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Horizon Scanning Technology

Prioritising Summary

LIPOchip DNA microarray for the detection of familial hypercholesterolaemia

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PRIORITISING SUMMARY

REGISTER ID: **000419**

NAME OF TECHNOLOGY: **LIPOCHIP**

PURPOSE AND TARGET GROUP: **GENETIC DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

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

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
Spain			✓

IMPACT SUMMARY:

Progenika-Biopharma markets the LIPOchip platform, which is designed to diagnose familial hypercholesterolaemia (FH). FH can result in premature death and is often undiagnosed until a coronary event occurs. The LIPOchip platform is a tiered system with a microarray based first tier coupled with genetic sequencing. This system is aimed at providing a definitive diagnosis (genotype) which is not possible using standard diagnosis based on clinical symptoms (phenotype). FH if diagnosed early can be treated with existing therapies.

BACKGROUND

Familial hypercholesterolaemia is a common but under-diagnosed disorder that results in an almost 100-fold increased risk of coronary artery disease (CAD) (Bates et al 2008). FH follows an autosomal dominant pattern of inheritance, with offspring having a 50 per cent chance to inherit the disorder. Homozygotes usually have a more severe phenotype than heterozygotes, but symptom severity also results from the specific mutation(s) in each subject (Emery et al 2007).

FH is a genetic disorder resulting mainly from mutations in the low-density lipoprotein receptor (LDLR) gene that encodes the LDL receptor protein, or the apolipoprotein B (ApoB) gene. Other mutations in different genes are known but are very rare. Although over 1,000 mutations have been identified, many are rare or family specific. FH is rarely diagnosed until a coronary event occurs in a proband,which may result in other family members being screened for their FH status. The clinical symptoms of FH manifest due to the impaired uptake of cholesterol, specifically LDL, resulting in high circulating cholesterol levels and a subsequent increased risk of cardiovascular disease. Standard diagnosis of FH is performed using family history and blood lipid examination. This results in a *phenotypic* diagnosis of the patient which, due to other causes of hypercholesterolaemia, may not correlate with their genetic FH status.

The LIPOchip platform is based on a tiered mutation identification algorithm. Initially the patient is assessed using a microarray based mutation detection system. The microarray is designed to detect 203 mutations in the LDLR gene and four mutations in the ApoB gene. The subject's genetic material is extracted from a blood sample and assessed with a microarray. If the patient has any of the 207 mutations the subject is deemed FH positive. If the subject is negative their sample is subjected to a second tier of large genetic rearrangement analysis[1]. If this tier is also negative then a third tier consisting of sequencing of the LDLR gene to assess the subject for novel mutations. If this step is also negative then the subject is deemed FH negative.

CLINICAL NEED AND BURDEN OF DISEASE

FH is a cause of premature cardiac death, with most cases not diagnosed until the primary cardiac event. It is estimated that 5-10 per cent of CAD before the age of 55 results from FH. It is thought that there may be 40,000 FH cases in Australia, with only 20 per cent correctly diagnosed and less than 10 per cent are treated with existing therapy. The prevalence of FH in the general population is thought to be 1 in 500, with sub-populations of certain ancestries having a higher prevalence, up to 1 in 70 for those of Afrikaaner origins (Emery et al 2007).

DIFFUSION

The LIPOchip is not in use within Australia at the time of writing.

COMPARATORS

The standard diagnostic method for FH is based on clinical testing and family history. The criteria for the standard diagnosis of FH are:[2]:

[1] This analysis will detect if the subject's genetic material has undergone any large scale rearrangements or deletions. This type of mutation would be expected to produce a negative result in the first tier as the subject's target sequence is missing or significantly damaged.

[2] Adapted from Emery, J., Barlow-Stewart, K. et al (2007). 'Genetics and preventive health care', *Aust Fam Physician,* 36 (10), 808-811.

a. Known FH DNA mutation;
b. Tendon xanthomas in patient or first/second degree relative;
c. Family history CHD <50 years of age in second degree relative or <60 years of age in first degree relative;
d. Family history of cholesterol >7.5 mmol/L in first or second degree relative;
e. Cholesterol >7.5 mmol/L (adult) or >6.7 mmol/L (age <16 years); and
f. LDL-C >4.9 mmol/L (adult) or >4.0 mmol/L (age <16 years).

Definite FH: (e or f) + a
Probable FH: (e or f) + b
Possible FH: (e or f) + (c +d)

It is recommended that when a FH proband is diagnosed that cascade screening of relatives occurs as there is a 50 per cent chance of first degree relations being FH positive(Emery et al 2007).

