



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1446 – Hepascore test to diagnose and monitor liver fibrosis severity in patients diagnosed with Hepatitis B and C***

**Applicant:** Professor Gary Jeffrey

**Date of MSAC consideration:** MSAC 80<sup>th</sup> Meeting, 26-27 November 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

An Applicant Developed Assessment Report (ADAR) requesting Medicare Benefits Schedule (MBS) listing of Hepascore (a serum fibrosis panel test) for diagnosing and monitoring liver fibrosis severity in patients with chronic hepatitis C (CHC) or chronic hepatitis B (CHB) infection was received from Professor Gary Jeffrey of the University of Western Australia (UWA) and Illuminate Health Consulting by the Department of Health.

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support MBS funding of Hepascore to diagnose and monitor liver fibrosis severity in patients diagnosed with hepatitis B or C. MSAC considered that there was limited clinical need for an additional test to diagnose liver cirrhosis. MSAC considered that Hepascore has limited clinical utility over existing tests and was unlikely to improve clinical management or health outcomes for patients with chronic hepatitis B or C. MSAC considered that there were significant issues with the economic model that meant it was not reliable for decision-making. MSAC also noted that the proposed MBS fee was lower than the fee currently charged by pathology providers and this could result in out-of-pocket costs for patients.

#### **Consumer summary**

Professor Gary Jeffrey (University of Western Australia) applied for public funding via the Medicare Benefits Schedule (MBS) for Hepascore to diagnose and monitor liver fibrosis in patients with hepatitis B or C.

Liver fibrosis happens when healthy tissue in the liver becomes scarred and does not work as well. If more of the liver becomes scarred, it can lead to liver cirrhosis. Liver fibrosis and cirrhosis can be caused by infection with the hepatitis B or hepatitis C viruses (among other things).

## Consumer summary

Hepascore is a method of calculating a person's risk of liver fibrosis. Patients have a blood test (about 5 mL of blood is taken) that measures the levels of four things (called gamma-glutamyl transferase, bilirubin, hyaluronic acid and alpha-2 macroglobulin). Hepascore combines the results of the blood test with the patient's age and sex to estimate their risk of liver fibrosis.

The Medical Services Advisory Committee (MSAC) noted that there are already many other tests for liver fibrosis. Hepascore would not replace any of these existing tests. If a person has a positive Hepascore result, it would likely be confirmed using one of the other tests. Because of this, MSAC did not see a clinical need for Hepascore.

MSAC felt that the clinical evidence for Hepascore was low quality. There was not enough high-quality data to show that Hepascore improves the accuracy of diagnosis, or results in changing treatment decisions that improve health outcomes for patients. MSAC also felt that there were issues with the economic evaluation that meant it could not be sure if Hepascore would be good value for money. MSAC was also concerned that there would be out of pocket costs for patients as the applicant has asked for a lower fee than pathology services are charging privately.

### MSAC's advice to the Commonwealth Minister for Health

MSAC did not support MBS funding for Hepascore in patients with hepatitis B or C. This is because MSAC did not see a clinical need for Hepascore, the quality of evidence was low, and MSAC could not be sure if Hepascore would provide value for money.

## 3. Summary of consideration and rationale for MSAC's advice

MSAC noted the purpose of the application was to request MBS listing for Hepascore, a serum-based marker for liver fibrosis that combines results for four laboratory markers (gamma-glutamyl transferase, bilirubin, hyaluronic acid and alpha-2 macroglobulin) with age and sex in a proprietary algorithm. MSAC noted the algorithm and formula used for Hepascore are in the public domain<sup>1</sup>.

MSAC considered that there was limited clinical need for an additional test to diagnose and monitor liver fibrosis given the variety of alternative tests available. MSAC agreed with the Evaluation Sub-Committee (ESC) that Hepascore would be an additional test (not a replacement test) to assess liver fibrosis. MSAC noted a positive result indicative of fibrosis or cirrhosis would likely be confirmed with additional testing due to Hepascore's low positive predictive value. MSAC noted the pre-MSAC response disagreed on the use of confirmatory testing. MSAC noted the pre-MSAC response considered that transient elastography (Fibroscan<sup>®</sup>) has limited access, however MSAC noted that it is routinely used in public hospitals. Additionally, MSAC noted that the AST to platelet ratio index (APRI) is calculated from routine monitoring tests and has similar specificity to Hepascore at a threshold of 2, meaning it can rule out cirrhosis as effectively as Hepascore. Decreasing platelet count may also be indicative of cirrhosis. MSAC also considered liver ultrasound may include shearwave elastography but this is considered less effective than transient elastography. MSAC acknowledged that Hepascore may be of value in rural and remote areas where transient elastography is less accessible.

<sup>1</sup> Adams LA, Bulsara M, Rossi E, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. *Clin Chem*. 2005;51(10):1867-1873.

MSAC noted several issues relating to the clinical evidence identified by the ESC and Commentary that included:

- A lack of evidence on how Hepascore would affect clinical management such as enabling earlier diagnosis of cirrhosis and reducing complications of cirrhosis;
- Use of studies that used different Hepascore and APRI cut-offs to diagnose cirrhosis;
- The presentation of a meta-analysis that could not be replicated;
- Inclusion of the Hepascore training and validation data in the meta-analysis;
- The studies of clinical assessment did not report how cirrhosis was diagnosed; and,
- The ultrasound studies mostly included other liver disease populations.

MSAC noted the ADAR did not provide any data on the reproducibility of Hepascore tests across different laboratories and how it will be benchmarked. MSAC was not convinced by the ADAR's claim that changes in clinical management would not result in safety concerns as no evidence was presented. However, MSAC considered that a false positive result was unlikely to lead to over treatment as it would be followed by a confirmatory test such as transient elastography. MSAC considered there would be minimal, if any, risks of suboptimal treatment in patients with false negative results, both because patients have their response to anti-viral treatment assessed as part of usual care, and because many hepatitis C treatment regimens are the same irrespective of cirrhotic status.

MSAC noted that the pre-MSAC response claimed that Huang (2020)<sup>2</sup> validated the prognostic value of Hepascore. MSAC considered this was not an accurate claim, as Huang (2020) evaluated liver-related outcomes of patients in West Australian patients who had received a Hepascore test, not the ability of Hepascore to predict liver health outcomes, which is the relevant consideration in the context of an application for public subsidy.

In view of these issues, MSAC considered Hepascore has limited clinical utility over existing tests and is unlikely to improve clinical management or health outcomes for patients with chronic hepatitis B or C. MSAC noted that although Hepascore was likely generalisable to the Australian population with chronic hepatitis B or C, generalisability could be limited because Australian patients commonly have several factors contributing to their liver disease.

MSAC noted that the economic model compared Hepascore with either clinical assessment, APRI, or ultrasound. MSAC considered that these comparisons did not reflect clinical practice as most patients would receive all three interventions. MSAC considered the model structure was reasonable and agreed with the ESC that there were several implausible assumptions such as the assumption that only 10% of misdiagnosed patients would be retested. MSAC agreed with the ESC that there was substantial uncertainty around the clinical inputs into the model as many were based on clinical experience while others were sourced from poor quality studies, different liver disease populations, and from patient groups with a much higher prevalence of cirrhosis than the Australian population. MSAC noted the pre-ESC response disagreed with the ESC about the uncertainties in the economic model, stating that the model inputs were based on clinicians' experience treating chronic hepatitis B and C.

