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FibroTest-ActiTest (Update): a diagnostic test for liver fibrosis in patients with hepatitis C.

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PRIORITISING SUMMARY: UPDATE

REGISTER ID: **000120**

NAME OF TECHNOLOGY: **FIBROTEST-ACTITEST**

PURPOSE AND TARGET GROUP: **A DIAGNOSTIC TEST FOR LIVER FIBROSIS IN PATIENTS WITH HEPATITIS C**

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	

At the time of writing this prioritising summary the FibroTest was not available in Australia.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
France	✓		
Australia	✓		

IMPACT SUMMARY:

This summary provides a 12 month update on the FibroTest-ActiTest, a non-invasive alternative to liver biopsy, which is manufactured by Biopredictive. The original Prioritising Summary for this device was compiled in July 2004. The FibroTest-ActiTest is a diagnostic blood test for liver fibrosis for patients infected with hepatitis C. It is in limited use in some European countries.

BACKGROUND

Hepatitis C is a blood-borne disease of the liver caused by the hepatitis C virus (HCV). The presence of anti-HCV antibody in serum of a patient indicates infection with the hepatitis C virus. Patients may be unaware that they are infected for some time, as acute symptoms are rare. In Australia, people infected with HCV must demonstrate a minimum stage of fibrosis on liver biopsy to qualify for the standard combination antiviral therapy. Therefore it is recommended that patients undergo a liver biopsy for the adequate management of hepatitis C (Rossi et al 2003).

FibroTest-ActiTest is a minimally invasive blood test that may be used as an alternative to liver biopsy. The FibroTest-ActiTest uses a combination of six serum biochemical markers (α_2-macroglobulin, haptoglobulin, γ-glutamyltranspeptidase, total bilirubin, apolipoprotein A1

and alanine aminotransferase) to assess the extent of liver fibrosis (FibroTest) and necroinflammatory activity (ActiTest). The test utilises an algorithm to combine the biochemical marker results obtained from standard diagnostic laboratory tests, with the patient's age and gender to give a numeric quantitative estimate of liver fibrosis ranging from 0 to 1, with scores >0.6 considered to represent significant fibrosis (Poynard et al (2004).

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that over 200,000 people in Australia are infected with the hepatitis C virus, with about 11,000 new infections occurring each year (Australian Government Department of Health and Ageing 2004). It is likely that prevalence of hepatitis C is underestimated due to the numbers of people with hepatitis C who are currently asymptomatic (Australian Government Department of Health and Ageing 2004).

Of annual total notifications to the National Notifiable Diseases Surveillance System between 1991 and 2000, approximately 65% of people diagnosed with HCV were aged between 20-39 years, with approximately 35% of all diagnoses in women. Approximately 75% of individuals infected with HCV will remain infectious and at risk of developing long-term sequelae, such as cirrhosis of the liver (7% of infected individuals). Rates of liver failure and hepatocellular carcinoma following cirrhosis have been estimated to be four and one percent, respectively (Australian National Council on AIDS, Hepatitis C and Related Diseases Hepatitis C Sub-Committee 2002).

Projections of the number of people living with HCV-related cirrhosis, incident cases of liver failure and hepatocellular carcinoma, and cumulative numbers of HCV related deaths were all projected to at least treble by 2020 (Australian National Council on AIDS, Hepatitis C and Related Diseases Hepatitis C Sub-Committee 2002).

The number of public hospital separations in Australia for chronic and acute viral hepatitis C (AR-DRG numbers B18.2 and B17.1) was 2,047 and 177, respectively, during the year 2001-02 (AIHW 2004).

In New Zealand, the estimated number of people with HCV antibodies to the end of 2000 was 25,200 people based on the mid-range intravenous drug user numbers (IDU) (with lower and upper limits of 22,900 to 27,500). If current trends continue it is estimated that the number of people with HCV antibodies could increase by 50% by 2010, however caution should be exercised in the use of this projection data due to uncertainties surrounding the future IDU numbers (Ministry of Health, 2000).

DIFFUSION

FibroTest-ActiTest is currently unavailable in Australia although a preliminary study has been conducted here. FibroTest-ActiTest is available in some European countries and it is expected to be released in the United Kingdom in 2004. FibroTest-ActiTest will be released in the United States in 2004 as HCV FibroSure (National Horizon Scanning Centre 2004).

