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Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group

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Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement

Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group

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ABSTRACT

The sudden unexpected death of a young person can have profound implications for the surviving family members beyond those associated with bereavement and the immediate sense of loss. Among these other sequelae may be a concern that the sudden death was caused by a genetic condition and that other family members may suffer the same fate. Increased awareness of these inherited conditions and the transfer of the techniques of genetic testing from the research laboratory into the clinical arena make it possible to identify genetically affected individuals before they have symptoms or experience sudden cardiac death. The development of such tests has been paralleled by the emergence of preventative treatments, which have amplified the clinical importance of such tests. This document provides recommendations regarding the clinical indications for these tests based on the best available evidence.

In the UK, the fact that effective evaluation of relatives, guided by genetic testing, can prevent further deaths in the family has been acknowledged in the National Service Framework for Coronary disease.¹ It is a quality requirement of this Framework that, "when sudden cardiac death occurs, NHS services have systems in place to identify family members at risk and provide personally tailored, sensitive and expert support, diagnosis, treatment, information and advice to close relatives." Although genetic testing forms a part of this process, its role varies with different tests and in different conditions. The overall objective of this document is to provide recommendations about the clinical indications for specific genetic tests for the familial sudden cardiac death syndromes based on the best available evidence. The clinical questions covered by this statement relate to the specific clinical circumstances in which genetic testing is likely to be most useful and the target population is the group of patients and their relatives considered to be at possible risk from one of these syndromes. The target users of this statement included all healthcare professionals involved in the management of this population.

DEVELOPMENT OF THE POSITION STATEMENT

A development group was selected by the Council of Heart Rhythm UK, consisting of people from all the relevant professional and lay groups: arrhythmologists, clinical geneticists, electrophysiologists, patient representatives and specialists in heart muscle disease. An experienced genetic counsellor

made additional significant input into the final document. A comprehensive review of evidence in English language publications about the role of genetic testing in familial sudden cardiac death syndromes was undertaken using systematic methods recommended by the AGREE tool.² A preliminary discussion document was produced, with initial recommendations, grades of recommendation and ranking of evidence upon which these recommendations were based. This document, together with discussion documents from a clinical geneticist and SADSUK, the patient support group, were circulated to all Development Group members. The costs of current genetic tests available at a large testing centre were made available to the Group and specific recommendations in the preliminary document amended and agreed at a meeting on 18 December 2006. Recommendations were made after discussion of specific key clinical scenarios using consensus techniques. The rarity of these conditions is such that randomised, controlled data are not available or not appropriate and the evidence upon which specific recommendations were based is cited in the document. A draft position statement was produced by the Group's chairmen and was agreed by all members before being sent to external expert reviewers for comment. The target users of this statement include all healthcare professionals involved in the management of patients and relatives suspected of being at risk from the inherited sudden death syndromes. The potential health benefits and risks of the recommendations were considered and recommendations contained within the statement have been piloted at a multidisciplinary inherited cardiac disease clinic in the North West of England.

FACTORS INFLUENCING CLINICAL ROLE OF GENETIC TESTING IN SPECIFIC CONDITIONS

A number of factors should be taken into consideration with regard to recommendations concerning genetic testing in specific conditions:

Sensitivity (yield) of testing

The sensitivity of genetic testing to define the underlying mutation in an affected person varies greatly between the different conditions but, with very rare exceptions (such as Timothy syndrome), falls significantly below 100% even when the clinical diagnosis is not in doubt. This is perhaps not surprising given that most of these conditions show significant genetic heterogeneity (more than one gene causing the disease) and many gene

defects remain undiscovered. As a consequence, it is rarely possible for genetic testing to completely exclude the possibility that a particular patient has the clinical condition for which they are being tested. The notable exception to this rule occurs when the genetic basis for the clinical abnormality has already been identified in another member of the family. Under these circumstances genetic testing can be considered essentially 100% sensitive and is likely to provide an extremely effective means of screening family members (see section on cascade screening below).