MSAC disagreed with the pre-MSAC response suggestion that Hepascore is usual clinical care, noting that although it is frequently used in Western Australia, this was not reflective of

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<sup>2</sup> Huang Y, Joseph J, de Boer WB, et al. Long-term Liver-related Outcomes of Patients With Chronic Liver Diseases in Australia. *Clin Gastroenterol Hepatol*. 2020;18(2):496-504.

other parts of Australia. MSAC noted that the Hepascore studies may have collected data that would allow APRI to be calculated and facilitate a direct comparison with APRI.

MSAC noted the financial estimates presented in the ADAR and the revised financial estimates calculated in the Commentary. MSAC noted the pre-ESC response that PathWest performs up to **redacted** Hepascore tests per year. MSAC raised concerns about the likely out-of-pocket costs for consumers, given that the applicant stated that PathWest requires an up-front payment of \$83.90<sup>3</sup>, but the applicant's proposed fee is \$40.50. MSAC considered that this would be unaffordable for many patients and may increase inequity.

Given these considerations, MSAC did not support public funding for Hepascore for use in diagnosing fibrosis or cirrhosis in patients with chronic hepatitis C (CHC) or chronic hepatitis B (CHB) infection. MSAC considered that similar issues would likely apply to public funding for Hepascore for use in patients with alcoholic or non-alcoholic fatty liver disease.

#### **4. Background**

This is the second ADAR for the Hepascore. A previous ADAR was submitted for consideration at the June 2019 Evaluation Sub-Committee (ESC) and July 2019 Medical Services Advisory Committee (MSAC) meetings. During the evaluation of the previous ADAR, it was considered that the subsidy request had numerous issues resulting in the ADAR not proceeding at that time.

#### **5. Prerequisites to implementation of any funding advice**

Hepascore is not registered with the Therapeutic Goods Administration (TGA), but the four component serum assays are registered under in vitro diagnostics (IVD) Class 2. This is a new intervention, as a panel of indirect non-invasive markers for quantitation of liver fibrosis is not available on the MBS.

The Royal College of Pathologists of Australasia (RCPA) Quality Assurance Programs (QAP) and National Pathology Accreditation Advisory Council (NPAAC) advised that Hepascore is an established and validated test and External Quality Assurance exists for half of the component tests. The remaining analytes have similar methodologies to other existing MBS items that have quality assurance arrangements in place and providers would have little problem working with Royal College of Pathologists of Australasia RCPA QAP to develop a quality framework for the remaining Hepascore analytes.

#### **6. Proposal for public funding**

The MBS item descriptor proposed is summarised in Table 1.

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<sup>3</sup> PathWest. Test Directory – Hepascore. Updated October 8 2020. Accessed March 3 2021. <https://pathwest.health.wa.gov.au/testdirectory/testdetail.aspx?TestID=1173>

**Table 1 Proposed MBS item descriptor**

Category 6 – PATHOLOGY SERVICES
Quantitation of liver fibrosis by proprietary clinical formula, Hepascore that incorporates, aside from, age and sex, a) serum bilirubin b) serum gamma-glutamyl transpeptidase c) serum alpha2-macroglobulin d) serum hyaluronic acid  For use in patients:  1) once in patients newly diagnosed with chronic hepatitis C as part of pre-assessment prior to assessing PBS funded direct acting antiviral (DAA) therapy
Fee: \$40.50
Quantitation of liver fibrosis by proprietary clinical formula, Hepascore that incorporates, aside from, age and sex, a) serum bilirubin b) serum gamma-glutamyl transpeptidase c) serum alpha2-macroglobulin d) serum hyaluronic acid  For use in patients:  1) once in patients newly notified with chronic hepatitis B to determine the presence of cirrhosis prior to assessing PBS therapy, and 2) then every two years, for patients with chronic hepatitis B, not diagnosed with cirrhosis, who require ongoing monitoring
Fee: \$40.50

Source: Table 26, pp 43-44 of the ADAR and the ratified PICO

The proposed fee in the ADAR and that in the PICO Confirmation differ, increasing from \$30.70 to \$40.50. The ADAR stated that this was due to increased overhead costs to allow private pathology laboratories to offer the test in rural and remote areas and the private health sector. MSAC noted that PathWest currently charges \$83.90, suggesting patients are likely to be charged a co-payment.

The pre-ESC response stated that a Hepascore prognostic report has been developed and is now in routine clinical use to guide clinical management and provide patients with prognostic information.

The ADAR proposed that the test can be requested by general practitioners (GPs) or specialists and be performed in any medical biochemistry laboratories.

## **7. Summary of public consultation feedback/consumer Issues**

Public consultation feedback was received from health care professionals (12) and professional organisations (3). The comments described a range of benefits of Hepascore including:

- Its simplicity (non-invasive blood test) and its ease of use in the community. It can be requested at the same time as other blood tests and is more accessible than other tests;
- The Gastroenterological Society of Australia (GESA) noted Hepascore's potential use as a triage tool prior to a subsequent test for cirrhosis (elastography). Similarly, other feedback noted that a high Hepascore should be confirmed with transient elastography (Fibroscan®). Conversely, it was noted that Hepascore could decrease inappropriate investigations;

- Early identification and diagnosis of people with cirrhosis promotes early intervention and treatment which improves clinical outcomes; and
- Increased detection of non-alcoholic fatty liver disease (NAFLD) & alcoholic liver disease, and earlier detection of hepatitis B related fibrosis by GPs.

This feedback was supportive of the evidence provided in the submission. Additional consumer feedback was sought from the Hepatitis Foundation which reported that the simplicity of Hepascore was of particular benefit to marginalised populations.

## **8. Proposed intervention's place in clinical management**

### **Description of Proposed Intervention**

Hepascore is an indirect serum fibrosis blood panel test that was developed in Australia to predict the presence and severity of liver fibrosis. It uses both laboratory (serum bilirubin, gamma-glutamyl transferase [GGT], hyaluronic acid [HA], alpha2-macroglobulin [ $\alpha$ 2-macroglobulin]) and demographic data (age, sex) in a proprietary formula to score fibrosis risk. The biomarkers are analysed using a 5 mL blood sample. The Hepascore test can be performed at the same time as blood is collected from patients for other purposes such as liver function tests at community pathology centres.