COMPARATORS

The gold standard for the assessment of HCV-related fibrosis and necro-inflammatory activity in the liver is liver biopsy. Liver biopsy is highly invasive and approximately 0.3% of patients develop substantial complications. In addition, liver biopsy is prone to sampling error due to the possibility of heterogenous distribution of pathology in the liver (Rossi et al 2003). One of the few validated scoring systems for necro-inflammatory activity and stage of fibrosis is called the METAVIR. Fibrosis is scored from F0-F4. A METAVIR score of F2 to F4 signifies significant fibrosis, while a score of F3 and F4 signifies advances fibrosis. METAVIR scores for necro-inflammatory activity range from A0 to A3 (A0= no activity, A1

= minimal activity, A2 = moderate activity, A3 = severe activity) (Blue Cross, Blue Shield 2005).

EFFECTIVENESS AND SAFETY ISSUES

AUGUST 2004

A study (Level 1 diagnostic levels of evidence) has been conducted in Australia, validating the accuracy of the FibroTest-ActiTest. Serum was obtained from 125 consecutive patients with confirmed hepatitis C who had undergone liver biopsy. The prevalence of fibrosis in this patient group was 0.38, determined by liver biopsy. The negative predictive value of a FibroTest score of <0.1 was reported as 85% and the positive predictive value of a FibroTest score >0.6 (significant fibrosis) was 78%. Thirty-three of the 125 patients had FibroTest scores of <0.1, however six of these patients (18%) were false negatives who had significant fibrosis as determined by liver biopsy. Conversely, 24/125 (19%) patients had FibroTest scores of >0.6 (significant fibrosis), of these 5 (21%) had mild fibrosis determined by liver biopsy. Of the 125 patients enrolled in the study, 57 (46%) could have avoided liver biopsy, however discrepant results were recorded for 11 of those 57 (19%) (Rossi et al 2003).

The cross-classification study by Poynard et al (2004) reported on the discrepancies between the FibroTest-ActiTest and the reference standard liver biopsy, in 537 patients with confirmed hepatitis C (level 2 diagnostic levels of evidence). Discordance between the two results was reported for 154/537 (29%) patients, and was attributed to failure of biopsy (poor quality) or the FibroTest-ActiTest, or both. For patients whose results were discordant due to failure of the FibroTest-ActiTest, there were seven (1.3%) false negatives and six (1.1%) false positives. However, 97 patients experienced biopsy failure with 77 (14%) false negatives and 22 (4.1%) false positives.

Several other studies have been published that have assessed the comparison of the FibroTest-ActiTest to liver biopsy, however the authors of this summary were unable to access these articles. These studies were assessed by the United Kingdom National Horizon Scanning Centre (2004) who found that their results supported the use of the FibroTest-ActiTest as an alternative to liver biopsy. However, due to changing clinical practice in the United Kingdom (reduction of the number of liver biopsies performed in favour of routine antiviral therapy), it was felt that the need for the FibroTest-ActiTest would be reduced.

EFFECTIVENESS AND SAFETY ISSUES

DECEMBER 2005

A meta-analysis (Level I diagnostic evidence) conducted by a stakeholder in the company manufacturing the FibroRTest, of diagnostic biochemical markers for liver fibrosis and necrosis recommended the FibroTest as an alternative to liver biopsy (Poynard 2004). One section of this meta-analysis compared the diagnostic value of FibroTest versus conventional liver biopsy (METAVIR results) for the detection of liver fibrosis and necrosis.

The area under receiver operating characteristics curve (AUROC) cut-off values for the FibroTest were 0.10, 0.30, 0.60 and 0.80, which corresponded to METAVIR values of F1 (portal fibrosis alone), F2 (portal fibrosis with rare septae), F3 (portal fibrosis with many septae) F4 (cirrhosis). The presence of stage F2, F3, or F4 was termed “significant fibrosis”, whereas the term “advanced fibrosis” was reserved for stage F3 or F4. F0 indicates no fibrosis (Adams et al 2005).

For the diagnosis of *significant* fibrosis by the METAVIR system, the AUROC of the FibroTest ranged from 0.73 to 0.87. Table 1 describes the sensitivity and specificity of the FibroTest for the METAVIR cut off levels. An increase in the severity of fibrosis results in the decrease in sensitivity with a corresponding increase in specificity. For the cut-off of 0.31,

the FibroTest negative predictive value (NPV) for *excluding significant fibrosis* was 91% (of the patients who test negative for significant fibrosis, NPV is the probability that the patient will *not* have significant fibrosis). The positive predictive value (PPV) for a FibroTest score of 0.58 (significant fibrosis) is 76% (of the patients who test positive for significant fibrosis, 76% of these patients will actually have significant fibrosis).

