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Genetic screening for Familial Hypercholesterolaemia

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PRIORITISING SUMMARY

REGISTER ID: **000248 REFERRAL FROM HEALTHPACT**

NAME OF TECHNOLOGY: **GENETIC SCREENING FOR FAMILIAL HYPERCHOLESTEROLAEMIA (FH)**

PURPOSE AND TARGET GROUP: **DNA DETECTION OF LOW DENSITY LIPOPROTEIN CHOLESTEROL RECEPTOR (LDLR) GENE MUTATIONS IN ASYMPTOMATIC INDIVIDUALS FOR THE DIAGNOSIS OF FH**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☐ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☒ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☐ No
- ☒ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Netherlands			✓
Denmark			✓
Finland			✓

DNA detection of low-density lipoprotein cholesterol receptor gene mutations is used routinely for the diagnosis of familial hypercholesterolaemia (FH) in the Netherlands, Denmark and Finland (Hamilton-Craig 2005).

IMPACT SUMMARY:

A program for identifying new cases of FH is currently offered free of charge in Australia to individuals registered with the MEDPED (Make Early Diagnosis to Prevent Early Deaths in Familial Hypercholesterolaemia) project. The MEDPED program is a research project, coordinated by the University of Utah. This project is funded by Pfizer to register and support the treatment of people with inherited cholesterol disorders, such as FH and operates in more than 30 countries with more than 50,000 registered patients (MEDPED Asia-Pacific 2006). Diagnosis of family members of individuals diagnosed with FH is primarily based on clinical criteria including family history and blood lipid analysis. This prioritising summary examines

the relevance of including a genetic test in screening programs (as opposed to clinical diagnosis alone) to detect individuals with inherited FH.

BACKGROUND

Familial hypercholesterolaemia (FH) is an inherited disorder of blood lipid metabolism that results in high levels of cholesterol (atherosclerosis). FH is characterised by one or more mutations in the LDL receptor (LDLR) gene, resulting in a deficiency of LDL receptors on the surface of blood cells, or an altered receptor structure that disrupts LDL uptake (Leren 2004). Individuals with FH have an increased risk of premature (<55 years in men and <65 years in women) cardiovascular disease and a reduced life expectancy. Approximately 85% of males and 50% of females with FH will suffer a coronary event before 65 years of age (Civeira 2004).

There are an estimated 800 different mutations identified to date that can occur in the LDL gene that cause FH (Graham et al 2005, Civeira 2004). The array of mutations varies in different populations.

FH follows an autosomal dominant pattern of inheritance. The risk that carriers of the faulty gene will develop coronary artery disease during their lifetime is different for males and females. Children of one heterozygote parent carrying the faulty LDLR gene have a 50% chance of inheriting the faulty gene. In heterozygous familial hypercholesterolaemia, a defective LDL receptor has either zero or reduced LDL uptake capacity. This results in approximately twice the normal[1] (7-10 mmol/L) levels of plasma LDL cholesterol. If both parents are heterozygote carriers of the faulty gene there is a 25% chance any offspring will inherit *both* copies of the faulty gene. Having two copies of the faulty gene causes severe disease, often with childhood onset of coronary artery disease. In homozygous FH there is almost no LDL receptor activity and LDL cholesterol levels are often extremely high >30mmol/L.

FH is rarely diagnosed before onset of premature CVD. A definitive diagnosis of FH can be achieved by the identification of known mutations. The genetic procedure developed for testing FH in Australia involves denaturing high-performance liquid chromatography (HPLC) and then confirming suspected mutations by DNA sequencing to detect mis-matches (personal communication, 22nd November 2006). HPLC is a method being adapted for the analysis of DNA fragments, by separating mixtures of DNA fragments based on size alone or based on size and sequence (Leonard 1999). This method can be used for mutation screening of large genes. Some international laboratories use DNA sequencing alone (personal communication, 22nd November 2006).

[1] Normal levels of LDL are 2.6 mmol/l

CLINICAL NEED AND BURDEN OF DISEASE

FH is thought to account for about 5-10 per cent of coronary artery disease that occurs before the age of 55. It is estimated that 1:500 people in most population groups are heterozygous carriers and $1:10^6$ are homozygous for the faulty gene (Leren 2004, Gillet and Burnett 2005). There is considerable variation in the FH genetic carrier frequency in populations with different ethnic backgrounds, such as Lebanese Australians, who may have a frequency as high as 1:70 (The Centre for Genetics Education 2006).

Without treatment, 50 and 12 per cent of heterozygote males and females, respectively, will develop coronary artery disease before the age of 50. By the age of 70 this rate increases to a 100 and 74 percent for males and females, respectively (The Centre for Genetics Education 2006). Homozygtes are at high risk of coronary heart disease. There are an estimated 40,000 people with FH in Australia, with only 20 per cent diagnosed and less than 10 per cent treated adequately (Burnett et al 2005).

Familial hypercholesterolaemia is one of the causes of premature sudden cardiac death. Other genetic mutations, such as hypertrophic cardiomyopathy and long QT syndrome, may also cause sudden cardiac death, however these conditions are less common than FH.

DIFFUSION

Nurse practitioners currently perform FH family cascade screening in collaboration with MEDPED-FH physicians in each capital city around Australia (Hamilton-Craig 2006). There are approximately 700 patients with FH registered with the program.

