of cascade genetic testing, therefore, needs to reflect this. This also highlights the need for evidence-based guidelines around management of silent gene carriers, to elicit greater confidence from the clinicians managing the families, and to avoid overzealous and unnecessary clinical investigations.

**Reasonable Response and Investigation of Uncertain Variants, Including Incidental Findings**

If variants in genes not related to a phenotype of HCM are identified, then by definition they are uncertain. The interpretation of a genetic result in a clinical setting must be limited only to those genes with clear established association with the phenotype in question. Investigation of new genes must be confined to research studies and centers with significant cardiac genetic expertise. The identification of uncertain and incidental variants can be problematic, but just as important is the clinician’s flow-on decisions. Care should be taken to avoid a reflexive reaction of comprehensive clinical investigations and segregation studies in the family members where there is no clear benefit.

**Pretest Genetic Counseling and Disease Expertize Makes for Informed Decision-Making**

Comprehensive pretest genetic counseling is an essential and necessary step before genetic testing. This means ensuring the participant is informed and aware of the possible outcomes, discussion of psychosocial considerations, and supporting an autonomous decision that is based on individual preferences and values. Another aspect of informed choice when considering cascade genetic testing is accurate and appropriate risk information, taking into account varying levels of health literacy across populations. Further understanding of the natural
history and clinical outcomes for silent gene carriers will provide a more sound evidence base on which family members can make a truly informed decision about whether to pursue genetic testing. The experience and expertise of high-volume specialized multidisciplinary HCM centers is increasingly valuable in this setting.23

Conclusions

Implementation of new technologies for early diagnosis, improving outcomes, and survival is commonplace in medicine. Foremost, the emergence of new genetic sequencing technologies has resulted in an exciting new phase in the field of cardiac genetic testing. In HCM, the potential for both benefits and harms is one that must be considered. Given the many considerations and potential outcomes of testing asymptomatic at-risk individuals, a balanced approach needs to be undertaken. This should consider the clinical situation, the patient needs, and the available genetic testing options, with the overall goal to contribute some improvement in clinical care.

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None.

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