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Australia and New Zealand Horizon Scanning Network

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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Genetic screening for hypertrophic cardiomyopathy

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*Adelaide
Health Technology
Assessment*

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PRIORITISING SUMMARY

REGISTER ID: 000188

NAME OF TECHNOLOGY: SCREENING FOR HYPERTROPHIC
CARDIOMYOPATHY

PURPOSE AND TARGET GROUP: IDENTIFYING INDIVIDUALS AT HIGH-RISK OF
SUDDEN CARDIAC DEATH

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|--|--|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication
or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input checked="" type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | |
|--|-------------|
| <input type="checkbox"/> Yes | ARTG number |
| <input type="checkbox"/> No | |
| <input checked="" type="checkbox"/> Not applicable | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓	✓	
United Kingdom	✓		
United States	✓		
Germany	✓		

IMPACT SUMMARY:

Diagnostic laboratories would be able to provide mutational analysis of the gene sequences identified as implicated in inherited hypertrophic cardiomyopathy with the aim of screening individuals at high-risk of sudden cardiac death. Mutation analysis of these gene sequences is currently not funded by the Medicare Benefits Schedule (MBS).

BACKGROUND

Hypertrophic cardiomyopathy (HCM) is one of the major causes of sudden cardiac death in people aged ≤ 35 years of age. In the majority ($> 90\%$) of sudden death cases where HCM is an underlying cause, the mechanism of death relates to ventricular arrhythmias. A large proportion of these individuals die during or immediately after vigorous physical exercise (Semsarian & Maron 2002).

Ninety per cent of HCM cases are familial and are caused by mutations (up to 200) in 12 different genes. These genes are inherited as an autosomal dominant trait and code for sarcomeric contractile proteins (components of the thick or thin filaments with contractile, structural or regulatory function). The majority of HCM cases are due to heterozygote

mutations in three genes: the β -myosin heavy chain (40% of adult cases), cardiac troponin-T and myosin-binding protein-C (30-40% of adult cases). A minority (1-15% of adult cases) of HCM cases may be caused by up to 150 rarer mutations, in addition to a small proportion of HCM cases with an unknown mutational basis (Maron 2002, Murphy & Starling 2005).

HCM is described clinically as an unexplained hypertrophy of the left ventricle, which is commonly asymmetric, involving the left ventricular septum (Figure 1). HCM is not generally an obstructive condition and approximately 75 per cent of patients do not have a significant resting outflow tract gradient. Symptoms may include chest pain, heart palpitations or syncope (Maron 2002, Murphy & Starling 2005).

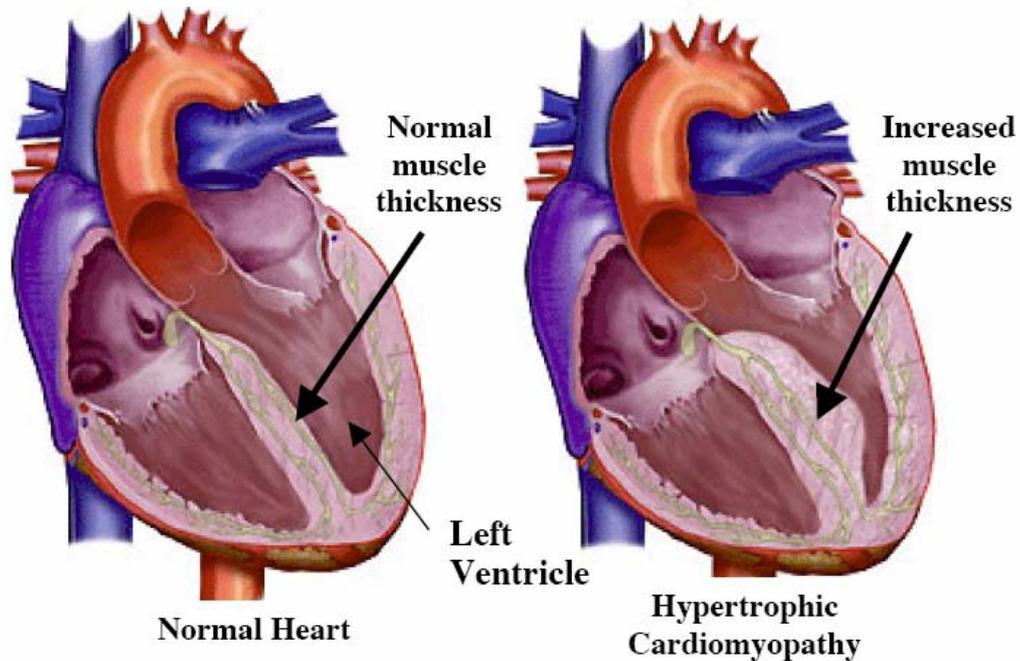


Figure 1 The normal heart and the heart affected by HCM (printed with permission of the Hypertrophic Cardiomyopathy Association www.4hcm.org).