### **Description of Medical Condition(s)**

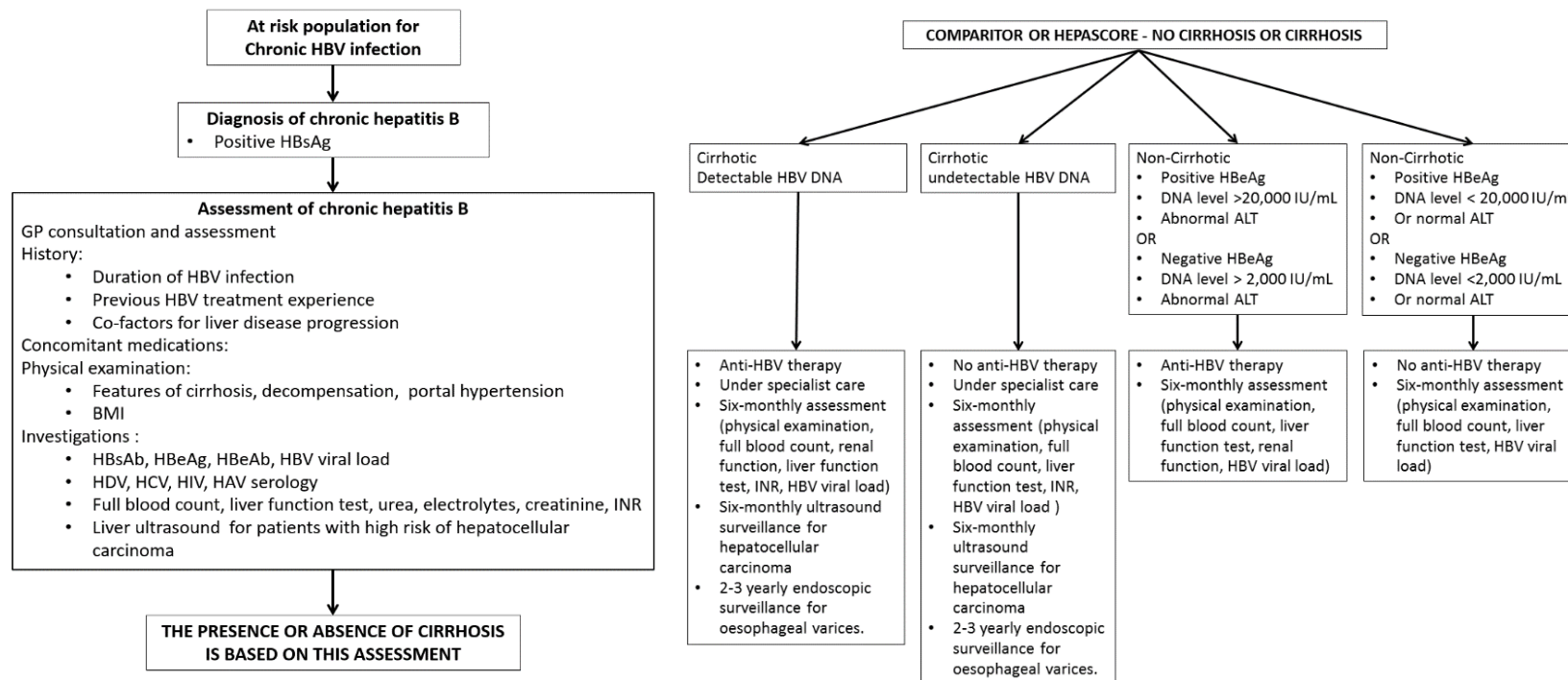
#### *Chronic hepatitis C (CHC)*

The target population is people who are newly diagnosed with chronic hepatitis C (CHC) by their GP. The clinical management algorithm is based on the requirement for pre-assessment for patients prior to receiving DAAs and to determine the presence or absence of cirrhosis. The presence of cirrhosis may have an impact on the duration of DAA therapy and also the need for further surveillance. The only difference between the current and proposed regimens (Figure 1) is the addition of Hepascore.

#### *Chronic hepatitis B (CHB)*

The target population of people diagnosed with CHB includes both newly diagnosed patients and those with ongoing infection. Patients who do not have cirrhosis are eligible for a Hepascore test once every two years. Patients diagnosed with cirrhosis will not have ongoing testing, although they remain eligible for PBS anti-viral therapy based on their viral load. In the proposed management algorithm, Hepascore is used in addition to routine monitoring, and does not change clinical management, except where cirrhosis is diagnosed. Patients diagnosed with cirrhosis can commence PBS-subsidised treatment with a lower viral load (Figure 2).

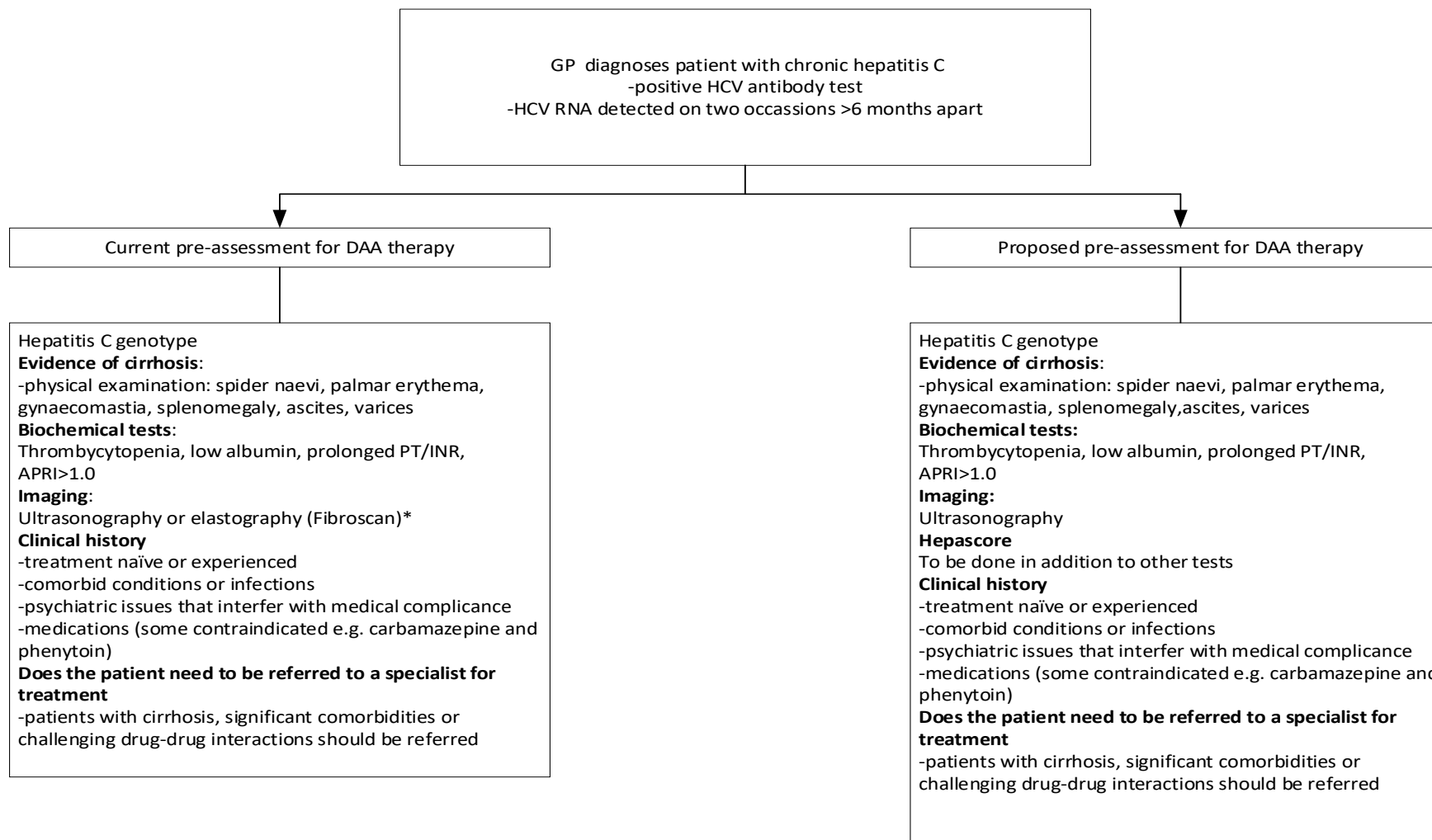
The Ratified PICO Confirmation requested that the economic evaluation explore the effect of testing once every 5 years in patients with a Metavir stage F0 or F1 (less than advanced fibrosis). The economic evaluation includes testing every two years for the first 5 year



