NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Virtual Touch Quantification to diagnose and monitor liver fibrosis

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

The Virtual Touch Quantification (VTq; Siemens) software application assesses the stiffness of liver tissue by measuring shear-wave speed. Liver tissue can be damaged by inflammation, causing high levels of collagen to be deposited in the liver cells (fibrosis), which become stiff.

VTq is used in combination with a Siemens Acuson S2000 or S3000 ultrasound platform. The VTq software uses acoustic radiation force impulse imaging technology to measure the elasticity of tissue. This type of imaging involves generating a shear wave by applying an acoustic ‘push pulse’ lateral to the area of interest identified during a conventional ultrasound scan. The speed of the shear wave is proportional to the stiffness of the tissue.

The VTq investigation comprises multiple measurements and is both non-invasive and painless. The software generates a report which includes a statistical summary of the median and mean shear-wave velocities. The reliability of VTq measurements is usually confirmed by calculating the ratio of the interquartile range to median, which should be less than 0.30.

A VTq test adds 5–10 minutes to a routine abdominal ultrasound scan or it can be done as a standalone test, taking no more than 15 minutes to complete. A suitably trained nurse, ultrasonographer, radiologist or hepatologist can perform the test and interpret the data, enabling reporting to the referring physician on the same day.

VTq received a Class II CE mark in 2008 and is reported to be installed in 28 sites in the UK. The software is indicated for adults or children needing assessment of liver fibrosis.

2 Proposed use of the technology

2.1 Disease or condition

Although liver fibrosis can result from a range of factors, including excessive alcohol consumption, non-alcoholic fatty liver disease and cystic fibrosis, the scope of this evaluation is limited to hepatitis (inflammation of the liver). Acute hepatitis may resolve without causing permanent damage to the liver. It can, however, persist for many years (chronic hepatitis) causing fibrosis and, in the most serious cases, loss of liver function (liver failure) which can be fatal. Hepatitis may be caused by a number of different disease processes including infection of the liver by the hepatitis viruses. Symptoms and signs of liver disease include jaundice, fatigue, itching, pain in the upper abdomen, distention of the abdomen and intestinal bleeding. However, liver disease may be symptom-free and only be detected following routine blood tests.

2.2 Patient group

The purpose of this evaluation is to assess the use of VTq in adults and children with chronic hepatitis B or C.

NICE's clinical guideline on hepatitis B states that approximately 19 people test positive for chronic hepatitis B per 100,000 population. A 2004 report from the Foundation for Liver Research stated that around 180,000 people in the UK have chronic hepatitis B, based on a World Health Organisation estimate that the UK prevalence of chronic hepatitis B infection is 0.3%. Other estimates put the figure for the UK at around 325,000 (Hepatitis B Foundation UK 2007). Chronic hepatitis B infection is most likely to develop in children under 6 years of age; up to 90% of infants infected in their first year of life will develop chronic infection. Less than 5% of otherwise healthy adults who are infected will develop chronic infection.

There were 10,873 reported new cases of hepatitis C in England during 2012, but the true figure is probably much higher. Injecting drug use continues to be the most important risk factor for hepatitis C infection in the UK. Data from the

Unlinked Anonymous Monitoring (UAM) survey of people who inject drugs suggest that levels of infection in this group remained high in 2013 (50% in England). It is estimated that around 214,000 people in the UK have chronic hepatitis C (Public Health England, 2014). Between 10% and 40% of people with untreated chronic hepatitis C develop cirrhosis, which increases the risk of liver cancer.

2.3 Current management

The NICE clinical pathway for chronic hepatitis B indicates that assessment usually takes place in primary care, through blood tests. All patients who test positive for hepatitis B surface antigen should be referred to a hepatologist, gastroenterologist or infectious diseases specialist with an interest in hepatology (children should be referred to a similar paediatric specialist in a secondary or tertiary centre).

In secondary or tertiary care patients are provided with information on disease progress, long-term prognosis, transmission and antiviral treatment options. Adult patients are then offered transient elastography as an initial test for chronic liver disease. Transient elastography (using, for example, the FibroScan device) is a non-invasive method of assessing liver fibrosis by measuring liver stiffness based on a mechanical wave generated by vibration. Children and young people are offered liver biopsy to determine the need for antiviral therapy, with appropriate information provided on biopsy limitations and risks.