Risk stratification should include a complete clinical-cardiological evaluation, confirmed by genetic screening of familial members of probands. Genetic screening requires patients to donate a 20 ml blood sample for DNA isolation. Currently mutational analysis is conducted on the entire coding sequence of seven genes known to cause HCM. Exons are amplified by polymerase chain reaction (PCR) and this mutational analysis takes approximately two weeks for a diagnostic laboratory to complete. A disease-causing mutation must satisfy three criteria: co-segregation with affected members of the same family; absence of mutation in control samples from healthy population; and conservation of the mutated residue among species and isoforms. It would not be practical to conduct universal population screening for HCM, however screening of family members of individuals who have died from sudden cardiac failure is recommended (Ingles et al 2006).

Primary prevention in individuals identified as being at high-risk of sudden cardiac death due to the presence of HCM genetic mutations include implantation with either a dual-chamber pacemaker or a cardioverter defibrillator (Megevand et al 2005, Jayatilleke et al 2004). Patients diagnosed with HCM are advised to avoid competitive sports, avoid excess consumption of alcohol and to encourage relatives to be screened (The Agnes Ginges Centre for Molecular Cardiology 2005).

CLINICAL NEED AND BURDEN OF DISEASE

Epidemiological studies have estimated the prevalence of HCM as 0.2 per cent of the population, or 1:500 individuals. HCM is not rare and is considered to be the most common known genetic cardiovascular disease. However, as a large proportion of individuals with a HCM are clinically undetected, these individuals account for only a small proportion of patients in cardiology clinics (< 1% of outpatients) (Maron 2002).

A recent Australian study set out to determine the causes of sudden cardiac death in people aged ≤ 35 years. This cross sectional study (level IV Aetiology evidence) was conducted on all autopsies performed on people ≤ 35 years at a major Sydney forensic unit from January 1994 and December 2002. During the study period there were 10,199 autopsies performed. Of these 2,986 (29.2%) were individuals aged ≤ 35 years and 193 were classified as sudden cardiac deaths. The cause of sudden death was as follows: not established but probable primary arrhythmia (31%), coronary artery disease (24%), hypertrophic cardiomyopathy / unexplained left ventricular hypertrophy (15%), viral myocarditis (12%), congenital heart disease (7%) and other (11%). Of the 193 sudden cardiac deaths 22 and 38 per cent occurred during exercise and minimal exertion or at rest, respectively. Forty per cent were not witnessed. It may also be likely that a number of deaths in young people that have previously been attributed to causes including drowning, motor vehicle accidents and sudden infant death syndrome may be attributable to HCM (Doolan et al 2004).

There was a total of 168 and 92 separations for ICD codes I42.1 and I42.2, respectively (obstructive HCM and other HCM) during the period 2003-04, in Australian hospitals. The average length of stay was 4.6 and 5.4 days (AIHW 2006). In New Zealand there was a total of 37 and 15 separations for ICD codes I42.1 and I42.2, respectively (obstructive HCM and other HCM) during the period 2001-02, in publicly funded hospitals. The average length of stay was 4.6 and 3.4 days (New Zealand Health Information Service, Ministry of Health).

DIFFUSION

Currently screening familial members of probands for HCM is restricted to only one centre in Australia, The Agnes Ginges Centre for Molecular Cardiology in the Centenary Institute, situated in the Royal Prince Alfred Hospital, Sydney. Only two other centres world wide offer commercial genetic screening for HCM: the Statens Serum Institute, Copenhagen and Havard Partners Healthcare, United States (personal communication Agnes Ginges Centre for Molecular Cardiology).

COMPARATORS

Family members related to individuals who have experienced sudden cardiac death and as such are suspected of suffering from HCM would be referred to a specialised clinic. A full clinical examination of these individuals would then be conducted, including an electrocardiogram (ECG) and cross section and M mode echocardiogram. In the absence of other underlying factors such as hypertension, diagnostic criteria for HCM would include a maximum left ventricular wall thickness of ≥ 13 mm on echocardiogram, or abnormalities in the ECG such as abnormal Q waves, left ventricular hypertrophy (voltage criteria) or T wave inversion (Ingles et al 2006).

Currently, the American College of Cardiology and the European Society of Cardiology recommends yearly screening with ECG and echocardiography, of first-degree relatives of patients with HCM, beginning at 12 years of age and continuing on into early adulthood (Murphy & Starling 2005).