**Figure 1 Current and proposed clinical management algorithm of patients with chronic hepatitis B infection**

Source: Figure 2, p52 of the ADAR and Ratified PICO

ADAR = Applicant Developed Assessment Report; ALT = alanine transaminase; DNA = deoxyribonucleic acid; HAV = hepatitis A virus; HBeAb = Hepatitis B e antibody; HBeAg = Hepatitis B e-antigen; HBsAb = Hepatitis B surface antibody; HBsAg = Hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; INR = international normalised ratio;



**Figure 2 Clinical management algorithms for pre-assessment of cirrhotic status in patients with chronic Hepatitis C for DAA therapy—current and proposed with Hepascore**

Source: Figure 1, p51 of the ADAR

ADAR = Applicant Developed Assessment Report; APRI=aspartate aminotransferase-to-platelet ratio index; DAA = direct-acting antiviral; GP = general practitioner; HCV = hepatitis C virus; INR = international normalised ratio; PT = prothrombin time; RNA = ribonucleic acid



## **9. Comparator**

The proposed comparator for both populations is usual clinical assessment that includes medical history, physical examination, LFTs, full blood count, international normalised ratio (INR), aspartate aminotransferase-to-platelet ratio index (APRI) and liver ultrasound where available (Wai et al., 2003). This was considered appropriate by the Commentary. APRI can be calculated using free, online calculators based on the results of two routine pathology tests.

The ADAR presented the following definition of the routine clinical assessment for chronic HCV and chronic HBV 1) Clinical assessment alone, 2) Clinical assessment including ultrasound scan, and 3) Clinical assessment including APRI. The ADAR implicitly acknowledged that this differed from the accepted comparator in the Ratified PICO. However, the ADAR stated that no study assessed the accuracy of a complete clinical assessment combined with ultrasound scan and APRI with the presence of cirrhosis as determined by the reference standard liver biopsy.

PASC did not consider Fibroscan® (transient elastography) an appropriate comparator, as it is not listed on the MBS. Liver biopsy is the reference standard however it is less frequently performed in the current era and it was not considered appropriate as the initial comparator. The Pre-ESC Response (p3) claimed that ultrasound elastography is performed by radiological providers using a liver ultrasound machine and is rebated as a liver ultrasound.

## **10. Comparative safety**

The systematic review in the ADAR did not identify any studies that directly compare clinical assessment with ultrasound scan or APRI to clinical assessment and Hepascore. A linked evidence approach was used.

**Table 2 Key features of the included linked evidence for CHC and CHB**

Type of evidence	Description	Number
<b>CHC</b>		
Comparative diagnostic performance <sup>a</sup>	Comparative diagnostic performance was not reported. A meta-analysis of diagnostic accuracy is presented.	k=0 n=0
Comparative clinical validity (CHC) <sup>a</sup>	Comparative clinical validity was not presented but indirect comparative clinical validity is presented	k=6 n=2,591 vs k=2 n=185 vs k=13 n=2,636
Therapeutic efficacy	Evidence to show that test results guides decisions about subsequent clinical management of patients is not presented	k=0 n=0
Therapeutic effectiveness	Not presented	k=0 n=0
<b>CHB</b>		
Comparative diagnostic performance <sup>a</sup>	Comparative diagnostic performance was not reported for either CHB or CHC populations. A meta-analysis of diagnostic accuracy is presented.	k=0 n=0
Comparative clinical validity (CHB) <sup>a</sup>	Comparative clinical validity was not presented but indirect comparative clinical validity is presented	K=3 N=510 vs k=2 N=185 Vs k=5 N=1,247
Therapeutic efficacy	Evidence to show that test results guides decisions about subsequent clinical management of patients is not presented	k=0 n=0
Therapeutic effectiveness	Not presented	k=0 n=0

Source: Table 3-4, p17-18 of the Commentary

CHB = chronic hepatitis B; CHC = chronic hepatitis C;

<sup>a</sup> reference standard available

The ADAR presented:

- a meta-analysis of six studies (N=2,591) that report the accuracy of Hepascore in CHC patients against liver biopsy;
- a meta-analysis of three studies (n=410) that report the accuracy of Hepascore in CHB patients;
- a meta-analysis of two studies (n=185) for clinical assessment without ultrasound in CHC populations;
- a meta-analysis of eight studies (n=2,739) for clinical assessment with ultrasound;
- a published meta-analysis (Lin 2011) reporting the diagnostic accuracy of APRI in patients with CHC; and
- a published meta-analysis (Xiao 2015) reports the diagnostic accuracy of APRI in patients with CHB.

The pre-ESC response considered that the clinical assessment of patients with CHC and CHB includes Hepascore, transient elastography (Fibroscan®) or ultrasound elastography where patients receive these services funded through other subsidy arrangements or pay privately. The pre-ESC response claimed that there can be no comparative studies of Hepascore versus clinical assessment excluding Hepascore.

The ADAR did not describe the specific meta-analysis methods used to combine individual trial results. The Commentary noted that there are potential statistical issues that may arise depending on the method used. The Commentary was able to replicate the meta-analysis of Hepascore in CHC using a hierarchical meta-analysis of test accuracy studies. The meta-analysis of Hepascore in CHB could not be replicated as a minimum of four studies is required to do a hierarchical meta-analysis of test accuracy studies. Neither of the meta-analyses for APRI could be validated during the evaluation.

The ADAR provided limited information detail on how it derived the 2x2 diagnostic accuracy tables for studies that only reported sensitivity and specificity. The ADAR clarified that the method described in Huang 2017 was used to derive relevant data and perform the meta-analysis. Implicitly, this suggested the ADAR included studies provided the area under ROC curve (AUROC, 95% CI) of Hepascore for different fibrosis stages and/or 2x2 table data could be calculated from at least one cut point. Huang 2017 also stated that a first meta-analysis was performed using the random effects model for all included studies that provided both AUROC and 95% CI. Secondly, a summary ROC (SROC) model was calculated for all included studies from which at least one 2x2 table could be created.

#### *Test adverse events*

The test is procedurally safe and relies on a blood sample often taken at the same time as other blood samples are taken.

#### *Adverse events from change in management*

The ADAR did not present any evidence for change in management. There is a risk of misallocation of patients to the different advanced fibrosis stages, which may affect the outcomes of the therapy subsequently selected. Although for CHC, some of the newer therapies may be administered in the presence or absence of cirrhosis, the duration of optimal treatment may vary based on cirrhotic status, and, consequently, there remains a risk of sub-optimal treatment associated with misallocation.

## **11. Comparative effectiveness**

Table 3 presents a summary of the sensitivity and specificity of Hepascore and its main comparators.