NICE's clinical guideline on hepatitis B recommends:

- Transient elastography as the initial test for chronic liver disease, offering antiviral treatment (without a liver biopsy) to patients with a transient elastography score ≥11 kPa.
- Considering liver biopsy in patients with a transient elastography score of 6–10 kPa.
- Offering liver biopsy to patients with a transient elastography score of <6 kPa if they are aged <30 years and have hepatitis B virus DNA of

>2000 IU/ml and abnormal alanine aminotransferase (ALT) on 2 consecutive tests conducted months apart.

- Annual reassessment of patients who are not taking antiviral treatment.

NICE is producing a clinical guideline for the management of hepatitis C, the development of which is currently paused. Patients who are hepatitis C virus RNA-positive on a blood test are referred to a hepatology clinic. The degree of fibrosis is assessed and treatment options are discussed depending on specific patient contraindications and the degree of liver disease.

Liver biopsy is considered to be the gold standard for assessing liver fibrosis for both hepatitis B and C. Histological assessment uses the Metavir score, based on an assessment of fibrosis and the degree of liver architecture disorganisation, and classifies the severity of liver disease from none (F0), through mild, moderate and severe (F1–F3), to cirrhosis (F4).

2.4 Proposed management with new technology

VTq is intended to replace transient elastography or liver biopsy (where transient elastography is not available) as an initial test for chronic liver disease following assessment in primary care and before the patient is referred to secondary or tertiary care. It is possible that VTq could replace transient elastography and liver biopsy for people with fibrosis for whom biopsy is currently considered following transient elastography, according to NICE's clinical guideline on hepatitis B. VTq may be used for annual reassessment in people not taking antiviral therapy.

VTq could be requested by primary care physicians at the same time as initial blood tests and diagnostic ultrasound. If the necessary Siemens ultrasound equipment is available, it can also be done in an outpatient setting during the first diagnostic ultrasound appointment. The company's submission states that the VTq software allows patients to be triaged in primary care, limiting unnecessary referrals to a consultant hepatologist.

2.5 Equality issues

No equality issues were identified.

3 Sponsor's claimed benefits

The benefits to patients as claimed by the company are as follows:

- VTq is painless and may be safer than liver biopsy as the standard of care.
- No hospital stay or post-procedure monitoring is needed with VTq because it can be done in an outpatient setting.
- VTq may avoid the need for serial biopsies over several years to monitor fibrosis progression, improving quality of life.
- VTq provides a more complete assessment of the liver; during the procedure, a sonogram allows visualization of the liver parenchyma, portal and hepatic veins, portal and hepatic venous and arterial blood flow measurements, and the biliary tree for possible obstructions.
- Hepatic cellular carcinoma surveillance is included during the sonogram in patients with cirrhosis.
- Early identification of fibrosis in people with viral hepatitis may allow earlier intervention with antiviral drugs, which can reverse the course of early disease.

The benefits to the health system claimed by the company are as follows:

- Potential for increased capacity because the VTq procedure does not need to be done by a consultant.
- Reduced procedure costs with fewer biopsies needed over several years (if fibrosis progression is monitored with VTq).
- Reduced resource costs because no hospital admission or stay is needed for VTq measurements in an outpatient setting.

4 Decision problem

Table 1 Summary of the decision problem

Population	VTq is intended for use in adults or children with chronic hepatitis B or C in whom assessment of liver fibrosis is indicated.
Intervention	The VTq software application used with the Siemens Virtual Touch Tissue Imaging systems (the Acuson S2000 and S3000 ultrasound platforms)
Comparator(s)	• Transient elastography • Liver biopsy
Outcomes	• Correlation in assessment of stage of liver disease • sensitivity and specificity (using AUROC) in assessment of liver fibrosis • correlation in assessment of stage of fibrosis using Metavir score • use of antiviral drugs • quality of life measures • hospital bed usage and length of stay • need for liver biopsy • device-related adverse events.
Cost analysis	The cost analysis should include both transient elastography and liver biopsy as comparators, depending on whether either or both of these represent standard care in the relevant patient population. Use in both primary and secondary care should be considered. Scenarios considered in the model should include settings both with and without a compatible Siemens ultrasound machine. Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared (taking into account, for example, ongoing fibrosis monitoring). Sensitivity analyses will be done to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Special considerations, including issues related to equality	None.