Specificity of genetic testing

In the UK there is a nationally integrated service for genetic testing (United Kingdom Genetic Testing Network) in which all participating laboratories adhere to quality criteria and standards of work within clinical governance arrangements. In addition, the tests offered on the Network undergo a rigorous process of evaluation to ensure test validity. Clearly it is important to have evidence that a particular gene mutation has a high probability of being the cause of disease before a molecular diagnosis is established and it is necessary to have knowledge of the common DNA variations (polymorphisms) present in the relevant genes to assess the clinical relevance of a particular result. If an identified mutation is already known to segregate with disease in other families with a given phenotype and is not present in significant numbers of controls then the test specificity will approach 100%. If the specific mutation is previously undescribed, but is absent in controls (ie, not a common polymorphism) then the testing laboratory should be able to provide the clinician with an estimate of the likelihood of the mutation being associated with disease, based on molecular genetic predictions and/or further studies (often requiring testing for segregation with disease in other family members). Thus, interpretation of genetic test results can be complex, frequently requiring specialist clinical genetics expertise.

Implications of the test result on patient lifestyle, clinical management or prognosis

If the results of a genetic test have a direct bearing on patient lifestyle, clinical management or prognosis over and above information gleaned from clinical assessment, then the test is likely to have value for the particular patient being tested. The extent to which this is the case will vary from condition to condition.

Implications of the test result for the screening of family members

As already discussed, if the genetic basis for the clinical condition can be reliably identified in one member of a family, subsequent genetic testing is likely to provide an extremely effective means of screening other family members as further clinical evaluation, risk stratification and prevention strategies can be focused on gene carriers. This approach has the potential to reduce anxiety, and the requirement for clinical evaluation and follow-up, for unaffected people and improve the cost efficacy of clinical screening. The extent to which genetic screening is better than clinical screening alone will be condition-specific and dependent on the sensitivity and specificity of the available methods of clinical evaluation. In general, the familial sudden cardiac death syndromes show considerable variability of clinical penetrance (with some

affected people showing little presymptomatic evidence of disease), leading to high rates of false-negative clinical assessments. As the main aim of screening is to assess risk of sudden cardiac death, this can be a major disadvantage of clinical methods. In particular, clinical forms of “cascade” screening (see below) of relatives will fail prematurely with each false-negative clinical result in a parent or sibling with offspring. Conversely, even expert clinical assessment can lead to false-positive diagnoses (with non-affected people being labelled as affected) owing to the presence of phenocopies (other clinical conditions with some similar features). This can result in inappropriate treatment in addition to unnecessary concern and insurance implications. It should not be forgotten that a broader clinical utility of genetic testing (reproductive decisions and psychosocial support) will also be important for many people.

Cost and cost efficacy of genetic testing

The cost of a particular genetic test to screen for a new mutation in a proband is dependent on the number and size of genes that are analysed and this varies from condition to condition. In many disorders costs are minimised by taking a “targeted” approach—that is, testing for just the most commonly involved genes (in general it is not possible in inherited sudden cardiac death syndromes to test for specific mutations as all are individually rare). Once a mutation has been identified, testing in relatives is much easier and less expensive (yielding an increased chance of cost effectiveness in large families). It can be seen from the considerations above that calculation of the cost efficacy of performing genetic tests in particular clinical situations is not a simple process. The rarity of these conditions is such that large randomised trials comparing genetic-versus-clinical approaches do not exist: cost-efficacy analyses are scarce³ and require assumptions that greatly limit their interpretation. There have been previous attempts to prioritise the role of genetic testing in various different conditions,⁴ using a scoring system based on diagnostic yield of testing and relevance to clinical management. In the current document we have made specific recommendations relevant to UK practice on the following clinical scenarios and conditions: sudden unexpected death under the age of 40 years; congenital long QT syndromes (LQTS); catecholaminergic polymorphic ventricular tachycardia (CPVT); Brugada syndrome (BS); familial dilated cardiomyopathy (DCM) associated with atrioventricular (AV) block; hypertrophic cardiomyopathy (HCM); and arrhythmogenic right ventricular cardiomyopathy (ARVC).

CASCADE GENETIC SCREENING

Cascade genetic testing is the process whereby a positive genetic test result is used to determine the risk status of people within a pedigree. The process usually starts with a positive clinical diagnosis in an affected family member (“the proband”). Once the mutation causing the disease has been identified, the result can be used very easily and accurately to determine which other members of the family have inherited that particular mutation and are therefore at risk of developing disease and require appropriate clinical management. The cascade proceeds from the proband to first-degree relatives (parents, children and siblings) and continues via those people who test positive to *their* first-degree relatives. Contact with family members is generally made by the proband or more recent people within the cascade. Direct approaches by doctors to other family members

have been tried in some countries but this is not common practice in the UK. The cascade stops in any particular branch of a family when it is shown that the person being tested has not inherited the causative mutation—for example, it is unnecessary to test the children of a person who has not inherited the disease-causing allele.