**Table 3 Summary of findings for the linked evidence comparison of Hepascore with liver biopsy and clinical assessment (with or without ultrasound) with liver biopsy in patients with HCV or HCB**

Intervention	N	K	Population	Quality of evidence <sup>a</sup>	Comparator	Sensitivity	Specificity
Hepascore	2,591	6	CHC	⊕⊕⊕⊕	Liver biopsy	0.77 (0.70-0.83)	0.86 (0.81-0.89)
Hepascore (threshold $\geq 0.84$ )	1,418	5	CHC	NR	Liver biopsy	0.76 (0.62-0.86)	0.89 (0.83-0.93)
Hepascore	510	3	CHB	⊕⊕⊕⊕	Liver biopsy	0.71 <sup>b</sup>	0.87 <sup>b</sup>
Clinical assessment (no ultrasound)	185	2	Chronic liver disease <sup>c</sup>	⊕⊖⊖⊖	Liver biopsy	0.63 <sup>b</sup>	0.66 <sup>b</sup>
Clinical assessment with ultrasound	2,739	8	Chronic liver disease <sup>d</sup>	⊕⊖⊖⊖	Liver biopsy	0.41 (0.29-0.55)	0.91 (0.85-0.95)
Clinical assessment with APRI (threshold 1.0)	2,636	13	CHC	⊕⊕⊕⊕	Liver biopsy	0.76 (0.71-0.80)	0.72 (0.70-0.74)
Clinical assessment with APRI (threshold 1.0)	1,247	5	CHB	⊕⊕⊕⊕	Liver biopsy	0.66 (0.47-0.85)	0.74 (0.56-0.84)
Clinical assessment with APRI (threshold 2.0)	1,445	6	CHC	NR	Liver biopsy	0.31 (0.13-0.63)	0.89 (0.81-0.96)
Clinical assessment with APRI (threshold 2.0)	2,429	11	CHB	NR	Liver biopsy	0.46 (0.41-0.51)	0.91 (0.90-0.93)

Source: Table 5, pp21-22; Table 24, p64, Table 28, p72; Table 29, p72-73 of the Commentary,

APRI = AST to platelet ratio index; AST = aspartate transaminase; CHB = chronic hepatitis B; CHC = chronic hepatitis C; NR = not reported

<sup>a</sup> GRADE Working Group grades of evidence (Guyatt 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

<sup>b</sup> ADAR stated that 95% confidence interval could not be generated for sensitivity and specificity due to small study number

<sup>c</sup> Both studies were in populations with hepatitis C (p65 of the Commentary)

<sup>d</sup> One study had a CHC population and another had a CHB population (p65 of the Commentary)

The ADAR nominated Hepascore thresholds of  $\geq 0.85$  for CHC and  $\geq 0.84$  for CHB to diagnose cirrhosis. However, the reported meta-analysis (for both the CHC and CHB populations) included studies that had cut-offs below this level. This included:

- Two studies that were substantially below the nominated cut-off of  $\geq 0.85$  for CHC: Boursier (2008), and Guechot (2010) that used 0.80 and 0.75, respectively;
- One study that was below the nominated cut-off  $\geq 0.84$  for CHB: Basar (2013) that used 0.518.

The pre-ESC response stated that the cut-points used in the analysis are those that have been developed in Australian patients. International studies developed slightly different values due to different clinical characteristics of the CHC and CHB patients as regards co-factors for cirrhosis such as NAFLD and excess alcohol use. In Australia 50% of patients with cirrhosis have multiple factors such as CHC and alcohol (Powell et al, 2019) and the Australian Hepascore cut-point takes this into account.

The Commentary considered that this makes it difficult to determine the diagnostic accuracy of Hepascore to exclude cirrhosis. The Commentary presented a revised meta-analysis that included only studies in the CHC population in which the cut-off for diagnosis of cirrhosis was 0.84 or greater (n=1,418, Table 3)

The Commentary was able to replicate the meta-analysis of Hepascore in the CHC population. The meta-analysis of Hepascore in the CHB population could not be validated as a minimum of four studies is required to do a hierarchical meta-analysis of test accuracy studies.

The Commentary noted that the meta-analysis of Hepascore in CHC inappropriately included the training cohort and the validation cohort used to develop Hepascore in diagnosing cirrhosis or advanced fibrosis.

The Commentary noted the clinical assessment studies did not include clinical criteria for diagnosing or excluding cirrhosis.

The meta-analysis of clinical assessment with ultrasound included populations that had different types of liver disease (predominantly chronic liver disease and not mono-infection with either CHB or CHC). Of eight studies included only one (Iacobellis 2005) was for a population of CHC and only one was for a population of CHB (Chen 2008). The approach was not justified in the ADAR. The Commentary considered that combining the studies was inappropriate as they were all reported as low-quality studies with inherent risk of bias, and the liver diseases differed between the studies so the study populations were not similar enough to be considered together or to be compared to the CHC population.

The ADAR presented two published meta-analyses however, only included sensitivity and specificity estimates for Clinical Assessment with APRI for the cut-off of 1.0. This was inconsistent with the cut-off described in the Ratified PICO of 2.0. However, the Commentary noted that the Australian guidelines for the treatment of HCV (Thompson 2020) recommends a cut-off of 1.0 to exclude presence of cirrhosis. The Commentary noted that the meta-analyses for Clinical Assessment with APRI could not be validated during the evaluation.

The ADAR presented two studies to support the reliability of Hepascore and clinical assessment. Guechot (2010) reported high reproducibility of estimating Hepascore using either automatic or manual hyaluronic acid assay. Ladenheim (1992) found that ultrasound assessment (using criteria proposed in a previous study - De Lelio 1989) had a low accuracy to diagnose cirrhosis with sensitivity of 0.13 and specificity of 0.88.

The ADAR did not address the question of the reproducibility of the automated Hepascore test across different laboratories or by different operators. The Hepascore test can be implemented by laboratories with the published algorithm, but the ADAR did not present information on how the test is to be benchmarked.

### *Clinical validity*

The Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee – Service Type: Investigative (p53, referred to hereafter as “MSAC Investigative Guidelines”) state that clinical validity relates to whether an investigative medical service answers the clinical question being asked, and refers to how an investigative medical service detects or predicts the target condition under consideration.

The ADAR presented estimates of PPV and NPV from the meta-analyses used to support the analytical validity of Hepascore. The ADAR reported that:

- Hepascore in the CHC population (k = 6, N = 2,079) had a pooled PPV of 0.38 and a pooled NPV of 0.97;
- Hepascore in the CHB population (n=410) had a pooled PPV of 0.41 and a pooled NPV of 0.95;
- Clinical assessment without ultrasound in a chronic liver disease population (k=2, n=185) had a pooled PPV of 0.33 and a pooled NPV of 0.86 and noted this evidence was considered a very low quality using the GRADE tool;
- Clinical assessment with ultrasound in a chronic liver disease population (k=8, n=2,739) had a pooled PPV of 0.40 and a pooled NPV of 0.73 and noted this evidence was considered a very low quality using the GRADE tool;
- APRI in the CHC population (k = 13, N = 2,636) had a pooled PPV of 0.39 and the pooled NPV of 0.93 based on a mean prevalence of 19%; and
- APRI in the CHB population (k = 5, N = 1,247) had a pooled PPV of 0.37 and the pooled NPV of 0.90 based on a mean prevalence of 18.7%.