The company did not change or add to the population, comparators or outcomes in its statement of the decision problem. The External Assessment Centre (EAC) noted that none of the studies submitted by the company contained evidence on the use of VTq in children and understood this was because of a lack of available evidence.

The company noted that liver biopsy is the reference standard in this evaluation, which led it to conclude that the outcomes for correlation are equivalent in assessing stage of liver disease and stage of fibrosis using Metavir scores. The company also considered that use of antiviral drugs, hospital bed usage and length of stay, and need for liver biopsy were secondary outcomes, which the EAC considered to be reasonable.

5 The evidence

5.1 Summary of evidence of clinical benefit

The company identified 23 published papers as suitable for full-text review. No unpublished studies were identified. After review, the company excluded 12 papers which were conference abstracts with insufficient information. Of the remaining 11 papers which formed the company's clinical evidence for VTq, 10 reported case-control observational studies and 1 was a meta-analysis of 8 studies.

The EAC considered that 8 of the 11 papers included by the company should be excluded from further assessment because they reported on studies with overlapping cohorts. The EAC reviewed the other 12 papers which the company had excluded, and agreed with the rationale for their exclusion. Details of these papers can be found in appendices 1 and 2 of the assessment report (pages 91–109). The 3 studies accepted for assessment by the EAC were Friedrich-Rust et al. (2014), Friedrich-Rust et al. (2013) and Sporea et al. (2012a).

The EAC carried out a further literature search using revised search terms and found an additional 7 papers, including papers by Yamada et al. (2014)

and Liu et al. (2014), identified in the company's literature searches but excluded from the final clinical evidence submission. In summary, the EAC considered 10 papers to be relevant to this evaluation, details of which are shown in table 2 (adapted from tables 3.1, 3.2 and 3.4 of the assessment report: pages 23, 29–30 and 36–39 respectively).

Seven of the papers evaluated VTq in people with hepatitis C and 3 evaluated VTq in people with hepatitis B. Five studies compared VTq with TE and liver biopsy and 5 compared it with liver biopsy only. Most studies refer to the intervention as ARFI carried out on a Siemens Acuson S2000 ultrasound machine, rather than as VTq, but this is the same technology. Optimal cut-off values for VTq measurements were calculated to classify people into fibrosis stages by Metavir score.

Chen et al. (2012) carried out a prospective observational study evaluating VTq used to measure fibrosis in 127 people with chronic hepatitis C attending a liver centre in Taiwan. ARFI (VTq) measurements were compared with liver biopsy and blood tests for fibrosis (FibroTest). Necro-inflammatory activity was also measured. Histological fibrosis staging was done using Metavir scoring by a pathologist blinded to the ARFI and FibroTest results. The Spearman correlation coefficient between ARFI and liver biopsy was 0.696 ($p<0.001$). The area under receiver operating characteristic (AUROC) curve measures for ARFI were: 0.847 for F1 compared with F2–4 (95% confidence interval [CI] 0.779 to 0.914); 0.902 for F1–2 compared with F3–4 (95% CI 0.835 to 0.97); and 0.831 for F1–3 compared with F4 (95% CI 0.723 to 0.939). The authors reported that that the degree of necro-inflammatory activity artificially raised the severity of fibrosis detected by ARFI, but concluded that ARFI (VTq) was a promising alternative technology to measure liver stiffness.

The paper by Friedrich-Rust et al. (2014) is a published abstract from a conference poster presentation reporting findings from a prospective international multicentre study. The study compared ARFI (VTq) with transient elastography (TE) in 253 people with chronic hepatitis C, using liver biopsy as a reference method. Each person had ARFI, TE and blood tests. The extent of

fibrosis was staged from liver histology using Metavir scoring by a single pathologist. The authors did an intention-to-diagnose analysis including 247 people and a per-protocol analysis including 182 people. They reported that both ARFI and TE correlated significantly with the histological staging and that no statistically significant differences were found between ARFI and TE for identifying fibrosis at stage F2 or higher in the per-protocol analysis. The authors concluded that ARFI and TE are comparable methods for non-invasive fibrosis staging.