EFFECTIVENESS AND SAFETY ISSUES

The study by Ingles et al (2006) reported on the genetic screening of 80 probands (index cases) (level IV Screening evidence). Screening was conducted for seven of the most common HCM mutations. In addition family members of probands were genotyped. A total of 24 mutations were identified in 23 probands (29%). Fifty-two percent of families where at least one mutation was identified had a family history of HCM. Single mutations (heterozygotes) were detected in 19/80 (24%) of probands. Of these 19 mutations, 11 were in the β -myosin heavy chain, four were in myosin-binding protein-C, three in cardiac troponin-I and one in cardiac troponin-T. Four probands (4/80, 5%) had more than one HCM mutation. Among these probands, one was a double heterozygote and the remaining three had compound mutations, both of which may result in a more severe clinical phenotype due to the “double dose” effect. Probands with compound mutations had a significantly greater left ventricular wall thickness than single mutation probands (30.7 ± 3.1 mm versus 24.4 ± 7.4 mm, $p < 0.05$). For the four multiple mutation probands, family pedigrees were constructed and where possible genotyping of family members was conducted. Of 49 family members, fourteen (28.6%) were clinically affected by HCM and six of these individuals (43%) experienced sudden cardiac death. In the families of single mutation probands, 55 relatives were clinically affected by HCM, of whom 10 (18%) suffered from sudden cardiac death. Of the living family members clinically affected by multiple mutations, 6/8 (75%) were clinically managed by implantation with a cardioverter-defibrillator.

The study by Doolan et al (level IV Screening evidence) evaluated 120 families for mutations in the cardiac troponin-I gene (cTnI) thought previously to have a prevalence of <1% in HCM families. Clinically significant mutations in the cTnI gene were detected in only four of the 120 families (3.3%). Follow-up family screening identified a further seven family members who were clinically affected by HCM and a further four who carry the mutation but with no clinical symptoms of the disease. A sudden cardiac death event had occurred to at least one member of each of the four families.

COST IMPACT

The cost-effectiveness of screening programmes for familial members has not been established. Currently the Centre for Molecular Cardiology conducts genetic screening for HCM for the most common genetic mutations for approximately \$2000. Costs must be fully met by the patient (personal communication Agnes Ginges Centre for Molecular Cardiology).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Family members should receive appropriate genetic counselling on the potential risks, benefits and implications (especially for medical and life insurance) of a positive test. A negative test may reassure the patient and extended family, however a positive test will have implications for further clinical follow-up and treatment options. Patients may carry the mutation but be asymptomatic, which has implications for future generations, therefore a full explanation of the inheritance of HCM should be an integral part of genetic counselling. (Murphy & Starling, 2005). Counselling is extremely important in patients found to have double or compound mutations, which dramatically increases the risk of children inheriting the disease (Ingles 2006).

OTHER ISSUES

No other issues were identified in the sources examined.

RECOMMENDATION:

There is limited evidence describing the effectiveness of screening family members, of individuals who have suffered sudden cardiac death, for genetic mutations implicated in

hypertrophic cardiomyopathy. The number of potential individuals who would require genetic screening would be small if screening was limited to only family members of probands and as such would not incur a great financial burden on the health system. However the benefit of identifying an undetected mutation to these individuals would be far reaching. Therefore it is recommended that the following be conducted:

- | | |
|--|--|
| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |

SOURCES OF FURTHER INFORMATION:

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AUGUST 2007 – UPDATE

AUGUST 2007 – COMPARATORS

Since the completion of the original summary several new methods for screening for HCM have been developed and assessed. One of these techniques involves screening using peripheral blood and the other utilises cardiac magnetic field mapping.

A recent, small study has shown promising results for genetic screening by direct sequencing for hypertrophic cardiomyopathy as well as several other cardiovascular diseases. In this study it was possible to screen for genetic mutations implicated in hypertrophic cardiomyopathy from RNA obtained from whole blood. In general, genetic screening can take place either at the DNA level, obtainable from any nucleated cell type, or at the RNA level, which is usually obtained from the tissue involved in the disease being screened for or from cells cultured outside of the body. Obtaining tissue from some organs or body locations may not be possible or practicable. Despite this, RNA level screening has several advantages over DNA level screening, such as: the intron/exon regions do not need to be known as the RNA has all introns spliced out; splicing errors are evident which may not be evident at the DNA level; some genes have very numerous splice sites or complex splicing patterns which makes screening at the DNA level time consuming and costly; and the RNA reflects the *actual* gene expression within a cell versus DNA which reflects *potential* gene expression. Screening for hypertrophic cardiomyopathy mutations at the RNA level in whole blood would greatly simplify genetic screening for HCM. A cost estimate was reported in this study and this technique provided a saving versus established methods of generic screening. The technique was also reported to have a faster turnaround versus DNA level genetic screening. The study reported that six known and two novel mutations were found in RNA from 10 probands, these mutations were later confirmed by genomic DNA testing, validating the utility of RNA screening (Miller et al 2007).