The Commentary highlighted that:

- the pooled prevalence of cirrhosis used to estimate PPV and NPV were not presented for all analyses; and
- the generalisability of these results to the target Australian population for this test cannot be determined from the information provided.

The MSAC Investigative Guidelines (p53) note that if an individual is symptomatic and the test is being used for diagnostic purposes, the probability of actually having underlying disease (if the test is positive) or not disease (if the disease is negative) is heavily dependent upon prevalence.

### *Clinical utility*

The ADAR considered that no study has directly measured the effect of Hepascore on patient management for those with CHC and CHB. The ADAR did not present additional information on how the use of Hepascore could change patient management and health outcomes such as potential benefit to patients from an earlier diagnosis of cirrhosis and associated changes in resource use or short-term and long-term complications. The MSAC Investigative Guidelines (p22) support a narrative linking of evidence assessing components of the test treatment pathway in order to come to a conclusion as to the impact on patient health outcomes as a result of performing the test.

In CHC, the ADAR considered that Hepascore will more accurately inform the selection of a DAA regimen. The ADAR considered that although some DAA regimens do not vary by cirrhosis status, the more commonly prescribed pan-genotypic glecaprevir + pibrentasvir regimen is shorter for patients without cirrhosis. The ADAR concluded that a more accurate diagnosis would result in better clinical outcomes from this regimen. The ADAR noted that a false positive diagnosis of cirrhosis would result in inappropriate, longer, more costly treatment with glecaprevir + pibrentasvir. A false negative diagnosis would result in a shorter duration of treatment and inferior outcomes. The Commentary noted that DAA for hepatitis C are subject to special pricing arrangements, therefore the true prices are unknown.

In CHB, the ADAR claimed that Hepascore will more accurately inform PBS eligibility for lifelong antiviral treatment as the current PBS restrictions for CHB treatments require a lower level of HBV DNA for patients with cirrhosis. The ADAR also noted that the presence of

hepatitis B e-antigen (HBeAg) also affects the level of HBV DNA that must present for PBS treatment eligibility. The ADAR noted that a false positive diagnosis will result in additional, inappropriate monitoring that will incur additional costs. A false positive diagnosis would result in patients not being monitored. This would result patients being diagnosed with hepatocellular carcinoma at a later stage. The ADAR considered that HCC screening was associated with improved survival based on a meta-analysis of HCC surveillance (Singal 2014).

### *Impact of repeat testing and monitoring*

For CHC, the minimum time interval between Hepascore tests that resulted in useful clinical information was one year (Jeffrey 2017). For CHB, the annual rate of change in Hepascore increased significantly without antiviral therapy whereas rates fell significantly during effective antiviral treatment (Raftopoulos 2012). Long term follow up of 10,993 Australian patients with chronic liver disease (HCV n=5566; HBV n=1989) found that Hepascore values were independently predictive of life threatening liver complications, liver transplantation and liver related death (Huang Y -submitted). There is unlikely to be harms for repeat testing using Hepascore.

### **Clinical claim**

The ADAR made the following clinical claims:

- In untreated chronic HCV patients Hepascore is more accurate than routine clinical assessment (the comparator) in determining the presence of cirrhosis. There are no additional safety risks. The use of Hepascore results in improved treatment outcomes and costs.
- In newly diagnosed chronic HBV patients and in prevalent chronic HBV patients, not diagnosed with cirrhosis, but requiring ongoing liver status monitoring, Hepascore is clinically superior to routine clinical assessment in determining the presence of cirrhosis. Hepascore is equivalent to the comparator for safety risk.

The Commentary considered that the clinical claims were not adequately supported by the evidence presented as:

- The meta-analyses supporting the effectiveness of Hepascore were difficult to interpret as they may have inappropriately combined studies that:
  - used different Hepascore cut-offs to diagnose cirrhosis,
  - could not be validated for the CHB population, and,
  - inappropriately included the studies used to develop and validate Hepascore
- The indirect comparisons of clinical assessment (with and without ultrasound) with Hepascore as the meta-analyses of clinical assessment were difficult to interpret as:
  - the clinical assessment studies did not include clinical criteria for diagnosing or excluding cirrhosis,
  - the meta-analyses of clinical assessment included studies were rated as low quality with a high risk of bias, and
  - the meta-analyses combined studies that included populations from different types of liver disease that should not be combined.
- The meta-analysis of Clinical Assessment with APRI could not be validated; and
- The ADAR did not present a rationale to support the clinical utility of Hepascore.

## **12. Economic evaluation**

The ADAR presented two cost-utility analyses. This was appropriate as the clinical evaluation suggested that relative to clinical assessment including APRI, Hepascore has non-

inferior safety and superior effectiveness based on the evidence profile in the ADAR. The same model structure was used for both the CHC and CHB (Table 4).

**Table 4 Summary of the economic evaluation**

Perspective	Payer, average patient
Comparator	Clinical assessment, Ultrasound
Type of economic evaluation	Cost-utility
Sources of evidence	Academic development and research, systematic review
Time horizon	45 years
Outcomes	QALYs
Methods used to generate results	Cohort Markov model
Health states	No fibrosis (F0), Mild fibrosis (F1), Moderate fibrosis (F2), Significant fibrosis (F3), Compensated cirrhosis (F4) decompensated cirrhosis (F5), Hepatocellular cancer (HCC), Liver transplant (LT), Post liver transplant (PLT), Death
Cycle length	1 year
Discount rate	5%
Software packages used	Microsoft Excel

Source: Table 5, p27-28 of the ADAR

ADAR = Applicant Developed Assessment Report; QALY = quality-adjusted life years

The economic models concluded that Hepascore was dominant for both CHC and CHB compared with clinical assessment, ultrasound and APRI.

The Commentary considered that the economic evaluation was unreliable as:

- The model assumes that 10% of false negative (FN) patients who are retested every second year in the first 5 years of the model. Thereafter, patients who are FN or false positive (FP) inappropriately remain in these states for the duration of the time horizon of the model (45 years). It was considered unlikely that patients would have an incorrect diagnosis for 45 years as guidelines for the treatment of CHC advise regular monitoring, and for CHB advise monitoring of patients every 6 months;
- The sensitivity and specificity estimates for Hepascore and clinical assessment and APRI applied in the model were not considered reliable; and,
- There was insufficient description of the source of many parameters used in the model.

The pre-MSAC response noted the ESC report (and the Commentary) incorrectly stated that Markov modelling approach resulted in patients who regress to less severe Metavir stage acquire the mortality risk of a younger patient. Mortality was calculated based on a weighted average age of 43 years at baseline.

Additionally, the Commentary presented an analysis of cost per FN or FP diagnosed correctly (Table 5).