Friedrich-Rust et al. (2013) report findings from a prospective, international multicentre study examining ARFI (VTq) used to assess liver fibrosis in people with chronic hepatitis B. In the study, 131 people attending hospitals in 3 European centres were recruited consecutively and tested with ARFI to assess the extent of fibrosis. Of the 131 people,105 also had TE (FibroScan). Liver biopsy was used as a reference method for histological assessment using Metavir scoring and blood tests were taken to confirm the diagnosis of chronic hepatitis B. Following exclusions because of invalid biopsy or ARFI measurement, data from 114 people were included in the final analysis. Of those, 92 also had TE and were included in an intention-to-diagnose analysis; a per-protocol analysis was done using data for 88 people who had valid ARFI and TE measurements. Diagnostic accuracy was determined by AUROC curves. Both ARFI and TE correlated significantly with liver biopsy results; the Spearman correlation coefficient was 0.415 ($p<0.001$) for ARFI and 0.556 ($p<0.001$) for TE. The diagnostic accuracy of ARFI was 0.66 for mild fibrosis (F1), 0.73 for significant fibrosis (F2), 0.94 for severe fibrosis (F3) and 0.97 for liver cirrhosis (F4). No statistically significant differences were found between ARFI and TE in either the intention-to-diagnose or per-protocol analyses.

Kuroda et al. (2010) carried out a prospective diagnostic accuracy study for ARFI (VTq) used in 70 people in Japan; 30 with chronic hepatitis C, 30 with liver cirrhosis and hepatitis C, and 10 healthy controls. The measurement of fibrosis with ARFI was compared with blood tests for serum markers of liver function. Liver biopsy for Metavir staging was done for 19 patients. Mean

shear wave velocity was 2.67±1.18m/s in the liver cirrhosis group, 1.33±0.54m/s in the chronic hepatitis C group and 0.99±0.21m/s in the control group. The authors reported that shear wave velocity measured by ARFI was significantly higher in the liver cirrhosis group ($p<0.001$) than in the chronic hepatitis C group, and significantly higher in the chronic hepatitis C group than in the control group ($p<0.0023$). Mean shear-wave velocity in each stage of fibrosis was: 1.09±0.22 m/s for F0–1; 1.24±0.52 m/s for F2; 1.61±0.79 m/s for F3; and 2.35±1.11 m/s for F4. ARFI measurements correlated significantly with fibrosis staging ($\rho=0.9772$, $p=0.002$) and all except 1 of the serum marker test results. ARFI showed better diagnostic accuracy for liver cirrhosis than the serum marker tests (AUROC: 0.930, no CI reported). The most appropriate cut-off value for shear-wave velocity was judged to be 1.59 (sensitivity 95%, specificity 83%).

Liu et al. (2014) explored the diagnostic accuracy of ARFI (VTq) compared with TE and a biochemical test, aspartate aminotransferase-to-platelet ratio index (APRI), in 95 people with hepatitis B and 16 healthy volunteers. All 95 people with hepatitis had a liver biopsy to stage fibrosis using Metavir scoring. The authors developed an optimal linear combination of the 3 methods and evaluated its accuracy. Results were analysed for 108 people; 3 were excluded because of TE failure. ARFI and TE correlated significantly with histological staging ($r=0.85$, $p<0.001$ for ARFI; $r=0.81$, $p<0.001$ for TE) and APRI correlated more moderately ($r=0.63$, $p<0.001$). The AUROC curve results reported for ARFI were 0.91 for $F\geq2$ and 0.96 for F4, and the results for TE were 0.87 for F2 and 0.96 for F4. The authors compared the combined accuracy of the 3 methods with their individual accuracy alone and found that accuracy improved, particularly for significant fibrosis (F2) and cirrhosis (F4).