Table 1

Cut off value	Sensitivity range	Specificity range
0.10 (F1)	92-100%	8-33%
0.30 (F2)	75-92%	39-66%
0.60 (F3)	42-79%	79-95%
0.80 (F4)	13-67%	92-98%

COST IMPACT

The cost of the FibroTest-ActiTest is approximately £70 ($180 on the 12th August 2004) per test National Horizon Scanning Centre (2004). The current Medicare Benefits Schedule fee for percutaneous liver biopsy is $145 (item number 30409). In addition, there may be associated costs involved in the performance of a liver biopsy such as the cost of an inpatient stay in hospital.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

In the August 2004 Prioritising Summary, one of the studies assessed was published by a Western Australian research group. The author of this paper (Rossi et al 2003) was contacted and asked if their group was continuing to use the FibroTest. Dr Rossi stated that their investigations into FibroTest had ceased for several reasons, the main ones being:
1. Their 2003 Clinical Chemistry paper found that the FibroTest did not perform as well as claimed.
2. The charge by the company BioPredictive for the use of FibroTest is high at approximately €30 (AUS $48).
3. The Western Australian group has chosen to develop their own serum model to diagnose fibrosis. This model is called Hepascore and is available free of charge. The equation for the model is published in the recent paper : Adams, L. A., Bulsara, M. et al (2005). '*Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection*', Clin Chem, 51 (10), 1867-1873.

The authors of this study do not know of any other uses of FibroTest in Australia (personal communication, 21st October 2005).

The first author of '*Prospective Analysis of Discordant Results between Biochemical Markers and Biopsy in Patients with Chronic Hepatitis C*', Poynard, is a consultant and has a capital interest in Biopredictive.

CONCLUSION:

The high quality evidence from the meta-analysis suggests that FibroTest could be used as an alternative to liver biopsy, however this evidence appears to be contradicted from experience in the Australian health setting.

HEALTHPACT ACTION DECEMBER 2005:

Therefore it is recommended that this technology be archived. An investigation into the Hepascore method from Western Australia may be warranted. It is likely that this technology will be superseded by a gene expression blood test.

SOURCES OF FURTHER INFORMATION:

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Australian Government Department of Health and Ageing 2004 *Commonwealth action on hepatitis C - How many people are affected by hepatitis C?* [Internet] Available at: http://www.health.gov.au/pubhlth/strateg/hiv_hepc/hepc/affected.htm [Accessed 5th August 2004].

Australian National Council on AIDS, Hepatitis C and Related Diseases Hepatitis C Sub-Committee 2002. *Estimates and Projections of the Hepatitis C Virus Epidemic in Australia 2002* [Internet] Available at: http://www.ancahrd.org/pubs/pdfs/epidemic_02.pdf [Accessed 11th August 2004].

Blue Cross, Blue Shield (2005) *Laboratory Section - Combination of Serum Markers for Liver Fibrosis in the Evaluation and Monitoring of Patients with Chronic Liver Disease* [Internet] Available at http://www.regence.com/trgmedpol/lab/lab47.html [Accessed 24th October 2005].

Halfon, P., Imbert-Bismut, F. et al (2002). 'A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease', *Comp Hepatol,* 1 (1), 3.

Imbert-Bismut, F., Messous, D. et al (2004). 'Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors', *Clin Chem Lab Med,* 42 (3), 323-333.

Ministry of Health (2000). *Hepatitis C infection in New Zealand: Estimating the current and future prevalence and impact.*

Munteanu, M., Messous, D. et al (2004). 'Intra-individual fasting versus postprandial variation of biochemical markers of liver fibrosis (FibroTest) and activity (ActiTest)', *Comp Hepatol,* 3 (1), 3.

National Horizon Scanning Centre (2004). *FibroTest-ActiTest, a diagnostic test for liver fibrosis in patients with hepatitis C* [Internet]. Available from http://www.publichealth.bham.ac.uk/horizon/2004reports/FibroTests.pdf [Accessed 11th August 2004].

Poynard, T., Munteanu, M. et al (2004). 'Prospective Analysis of Discordant Results between Biochemical Markers and Biopsy in Patients with Chronic Hepatitis C', *Clin Chem,* 50 (8), 1344-1355.

Rossi, E., Adams, L. et al (2003). 'Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients', *Clin Chem,* 49 (3), 450-454.

SEARCH CRITERIA TO BE USED:

Aspartate Aminotransferases/blood
Hepatitis C, Chronic/*complications
Human
Liver Cirrhosis/blood/*diagnosis/pathology/*virology