Cascade genetic testing offers a number of advantages over routine clinical screening for inherited cardiovascular disease, not least of which is the absence of the possibility of a falsely reassuring normal clinical test in a person who is in fact a non-penetrant gene carrier. Such a person may still be at some personal risk of developing overt cardiac disease and will have a risk of transmission of the disease gene to future generations. However, as it is not always possible to find a mutation in all families and because occasionally a result is generated the significance of which is not immediately obvious, it is important that probands and family members receive appropriate and accurate genetic counselling before the cascade process begins.

GENETIC COUNSELLING

Genetic counselling can be defined as the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- ▶ Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- ▶ Education about inheritance, genetic testing, management, prevention, resources and research.
- ▶ Counselling to promote informed choices and adaptation to the risk or condition.

In the UK, most genetic counselling is currently provided in regional genetic services by multidisciplinary teams including medically trained clinical geneticists and genetic counsellor colleagues. Genetic counsellors contribute particularly to the educative and psychosocial aspects of genetic counselling. There is a registration mechanism for genetic counsellors in the UK organised by the Association of Genetic Nurses and Counsellors which is a subgroup of the British Society of Human Genetics.

EXPERT CLINICAL AND DETAILED FAMILY ASSESSMENT

Reference is made throughout the document to *expert clinical and detailed family assessment*. This may exist in a number of settings but will involve a multidisciplinary team including a cardiologist with specialist experience of management of these conditions and individuals with specific clinical genetics training and expertise.

RECOMMENDATIONS FOR GENETIC SCREENING

Sudden unexpected death under the age of 40 years

When a young person dies suddenly for no obvious reason, and the heart is considered structurally normal after expert cardiac pathological review and negative toxicological testing, the possibility that death was a consequence of one of the familial sudden death syndromes is raised. In general, there are two different potential approaches to the evaluation of the surviving relatives. The most common approach is based on comprehensive and expert clinical assessment of surviving first-degree relatives, with targeted genetic analysis in those with clinical abnormalities.^{5,6} An alternative approach is based on initial genetic analysis of material taken at post mortem from the

sudden death victim (“molecular autopsy”).⁷ These approaches are not mutually exclusive.

Assessment of surviving relatives

Behr *et al* performed a restricted clinical evaluation (including ECG, echocardiogram and Holter monitoring) of 109 first-degree relatives of 32 cases of sudden unexplained cardiac death (sudden arrhythmic death syndrome (SADS)) identified throughout the UK and showed that 22% of these families had evidence of inherited cardiac disease, with the majority having clinical features suggestive of LQTS.⁵ Tan *et al* evaluated 183 surviving members of 43 families with at least one sudden death victim less than 40 years of age.⁶ All relatives studied underwent ECG (rest and exercise) and echocardiography; selected patients underwent flecainide testing or magnetic resonance imaging when clinically indicated. A clinical diagnosis of inherited disease was made in 17 families (40%) and members of 16 of these families subsequently underwent genetic testing using a candidate gene approach driven by the clinical abnormalities. The breakdown of clinical diagnoses was CPVT (five), LQTS (four), BS (two), LQTS/BS (one), ARVC (three), HCM (one) and familial hypercholesterolaemia (one). Molecular genetic analysis provided confirmation in 10 families. Together, these reports suggest that familial syndromes can be identified in a substantial minority of autopsy-negative sudden death victims using this approach.

“Molecular autopsy”

Incomplete penetrance and variable expression are common in arrhythmia syndromes such as LQTS and CPVT and consequently lead to “concealed” forms of these disorders.^{8,9} According to Priori *et al*,⁸ LQTS has a penetrance of only 25% among families and conventional clinical diagnostic criteria only had 38% sensitivity in correctly identifying carriers of the familial genetic defect. Furthermore, 17% of RyR2 gene carriers from CPVT families displayed no phenotypic features, and a further 75% of genetically affected parents transmitted the disorder but were asymptomatic.^{8,10} Therefore, clinical assessment of surviving family members of SADS victims may not be enough to detect LQTS or CPVT in relatives. A molecular diagnosis in the sudden death victim potentially overcomes this limitation and provides the means by which further deaths in surviving family members can be prevented. The limited data available suggest that a diagnosis relevant to family members’ prognosis and future management could be made in possibly 30% of sudden arrhythmic death families independently of expensive and time-consuming clinical evaluation.