**Table 5 Cost per additional false negative and false positive patient diagnosed**

Indication	Cost per test	Change in incorrect diagnoses <sup>a</sup>	Incremental cost/patient
CHC	\$40.50	FN = 0.09% FP = 12.74%	\$45,000 per FN avoided \$317.9 per FP avoided
CHB		FN = 0.69% FP = 11.44%	\$5,903.79 per FN avoided \$354.08 per FP avoided

Source: Table 38, p99 of the Commentary

APRI = AST to platelet ratio index; AST = aspartate transaminase; CHB = chronic hepatitis B; CHC = chronic hepatitis C; FP = false positive; FN = false negative

<sup>a</sup> compared with APRI

The Commentary highlighted that because the sensitivities of APRI and Hepascore are almost identical, few false negatives avoided in either CHC and CHB, suggesting that the risks of poor outcomes due to missing cirrhosis is very low and possibly non-existent in CHC. The Commentary considered the ADAR's claim of reducing the potential for inadequate treatment and necessary retreatment in CHC is not supported by the ADAR's estimates of diagnostic accuracy, given the very small, estimated difference in false negatives (FNs) and the consequent high cost per FN avoided. There is a potential for savings to be made in FP avoided, as a FP may require a longer initial DAA treatment. Accurately estimating drug cost offsets in CHC would require effective prices and modelling that accounts for comparative retreatment rates or failure rates in patients who receive inadequate treatment.

### 13. Financial/budgetary impacts

The ADAR used an epidemiological approach to estimate the financial implications of Hepascore (Table 6). The ADAR forecast hepatitis C diagnoses based on 2015 data and assumed new cases would increase at the same rate as population growth (1.6% per year). The Commentary considered this may be an overestimate and that it may be more appropriate to forecast a reduction in new hepatitis C cases due to the PBS listing of DAAs.

The ADAR estimated use in the hepatitis B population to consist of 1) newly diagnosed patients 2) patients requiring monitoring, and 3) Aboriginal and Torres Strait Islander population with CHB. CHB patients requiring monitoring was estimated based on expert opinion. The Commentary considered the population to be underestimated and presented revised estimates. This was based on the assumption that newly diagnosed CHB patients will receive a test when diagnosed, and a larger prevalent population being actively monitored can receive a test every two years.

The ADAR estimated 23,568 services in Year 1, increasing to 29,545 in Year 5. The pre-ESC response stated that PathWest performs up to **redacted** tests per year but also noted that Hepascore is used in Australia in patients with non-alcoholic liver disease and alcoholic liver disease.

**Table 6 Total costs to the MBS associated with Hepascore (alternatives calculated during the evaluation are presented in italics).**

-	2019-20	2020-21	2021-22	2022-23	2023-24
<b>CHC</b>					
Number of services	9,164	9,858	11,129	11,307	11,488
Sub-total cost	\$371,136	\$399,255	\$450,714	\$457,926	\$465,253
<b>CHB</b>					
Number of services	14,404	15,495	17,493	17,772	18,057
Sub-total cost	\$583,366	\$627,565	\$708,451	\$719,786	\$731,302
<b>Total number of services</b>	<b>23,568</b>	<b>25,354</b>	<b>28,621</b>	<b>29,079</b>	<b>29,545</b>
<i>Revised number of services</i>	<i>79,898</i>	<i>49,631</i>	<i>52,104</i>	<i>53,521</i>	<i>54,978</i>
Total cost minus co-pay	<b>\$811,327</b>	<b>\$872,797</b>	<b>\$985,290</b>	<b>\$1,001,055</b>	<b>\$1,017,072</b>
<i>Total cost minus co-pay</i>	<i>\$2,750,502</i>	<i>\$1,708,542</i>	<i>\$1,793,677</i>	<i>\$1,842,453</i>	<i>\$1,892,616</i>

Source: 6, p24 of the Commentary

CHB = chronic hepatitis B; CHC = chronic hepatitis C; MBS = Medicare Benefits Scheme

#### 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Clinical need for Hepascore	Hepascore is proposed to be used in addition to other existing non-invasive tests and scoring systems, not as a replacement. ESC therefore queried the clinical need for Hepascore, given that multiple alternative tests are available, the incremental benefit of Hepascore is not known, and Hepascore is not required for patients to access PBS-listed treatment. A positive Hepascore result would also require additional confirmatory testing due to its low positive predictive value. ESC also noted MSAC's March 2016 decision not to recommend transient elastography (Fibroscan®, a diagnostic tool used in clinical practice) for MBS listing. Additionally, ESC noted that there was limited evidence to justify the use of Hepascore as a prognostic tool.
Low quality evidence for improvement in diagnostic accuracy and limited evidence for improvement in clinical outcomes	ESC considered the quality of clinical evidence to be low. There are no comparative studies of Hepascore vs clinical assessment, nor any direct or indirect evidence for the diagnostic accuracy, or clinical utility of Hepascore for cirrhosis. Evidence of the benefit of an accurate and early diagnosis of cirrhosis to patients and changes to clinical management are not presented. These clinical uncertainties flow through to the economic evaluation.
High level of uncertainty in the economic evaluation	ESC considered that the modelled impacts of Hepascore as an additional test and the impact on lifetime outcomes were not plausible. The economic model is unnecessarily complex and includes several structural assumptions that are not supported by evidence which generally favoured Hepascore and have a large impact on economic outcomes. The results of the applicant's model indicate that Hepascore is dominant; however, the clinical issues relating to the model inputs and assumptions in the base case make this highly uncertain.
Uncertain financial impacts	ESC considered the financial and budgetary implications to be highly uncertain due to the assumptions about size of the eligible chronic hepatitis B and chronic hepatitis C populations.

#### ESC discussion

ESC noted the purpose of the application was to request Medicare Benefits Schedule (MBS) listing for Hepascore, a serum-based marker for liver fibrosis that combines laboratory markers (gamma-glutamyl transferase [GGT], bilirubin, hyaluronic acid and alpha-2

macroglobulin) with age and sex in a proprietary algorithm. ESC noted that a previous application for Hepascore had been submitted to the Department of Health in 2019, but due to numerous issues identified during the evaluation, the application did not proceed to ESC or MSAC at that time.

The ESC noted that the PathWest-patented algorithm and the Hepascore formula is in the public domain.

ESC noted the proposed populations for Hepascore testing:

- newly diagnosed chronic hepatitis C (CHC) patients to determine the presence or absence of cirrhosis before commencing Pharmaceutical Benefits Scheme– (PBS)-listed direct-acting antiviral agents (DAA) therapy
- newly diagnosed hepatitis B patients who require assessment of the presence or absence of cirrhosis before accessing PBS-listed therapy;
- the prevalent population of patients diagnosed with hepatitis B, not diagnosed with cirrhosis, for ongoing monitoring of their liver status every 2 years.

ESC noted the claim in the applicant-developed assessment report (ADAR) that Hepascore will benefit marginalised populations which was supported by input from the Hepatitis Foundation. However, no further evidence in support of this claim was provided. ESC queried the extent of access issues for marginalised groups. ESC noted that imaging-based assessments such as transient elastography (Fibroscan®) and acoustic radiation force impulse (ARFI) were provided in public hospitals. Additionally, ESC noted that mobile transient elastography (Fibroscan®) and the Enhanced Liver Fibrosis test (ELF™, another non-invasive algorithm using blood test parameters) are routinely performed for patients in rural and remote areas and their cost is usually paid for by local health services. Similarly, ESC noted that health services providing care to prison populations use aspartate aminotransferase-to-platelet ratio index (APRI) and mobile transient elastography (Fibroscan®) when assessing prisoners with liver disease. ESC noted that additional consumer feedback was sought from the Hepatitis Foundation which reported that the simplicity of Hepascore was of particular benefit to marginalised populations.