Nishikawa et al. (2014) investigated the correlation between ARFI and fibrosis stage as well as other factors including BMI, hyaluronic acid blood level, gamma-glutamyltranspeptidase level and inflammation. ARFI (VTq) was used in 108 people with chronic hepatitis C attending hospital in Japan. All patients had liver biopsy for histological staging of fibrosis using Metavir scoring, by

assessors blinded to the clinical data; the investigators carrying out ARFI and clinical tests were blinded to the histological data. Multiple regression analysis showed that ARFI correlated significantly with fibrosis stage (β=0.1865, p<0.0001) and hyaluronic acid levels (β=0.0008, p<0.0039) independently in all patients. ARFI correlated significantly with BMI in F≤1 fibrosis, with gamma-glutamyltranspeptidase level in F2 fibrosis, and with fibrosis stage and hyaluronic acid levels in F3 and F4 fibrosis, indicating that these factors could affect ARFI measurements. ARFI did not correlate with inflammation.

Rizzo et al. (2011) report findings from a study comparing ARFI (VTq) and TE with liver biopsy in people with chronic hepatitis C. In the study, 139 people were recruited consecutively from 2 hospitals in Italy and each had both ARFI and TE. Fibrosis staging was done using Metavir scoring by an assessor blinded to clinical data. No invalid measurements were reported for ARFI, but TE was invalid in 9 people (6.5%). Using pairwise AUROC analysis, ARFI was significantly more accurate than TE for diagnosing significant and severe fibrosis (F≥2 and F≥3; 0.86 compared with 0.78, p=0.024 and 0.94 compared with 0.83, p=0.002 respectively) but not for cirrhosis (F4; 0.89 compared with 0.80, p=0.09). Partial AUROC analysis showed that ARFI was statistically significantly more accurate than TE for all stages of fibrosis.

An international multicentre study was carried out by Sporea et al. (2012a) in 10 centres across 5 countries in Europe and Asia. Liver biopsy (using Metavir scoring) and ARFI (VTq) measurements of fibrosis were compared for 911 people with chronic hepatitis C. A subset of 400 people also had TE and their results were compared with ARFI and biopsy. Diagnostic accuracy was assessed using AUROC curves. ARFI correlated significantly with liver biopsy staging (Spearman correlation coefficient r=0.654, p<0.0001). In the subgroup receiving TE and ARFI, the overall correlation with liver biopsy staging was reported as being similar for both ARFI and TE (r=0.689, p<0.001 and 0.728, p<0.001 respectively). The number of people with reliable measurements was significantly higher for ARFI (98.8%) compared with TE (93.7%; p=0.003). The authors reported that ARFI was less effective than TE in predicting liver

cirrhosis (F4; AUROC 0.885 compared with 0.932; p=0.01). However, for severe or significant fibrosis (F2–3), ARFI and TE showed equivalent effectiveness. The authors also noted that the cut-off levels for ARFI to determine fibrosis at stages F≥2 and F4 were different for European and Asian people. It is not clear how these subgroups were identified and the authors note that more people in the Asian group either did not have fibrosis or had mild fibrosis (F1), which could have influenced this finding.

A study done in Japan by Yamada et al. (2014) evaluated the accuracy of ARFI (VTq) in assessing liver fibrosis in people with chronic hepatitis C as well as the association between ARFI and the response to antiviral therapy. Of the 124 people enrolled in the study, 94 had genotype 1 hepatitis C virus, 46 of whom had antiviral pegylated interferon and ribarin combination therapy. Although not stated, it can be assumed that the remainder had genotype 2 hepatitis C virus, 15 of whom had antiviral therapy. Forty (30%) people were judged to have moderate (F2) fibrosis. ARFI was found to have a strong correlation with fibrosis stage (p<0.001). People with the genotype 1 hepatitis C virus and less severe fibrosis (indicated by lower ARFI measurements, less than 1.40 m/s) showed a better response to treatment, indicating that ARFI could have some benefit in predicting response. ARFI could not predict treatment response in people with genotype 2 hepatitis C virus.

Ye et al. (2012) assessed the performance of ARFI (VTq) to measure liver and spleen stiffness in 204 people with chronic hepatitis B and 60 healthy volunteers. Of those with hepatitis B, 66 had liver biopsy and 138 had been diagnosed with cirrhosis. Histological staging using Metavir scoring was done by an experienced pathologist for those people having biopsy. ARFI measurements showed good correlation with fibrosis stage using Spearman's correlation coefficient (r= 0.87, p<0.001), and a high diagnostic accuracy between early/intermediate and advanced fibrosis stages (AUROC curve values F0–2 compared with F≥3=0.99; F0–2 compared with F4=0.97).