Two small postmortem series have identified long QT gene mutations as causes of sudden cardiac death in a small proportion of young sudden death victims.^{11,12} Recently, Tester *et al* completed a much larger molecular autopsy series of sudden arrhythmic death.⁹ Comprehensive mutational analysis of all 60 translated exons in the LQTS-associated genes—KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2—and targeted analysis of the CPVT1-associated, RyR2-encoded cardiac ryanodine receptor was conducted in a series of 49 sudden cardiac death victims. Over one-third of SADS cases harboured a presumed pathogenic cardiac ion channel mutation, with mutations in RyR2 alone accounting for nearly 15% of the cases.

Although a “molecular autopsy” might at first sight seem a more logical approach to identifying possible inherited sudden death syndromes in sudden death victims than clinically guided testing in the surviving relatives, the method has a number of

disadvantages if used in isolation: (a) in the absence of a detailed clinical history from the sudden death victim (most have never presented to medical attention before death), it is not possible to “target” genetic testing; (b) genetic testing of the victim may not identify some cases of ion channelopathy or cardiomyopathy (tests far from 100% sensitive) that clinical examination of relatives may disclose; and (c) the limited studies performed to date (see above) do not suggest a greater yield of this approach than the more conventional method of genetic testing of surviving relatives guided by clinical features.

Recommendations

1. **The sudden unexplained death of a young person (<40 years) should prompt comprehensive and expert clinical assessment of surviving relatives, with targeted genetic analysis in those with clinical abnormalities.**
2. **Material appropriate for DNA analysis should be obtained from the deceased person at the time of the postmortem examination, and targeted genetic analysis from this material should be considered in the context of the clinical details of the death and clinical assessment of the surviving family members.**

Congenital LQTS

The relative clinical usefulness of genetic testing in the congenital LQTS is dependent to some extent upon the clinical and molecular subtype. The Romano–Ward syndrome is the most common clinical syndrome associated with a long QT interval, typically presenting with ventricular arrhythmias, syncope or sudden death in the absence of extracardiac features. Over 400 mutations in five cardiac channel-encoding genes have been identified; LQT1 (KCNQ1-encoded potassium channel [I_{Ks}] mutations), LQT2 (KCNH2-encoded potassium channel [I_{Kr}] mutations), LQT3 (SCN5A-encoded sodium channel mutations) and LQT5 and LQT6 (KCNE1- or KCNE2-encoded potassium channel β -subunit mutations). In patients with a definite clinical diagnosis of the congenital LQTS (Schwartz and Moss score ≥ 4),¹³ the sensitivity of genetic testing for these five LQTS-associated channel genotypes is approximately 70%¹⁴ and a positive result has considerable relevance for clinical management and prognosis. The triggers for lethal and non-lethal cardiac events differ depending upon genotype,¹⁵ and knowledge of genotype allows specific lifestyle advice to be given to the patient. The most commonly prescribed treatment, oral β -blockade, differs in its efficacy according to genotype¹⁶ and may be ineffective in patients with LQT3. Prognosis varies according to genotype both in asymptomatic patients¹⁷ and those taking β -blockers.¹⁶ Once the genetic basis for the condition has been determined, genetic testing is likely to be much more effective and cost effective than clinical methods of screening family members; as in a number of other conditions for which a scoring system of “diagnostic” clinical features has been proposed,¹³ clinically derived false-positive and false-negative results are common. For all these reasons, an extremely strong case can be made for genetic testing of patients presenting with features typical of the congenital LQTS.

Recommendation

- **Genetic testing is recommended for all patients with a firm clinical diagnosis of the congenital LQTS irrespective of the presence of symptoms or the existence of other family members.**

When a family history is absent or when clinical features are uncertain or “borderline” according to clinical scoring methods,

there is a significant fall-off in the yield of genetic testing from 70% to about 45%.¹⁴ Given the fact that a negative genetic test does not exclude the diagnosis, it is likely that genetic testing will be unhelpful from a diagnostic point of view in the majority of such cases. Consequently, it seems prudent to restrict such diagnostic testing to clinical environments in which expert clinical and detailed family assessment is available.