ESC reviewed the proposed clinical management algorithms and noted that Hepascore is proposed to be used in addition to other existing non-invasive tests and scoring systems, not as a replacement. ESC therefore queried the clinical need for Hepascore, given that multiple alternative tests are available and a Hepascore result is not required for patients to access PBS-listed treatment. For the hepatitis B population, ESC also queried whether the proposed clinical management algorithm included the full range of investigations that would be conducted for these patients.

ESC considered that the item descriptors should state “prior to accessing” PBS listed antiviral medication rather than “prior to assessing”.

ESC noted a discrepancy in the proposed fee from \$30.70 in the PICO confirmation to \$40.50 in the current ADAR. The applicant claimed that the increase was due to higher overhead costs. The ESC noted that serum bilirubin and GGT would normally be performed under MBS item 66503 at a fee of \$11.65. The applicant indicated that alpha-2-macroglobulin is measured by a similar technique to beta-2-microglobulin (MBS item 66629 fee \$20.10) and hyaluronic acid is measured by a technique similar to the items in MBS item 66779 (fee \$39.95). The ESC considered that the proposed fee might be reasonable based on the fees for

similar items above. ESC also noted that the February 2015 application for Hepascore indicated that it is performed in both community and hospital settings at a cost of \$74.39 and queried whether there would be an out-of-pocket costs for consumers.

ESC noted that although liver biopsy is considered the reference standard for a diagnosis of cirrhosis, it is rarely used to diagnose cirrhosis in clinical practice. ESC noted that in clinical practice a variety of tests are used and interpreted incrementally. These include ultrasound, APRI, shear wave elastography, acoustic radiation force impulse (ARFI), transient elastography (Fibroscan®) and enhanced liver fibrosis (ELF). ESC noted that the comparator used in the application was clinical assessment with or without APRI. ESC also noted the March 2016 decision by MSAC not to support public funding for transient elastography (Fibroscan®).

ESC noted the lack of comparative studies comparing Hepascore with standard clinical assessment. The linked evidence approach taken in the application relies on naive indirect comparisons of non-comparative single-arm studies. The evidence presented included:

- meta-analysis of six studies (N = 2,591) that report the accuracy of Hepascore in hepatitis C patients against liver biopsy
- meta-analysis of three studies (N = 410) that report the accuracy of Hepascore in hepatitis B patients
- meta-analysis of two studies (N = 185) for clinical assessment of cirrhosis without ultrasound in hepatitis C populations
- meta-analysis of eight studies (N = 2,739) for clinical assessment with ultrasound in chronic liver disease (non-hepatitis) populations
- meta-analysis (Lin 2011) reporting the diagnostic accuracy of APRI in patients with hepatitis C
- meta-analysis (Xiao 2015) reporting the diagnostic accuracy of APRI in patients with hepatitis B.

ESC considered the quality of evidence to be low, and no studies assessed changes in clinical outcomes or patient management following Hepascore. Cut-offs to define cirrhosis also varied between studies and were not always pre-determined. The ADAR nominated Hepascore thresholds of  $\geq 0.85$  for hepatitis C and  $\geq 0.84$  for hepatitis B to diagnose cirrhosis. However, the reported meta-analyses for both populations included studies that had cut-offs below this level. The commentary also noted that the meta-analysis in the hepatitis B population could not be replicated.

ESC noted that the negative predictive value (NPV) of Hepascore was high (approximately 0.9 or greater, similar to other predictive markers of fibrosis) suggesting Hepascore can accurately indicate the absence of cirrhosis. The positive predictive value (PPV) was low (0.37 to 0.41), meaning positive results are not highly indicative of cirrhosis. ESC considered that patients identified as having cirrhosis with Hepascore would likely receive further confirmatory testing. ESC also noted that the studies that assessed clinical validity (NPV and PPV) of Hepascore were in populations with cirrhosis prevalence of around 18%, which is not typical of Australian populations, or prevalence was not reported. ESC also noted that the studies in non-hepatitis populations may not be generalisable to the proposed population in this application. ESC considered that there was limited evidence to justify the use of

Hepascore as a prognostic tool. ESC noted that the prevalent population with CHB is generally young and relatively healthy and most are not regularly screened for fibrosis. ESC considered that regular screening in a CHB population with a very low risk of cirrhosis would identify few additional patients with cirrhosis and would likely have a high number needed to treat. Overall, ESC considered that the application did not adequately demonstrate the clinical utility of Hepascore.

ESC reviewed the comparative safety of Hepascore and considered there were no substantial safety issues. ESC considered that false positives were unlikely to lead to overtreatment as a positive result would be confirmed using another of the available tests.

ESC considered that the model used in the economic evaluation was unnecessarily complex with a total of 28 health states (including subgroups) and several structural assumptions that had a large impact on economic outcomes. ESC noted that the visualisation of the model structure presented in the application was based on the published literature, but the model itself did not reflect this structure – the model has additional disaggregated health states for fibrosis stages, and allows the possibility of regression in fibrosis stages over the first 5 years of treatment.

Other assumptions that affect the economic model were based on clinical experience with no supporting evidence; these include the following:

- Only 10% of misdiagnosed (false negative and false positive) patients are retested; others remain in the model without correct diagnosis for 45 years – ESC considered that this was highly underestimated and favoured Hepascore.
- Only 10% of false negative CHC patients who receive a lower antiviral dose may receive a higher dose during the first 5 years – ESC considered that this was highly unlikely (as patients are continually monitored) and favoured Hepascore.
- False positive patients are assumed to accrue 100% of survival benefits (that is, no difference between false positive and true negative patients).
- False negative patients with CHC have the same likelihood (90%) of achieving a sustained virologic response to antiviral therapy as true positive patients despite being treated with a shorter antiviral regimen intended for patients without cirrhosis. ESC considered this may not be logical.
- Regression in fibrosis states is assumed for the first 5 years only.

The results of the model indicated that Hepascore is dominant; however, ESC considered that the clinical issues relating to the model inputs and assumptions in the base case made the results of the model uninformative. ESC considered that the modelled impacts of Hepascore as an additional test and the impact on lifetime outcomes were not plausible.

ESC noted the financial and budgetary implications in the application, but considered that these were highly uncertain due to the assumptions made. This included underestimating utilisation in the eligible patients with CHB, uncertain cost savings to the MBS from reductions in monitoring costs, liver transplantation and HCC, and uncertain cost savings to the PBS based on reduced use of antiviral medication. ESC also noted there is potential for leakage into other chronic liver disease populations.

ESC acknowledged the applicant's pre-ESC response.

**15. Other significant factors**

Nil.

**16. Applicant comments on MSAC's Public Summary Document**

The applicant disagrees with MSAC and ESC on the appropriateness of liver biopsy as a comparator, the interpretation of clinical data, the assessment of the economic evaluation, and the clinical need for Hepascore. The applicant disagrees with MSAC that the proposed MBS fee would result in out-of-pocket costs for patients and considers this a major misperception. The application stated that private pathology laboratories can perform the test in the community with a rebate fee of \$40.50. Therefore, the applicant believes that is it not valid to conclude that pathology providers would charge a higher price than the MBS rebate.

**17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website [visit the MSAC website](#)