SAFETY AND EFFECTIVENESS ISSUES

Several studies have used the LIPOchip to diagnose FH affected individuals. The LIPOchip has several versions with the array being updated yearly to be able to detect newly discovered mutations, and as such only the most recent studies are included.

A study using the LIPOchip investigated 825 consecutive subjects attending three Spanish lipid clinics (level IV diagnostic evidence). Subjects were suspected of having FH due to: very high familial total or LDL cholesterol levels; possible family history of premature CAD; and possible tendon xanthomas[3]. The version of the LIPOchip used screened for 203 mutations in the LDLR gene and four in ApoB. Subjects who had negative results were subsequently assessed for large genetic rearrangement analysis. If they were negative for this also, then genetic sequencing of the promoter, 18 exons and flanking introns was performed to uncover new mutations. Overall 459 subjects were found to have FH-causing mutations. Those who were positive for mutations were found to be more likely to have a family history of tendon xanthomas (OR 7.779 (95% CI [3.639–16.712])), more likely to have tendon xanthomas (OR 3.675 (95 % CI [1.583–8.528]), and more likely to be female (OR 1.966 (95 % CI [1.059–3.649])). No problems were reported with using the LIPOchip (Civeira et al 2008b).

A second study by the same researchers investigated the overlap of FH with familial combined hyperlipidaemia (FCH)[4]. The population consisted of 143 FCH patients

[3] Subcutaneous depositions of fat associated with tendons, especially the Achilles tendon, or those of the hands and feet. Caused by severe hypercholesterolaemia.
[4] The diagnostic criteria for FCH are equivocal and overlap with those of FH, and include hyperlipidaemia and hypercholesterolaemia. FCH is linked with obesity and diabetes, which is not necessarily true for the general FH positive population. The authors therefore aimed to definitively

from two Spanish lipid clinics. These subjects could be classified as FH clinically and thus were investigated using the definitive genetic analysis provided by the LIPOchip. Mutations in the LDLR gene were discovered in 28 (19.6 %) of FCH subjects. This indicated that there is some diagnostic overlap of these two disease types and may explain why some FH patients present with high triglycerides (Civeira et al 2008a) (level IV diagnostic evidence).

As the identification of genetic mutations is the definitive diagnostic method for FH the LIPOchip studies presented here were unable to be compared against a suitable control. The clinical diagnosis of FH is certainly less accurate than genetic methods. Because the LIPOchip was not able to be compared to a gold standard it is not possible to comment on the effectiveness of the system, that is the FH cases missed due to rare or undetected mutations. As the system now stands it seems to be a useful tool for the definitive diagnosis of FH subjects in very high risk populations. Larger and longitudinal studies are required to assess the effectiveness of the LIPOchip.

COST IMPACT

The manufacturer was contacted for pricing details but at the time of publication there was no response.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

According to the Progenika-Biopharma website a clinical trial is planned in the USA.

SUMMARY OF FINDINGS

The LIPOchip seems to function well in populations at high risk of FH, although longer term outcomes of patients diagnosed by the LIPOchip are not available as yet. As no better standard exists than genetic diagnosis, the level of misdiagnoses is not apparent. Comparisons with other genetic methods for diagnosis of FH are needed.

HEALTHPACT ACTION:

A number of diagnostic genetic tests for familial hypercholesteraemia are likely to come on to the market in the near future. HealthPACT recommends that all genetic tests for FH, including the LIPOchip, be monitored for further information in 12-months time.

NUMBER OF INCLUDED STUDIES

Total number of studies	
Level IV Diagnostic evidence	2

diagnose subjects who may be clinically diagnosed as FH positive but in fact be FH negative genetically and therefore more likely to misclassified FCH positive subjects instead.

REFERENCES:

Bates, T. R., Burnett, J. R. et al (2008). 'Detection of familial hypercholesterolaemia: a major treatment gap in preventative cardiology', *Heart Lung Circ,* 17 (5), 411-413.

Civeira, F., Jarauta, E. et al (2008a). 'Frequency of low-density lipoprotein receptor gene mutations in patients with a clinical diagnosis of familial combined hyperlipidemia in a clinical setting', *J Am Coll Cardiol,* 52 (19), 1546-1553.

Civeira, F., Ros, E. et al (2008b). 'Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia', *Am J Cardiol,* 102 (9), 1187-1193, 1193 e1181.

Emery, J., Barlow-Stewart, K. et al (2007). 'Genetics and preventive health care', *Aust Fam Physician,* 36 (10), 808-811.

SEARCH CRITERIA TO BE USED:

DNA Mutational Analysis
Receptors, LDL/ blood
Cholesterol, LDL/ blood
Receptors, Lipoprotein/ blood