Recommendation

- **Genetic testing is not recommended for diagnosis of uncertain or “borderline” congenital LQTS outside the setting of expert clinical and detailed family assessment.**

The Jervell and Lange-Nielsen syndrome is a recessive form of the LQTS characterised by a prolonged QT interval, congenital deafness and a high incidence of sudden death in childhood. It is caused by homozygous or compound heterozygous mutations in two genes (KCNQ1 and KCNE1) in at least 80% of cases.⁴ Consequently, genetic testing is rapid and has a high yield. In addition, it confers prognostic information relevant to important management decisions as patients with Jervell and Lange-Nielsen KCNQ1 mutations have an almost sixfold greater risk of arrhythmic events.¹⁸

Timothy syndrome is characterised by a long QT interval, malignant arrhythmias, webbing of fingers and toes, congenital cardiac abnormalities and autism.¹⁹ As all patients share the same mutation in the CACNA1c gene, genetic testing is fast, cheap and sensitive. The diagnosis carries important prognostic information and is relevant to reproductive counselling.

Andersen syndrome is characterised by a long QT interval, ventricular arrhythmias, periodic paralysis and skeletal developmental abnormalities.²⁰ It is caused by mutations in KCNJ2, which encodes the inward rectifier K⁺ channel Kir2.1. Genetic testing has high yields and is important for reproductive counselling.

Recommendation

- **Genetic testing is recommended for patients with a clinical diagnosis of Jervell Lange-Nielsen, Timothy or Andersen syndromes.**

Catecholaminergic polymorphic ventricular tachycardia

CPVT is a syndrome of exercise- or emotion-induced polymorphic (often bidirectional) ventricular tachycardia or ventricular fibrillation in children or young adults, occurring in a structurally normal heart. In about 30% of cases, the family history reveals one or multiple premature sudden deaths that usually occur during childhood.^{21 22} Mutations in the RyR2-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT^{10 23 24} (CPVT1) and account for about 50% of cases. A rare subtype of CPVT arises in an autosomal-recessive fashion with mutations in calsequestrin encoded by CASQ2 and is known as type 2 CPVT (CPVT2).^{21 22}

Although the clinical presentation of CPVT is similar in many respects to the LQTS there are important differences that are relevant to genetic testing. CPVT appears to be a more malignant condition, as many people are asymptomatic before the index lethal event and the majority of cardiac events occur before 20 years of age. Affected people are advised to avoid exercise-related triggers and start prophylactic β -blockade with dose titration guided by treadmill testing. In up to 40% of cases, particularly male subjects, β -blockade is ineffective in the

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suppression of ventricular tachycardia and an implantable cardioverter-defibrillator (ICD) may be indicated.^{10 25 26} In a mean follow-up of 2 years half the number of patients implanted with an ICD and receiving β -blockers were treated appropriately. Clinically the condition is difficult to diagnose in asymptomatic family members as the ECG and echocardiogram are completely normal at rest. Exercise stress testing is advised in family members in order to identify exercise-induced ventricular arrhythmias but the sensitivity of this clinical test is unknown.

Although the diagnostic yield from genetic testing is less than that for the LQTS (about 50%) in patients with typical clinical features, a positive genetic test is of great value for the individual patient (given the prognostic implications) and for screening family members (given the difficulties in clinical screening methods). The RyR2 gene is large and a "targeted" approach is usually undertaken, in which only exons that have been previously implicated are examined.

Recommendation

- ▶ **Genetic testing is recommended in individuals with clinical features considered typical of CPVT following expert clinical assessment.**

Familial DCM associated with AV block

Although the genetic basis for familial DCM is unknown in the majority of cases, a specific gene abnormality (defects in the lamin A/C (LMNA) gene) has been identified in over 30% of cases of familial DCM associated with AV block.²⁷ Lamins A and C are important constituents of the nuclear lamina, the proteinaceous network underlying the inner nuclear membrane, and defects in this membrane can lead to progressive cardiac myocyte death and AV nodal/bundle branch conduction abnormalities. Skeletal muscle involvement—for example, as indicated by raised creatine kinase levels in plasma, is common. Genetic testing is straightforward (only one gene involved) and has significant clinical implications as carriers of these mutations are at risk of sudden death, even after cardiac pacing; ICD implantation should be considered for such people, although data are sparse. The disease shows an age-dependent penetrance (many developing the condition before age 40 years) and current evidence suggests that eventually most carriers develop the phenotype: as a consequence genetic testing provides a particularly effective means of early identification of carriers among family members.