A study using map topology quantification by Kullback-Leibler (KL), entropy and regional magnetic field strength parameters to diagnose hypertrophic cardiomyopathy reported a sensitivity of 84.8% and a specificity of 88.9%. This study, using cardiac magnetic field mapping, was conducted on 33 patients with confirmed HCM, 42 patients with cardiac hypertrophy due to arterial hypertension, and 57 normal subjects. The technique was also able to distinguish between obstructive and non-obstructive hypertrophic cardiomyopathy with a correct classification rate of 97%. Using this diagnostic method to prospectively screen two families with hypertrophic cardiomyopathy resulted in the correct diagnosis of all 22 family members (Schirdewan et al 2007).

Screening the 3 most prevalent hypertrophic cardiomyopathy related genes, MYBPC3, MYH7 and TNNT2, for mutations in 88 unrelated confirmed hypertrophic cardiomyopathy patients was able to identify mutations in 50 patients (57%). This study used denaturing HPLC to sieve the samples into normal and mutated categories followed by the sequencing of the mutant specimens (Girolami et al 2006) (level IV diagnostic evidence).

AUGUST 2007 – SAFETY AND EFFECTIVENESS ISSUES

A single study was identified which reported relevant safety and effectiveness outcomes. A genetic screen of 30 patients with clinical hypertrophic cardiomyopathy was undertaken using a new pre-sequencing screening technique. Denaturing gradient gel electrophoresis (DGGE) was used to screen for mutant exons before direct sequencing of the identified mutant candidates. This vastly reduced the time, cost and effort needed to diagnose the patients. It was reported that 286 of 312 exons from 25 genes were able to be screened using the DGGE based technique. In DGGE, mutations in amplicons manifest as differing migration patterns for homo- and hetero- duplexes. The only samples that need to be sequenced are the samples that contain amplicons that exhibit differing migration on a gel compared to the wild-type reference (Zeller et al 2006)(level III-3 diagnostic evidence).

AUGUST 2007 – SUMMARY OF FINDINGS

Even with comprehensive genetic analysis of the genes known to perform a role in hypertrophic cardiomyopathy, it is unlikely that a mutation will be found in more than 50-60 percent of known hypertrophic cardiomyopathy patients. As a screening tool in families of the proband, who are likely to be a mixed group of diagnosed and undiagnosed hypertrophic cardiomyopathy sufferers, and unaffected subjects, this level of sensitivity would lack diagnostic certainty. Despite this, the benefits to those identified correctly would be great. No studies were identified which assessed the long term outcome of the patients identified by hypertrophic cardiomyopathy screening. So it is not clear if those identified benefited from their diagnosis.

New methods of increasing the efficiency of genetic screening for hypertrophic cardiomyopathy are being developed and although these will not increase the sensitivity of screening, they should reduce the time to perform, complexity of, and cost of the genetic screening tests.

AUGUST 2007: HEALTHPACT ACTION:

A potential new technique for diagnosing hypertrophic cardiomyopathy using cardiac magnetic field mapping showed great sensitivity and specificity in a small population and may be a better method for screening for and diagnosis of hypertrophic cardiomyopathy. Therefore HealthPACT have recommended that this technology be monitored for further information in 12-months time.

NUMBER OF STUDIES INCLUDED

Total number of studies	
Level III-3 intervention evidence	1
Level IV intervention evidence	1

AUGUST 2007 – REFERENCES

Girolami, F., Olivotto, I. et al (2006). 'A molecular screening strategy based on beta-myosin heavy chain, cardiac myosin binding protein C and troponin T genes in Italian patients with hypertrophic cardiomyopathy', *J Cardiovasc Med (Hagerstown)*, 7 (8), 601-607.

Miller, T. E., You, L. et al (2007). 'Whole blood RNA offers a rapid, comprehensive approach to genetic diagnosis of cardiovascular diseases', *Genet Med*, 9 (1), 23-33.

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Zeller, R., Ivandic, B. T. et al (2006). 'Large-scale mutation screening in patients with dilated or hypertrophic cardiomyopathy: a pilot study using DGGE', *J Mol Med*, 84 (8), 682-691.

SOURCES OF FURTHER INFORMATION:

No other sources were identified.