COMPARATORS

The current method for diagnosing FH is clinical assessment. Assessment includes ascertaining an individual's family history of cardiovascular disease (CVD) in first degree relatives (consistent with autosomal dominant inheritance), plasma analysis of total and LDL cholesterol levels and/or a physical examination for signs of cholesterol deposition affecting the corneas, eyelids and extensor tendons. The diagnostic assessment may follow recognised diagnostic criteria such as the Simon Broome or the Dutch Lipid Network which assign points to specific diagnostic criteria. Both models include but are not limited to DNA analysis alone for evidence of genetic mutation of the LDLR gene (Yuan et al 2006).

EFFECTIVENESS AND SAFETY ISSUES

Several studies (level IV Screening evidence) report the detection rates of FH with genetic testing compared to clinical diagnosis (Damgaard et al 2005, vanAalst-Cohen et al 2006 and Fouchier et al 2001). In one of these studies, 408 patients were retrospectively categorised according to three different sets of clinical criteria and

their distribution of patients was compared to the results of the genetic test. A mutation was found in 33% (135) of the patients and only 71% of the mutation carriers fulfilled two out of three criteria for a clinical diagnosis of FH (Damgaard et al 2005).

The large study by vanAalst-Cohen et al (2006) found an LDLR mutation in 2400/4000 (52%) of patients who had previously been clinically defined with FH. This testing procedure involved identifying the 14 most prevalent Dutch LDLR gene mutations. This study examined whether patients with a genetic diagnosis differed significantly from clinically diagnosed patients. The authors report that LDL cholesterol levels were higher in patients diagnosed genetically and that triglycerides levels were higher in patients without a genetic mutation (Damgaard et al 2005).

The potential value of genetic screening program depends on the prevalence of identified mutations in a population. The literature suggests that genetic testing should be limited to populations in which only a few mutations account for most FH cases, populations in which most causative mutations are known and in individuals with an uncertain clinical diagnosis with family members with known FH (Civeira 2004).

COST IMPACT

The potential cost impact of a screening program for FH will depend on the screening strategy utilised. Computer modelling has shown that case finding amongst relatives of probands is the most cost-effective strategy for diagnosing FH in the adult population (Marks et al 2000, Marks et al 2002). Universal screening, which can be complementary to family tracing has been found to be cost-effective at only young ages (<16 years) (Marks et al 2002).

A cost-effectiveness study compared the identification and treatment of FH patients by universal screening, opportunistic screening in primary care, screening of patients with premature MI or tracing family members in the United Kingdom (Marks et al 2002). Cost-effectiveness was calculated as cost per life-year gained including screening and treatment costs. The most cost-effective strategy was screening via family member tracing with AUD$7,400 per life year gained. If the genetic mutation was known within the family the cost per life year gained was only slightly increased by genetic confirmation of the diagnosis. Universal screening was the least cost-effective strategy and for all strategies it was more cost-effective to screen younger people and women.

At the time of writing this summary only one cost-effectiveness study of a nationwide genetic screening population in the Netherlands was available (Wonderling et al 2004). This screening program tested relatives of individuals with a known genetic mutation with no symptoms of CVD and aimed to identify new cases. New cases

diagnosed by the screening program gained an average 3.3 years of life each. In addition, 26 myocardial infarctions could be avoided for every 100 persons (aged 18-60 years) treated with statin therapy. The average total lifetime incremental costs, over all age ranges and both sexes, including costs for screening and testing, lifetime drug treatment and treatment of cardiovascular events, was AUD$635per new case identified. Cost per life-year gained was AUD$11,200. The authors concluded that systematic genetic screening of family members of persons diagnosed with FH was cost-effective in the Netherlands and recommended further implementation in other settings.

The total cost for genetic testing will vary as a negative result does not exclude a FH diagnosis as other genes may be involved in approximately 30% of cases. Where a mutation is known is the cost is approximately $600 (personal communication, 22nd November).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Genetic screening for FH meets the WHO criteria for the implementation of screening programs. These criteria include that the disease is a serious health problem and that both a definite diagnostic test and effective treatment measures are available (Leren 2004). If detected early, FH can be treated by lifestyle modification and cholesterol lowering drugs.

There are several issues that arise with regards to how family members are approached and psychological effects of genetic screening have been examined in studies that report no adverse effects on either short or long-term quality of life (vanMaarle et al 2003 and Marks et al 2000).

OTHER ISSUES

The Cardiac Society of Australia and New Zealand has established a working party to investigate cardiac genetic disorders, including FH (Hamilton-Craig 2005).

CONCLUSION:

It is likely that a family cascade screening program in Australia would increase public costs of drug therapy due to greater detection of FH. However, successful treatment regimes have demonstrated cost-effectiveness and may have the potential to reduce the risk of CVD in patients who are currently asymptomatic.

HEALTHPACT ACTION:

Given the potential positive therapeutic benefits of identifying family members of familial hypercholesteraemia probands, HealthPACT recommended that a Horizon Scanning Report be conducted on this technology.

SOURCES OF FURTHER INFORMATION:

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LIST OF STUDIES INCLUDED

Total number of studies	
Level IV Screening evidence	2

SEARCH CRITERIA TO BE USED:

DNA Mutational Analysis
Hypercholesterolemia, Familial/blood/diagnosis/ genetics
Molecular Diagnostic Techniques
Receptors, LDL/genetics