Recommendations

1. **Genetic testing is recommended for patients with a combination of AV block and DCM, or where the family history shows evidence of DCM and AV block in different relatives.**
2. **Genetic testing is not recommended for patients with unexplained DCM alone or unexplained AV block alone.**

Brugada syndrome

Brugada syndrome is an inherited condition comprising a specific ECG abnormality and an associated risk of ventricular fibrillation/sudden death in the setting of a structurally normal heart.²⁸ To date the great majority of identified disease-causing mutations have been located in the SCN5A gene encoding the α subunit of the human cardiac voltage-gated sodium channel but such mutations can be identified in, at most, 30% of affected people.^{29–34} Moreover, a positive genetic test adds little or

nothing to the clinical management of such a person. The identification of an SCN5A mutation does, of course, allow rapid and accurate screening of family members but the usefulness of genetic screening may be less than for other familial syndromes, however, given that the routine 12-lead ECG (with or without provocative drug testing) appears to be a relatively effective method of screening for the condition.³⁵

Recommendation

- ▶ **Genetic testing is not recommended as routine in known or suspected cases of Brugada syndrome, but may be considered in the setting of expert clinical and detailed family assessment.**

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a relatively common clinical condition (1 in 500 people) characterised by unexplained cardiac hypertrophy, myocyte disarray and fibrosis. On a genetic level, HCM is caused by mutations in genes encoding a number of cardiac sarcomeric proteins. A large number of mutations have been implicated in the disease, although the great majority occur in the MYH7 and MYBPC3 genes. The diagnostic yield of genetic testing in clinical cases of clear familial HCM is in the region of 60%³⁶; the yield is dependent upon patient selection and genes tested, falling to around 40% if familial disease is not confirmed.³⁷ It remains unclear whether specific mutations have clinical significance for prognosis, principally because all mutations are individually rare and so data are limited. Currently genetic testing is thought to have little or no role in management of the individual patient with a clearcut clinical diagnosis. The identification of a disease-causing mutation does, of course, allow rapid and accurate screening of family members. In this condition cascade screening may have particular advantages over clinical screening of family members for HCM, as ECG or echocardiographic abnormalities may be absent, subtle or develop late in life.

Recommendations

1. **Genetic testing is not recommended for diagnosis of hypertrophic cardiomyopathy outside the setting of expert clinical and detailed family assessment.**
2. **Genetic testing should be considered for patients with a firm clinical diagnosis of hypertrophic cardiomyopathy as a means of cascade screening of relatives, in the setting of expert clinical and detailed family assessment.**

Arrhythmogenic right ventricular cardiomyopathy/dysplasia

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is a familial cardiomyopathy that may result in arrhythmia, heart failure and sudden death. It is characterised pathologically by progressive myocyte loss and fibrofatty replacement, with a predilection for the right ventricle. Most cases are thought to be caused by autosomal dominantly inherited mutations in genes encoding different proteins of the desmosome of cardiomyocytes. The diagnostic yield for the commonest, the PKP2 gene, is 30% or less.^{38 39} At present there is little evidence to indicate that identification of a disease-causing mutation has any clinical or prognostic significance but the identification of disease-causing mutations does, of course, facilitate rapid and accurate screening of family members. This form of screening may have major advantages over clinical screening of family members for ARVC, as clinical expression of

all mutations is heterogeneous even among first-degree relatives, ranging from a complete lack of symptoms and/or clinical manifestations to a severe disease phenotype.⁴⁰

Recommendations

1. **Genetic testing is not recommended for diagnosis of ARVC outside the setting of expert clinical and detailed family assessment.**
2. **Genetic testing should be considered for patients with a firm clinical diagnosis of ARVC as a means of cascade screening of relatives, in the setting of expert clinical and detailed family assessment.**

CONCLUSION AND FUTURE PLANS

The recommendations in this document are based on the best available evidence and contemporary opinion as of February 2007. There is little doubt that in the future the indications for genetic testing in the familial sudden cardiac death syndromes will change and indeed that new tests will emerge. A review of this position statement is planned for February 2009 or earlier if advances necessitate more urgent review. It is recognised that significant organisational change, such as the provision of a national network of inherited cardiac disease clinics, may be required for full implementation of these recommendations and that specifically allocated resources may be necessary. This statement may be useful as a tool to measure adherence of such clinics to the recommendations regarding indications for genetic testing. This statement has been developed without external funding.

Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group

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