Table 1 Studies included as clinical evidence by EAC

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Full, peer-reviewed articles					
Chen et al. (2012)	Prospective, observational, operator-blind study (Taiwan/China)	127 people with chronic hepatitis C. Mean age 51.6 years. 51 male, 58 female	VTq, liver biopsy. Liver biopsy within 1 hour of ARFI measurements No follow-up.	Correlation: Spearman's rank CC 0.696 (p<0.001). AUROCs were: F1 vs F2–4=0.847 (CI 0.779 to 0.914), F1–2 vs F3–4=0.902 (CI 0.835 to 0.97), F1–3 vs F4=0.831 (0.723 to 0.939).	EAC identified and included. Although there was a statistically significant correlation between ARFI and liver biopsy, the degree of concurrent hepatic necro-inflammatory activity significantly affected the measurements of liver fibrosis using ARFI.
Freidrich-Rust et al. (2013)	Prospective, cohort, multicentre study (Germany, Netherlands)	114 people with chronic hepatitis B. Mean age 39 years±12. 77 male, 37 female 92 with valid VTq 92 used in ITD analysis and 88 (due to failure of 4 TE) in per protocol analysis.	VTq vs TE, liver biopsy.	Correlation with histological fibrosis stage: VTq Spearman's rank CC r=0.415 (p<0.0001); TE r=0.556 (p<0.0001). AUROC stage for ARFI (n=114): F≥1: 0.66 (CI 0.55 to 0.78); F≥2: 0.73 (0.61 to 0.85). F≥3: 0.94 (0.88 to 0.997); F≥4 0.97 (0.93 to 1.00). No significant differences at the 5% level found for ARFI and TE in ITD (n=92) and per-protocol (n=88) comparisons. ARFI: high sensitivity to exclude and high specificity to diagnose F≥2 fibrosis. Cut-off (m/s): 1.03 and 1.39 respectively; sensitivity 91% (75% to 98%) and 50% (32% to 68%); specificity 26% (17% to 36%) and 90% (82% to 96%).	ROC curves used for comparisons at different levels of severity based on histology (liver fibrosis). Aims addressed. CIs calculated. Full paper. Sponsor identified and included. EAC accepted.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Friedrich-Rust et al. (2014)	Cross-over; international multicentre study. (Germany, Netherlands, Romania)	People with chronic hepatitis C (n=253)	VTq vs TE, LB Prospective assessment using VTq, TE and blood tests. LB histology used as reference.	Correlation: VTq and TE significant with histological fibrosis stage. No significant difference found between TE and VTq for the diagnosis of F ≥ 2 (p=0.15), F≥3 (p=0.11) and F=4 (p=0.19). AUROC (95% CI) of VTq vs TE (intention to diagnose n=247): F≥1: 0.69 (0.60-0.79) vs 0.76 (0.70-0.83);p=0.21 F≥2: 0.77 (0.71-0.83) vs 0.85 (0.80-0.89);p=0.032 F≥3: 0.83 (0.77-0.89) vs 0.88 (0.83- 0.93);p=0.15 F=4: 0.84 (0.77- 0.91) vs 0.89 (0.84-0.95);p=0.18 AUROC (95% CI) of VTq vs TE (per protocol n=182): F≥1: 0.75 (0.67-0.83) vs 0.80 (0.72-0.88);p=0.28 F≥2: 0.81 (0.74-0.88) vs 0.85 (0.80-0.91);p=0.15 F≥3: 0.88 (0.82-0.94) vs 0.92 (0.89- 0.97); p=0.11 F=4: 0.89 (0.83- 0.96) vs 0.94 (0.90-0.98); p=0.19.	Conference abstract only. CIs reported. Study aim/hypothesis addressed. Sponsor identified and included. EAC accepted.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Kuroda et al. (2010)	Prospective, diagnostic accuracy study (Japan)	n=70: 30 people with chronic hepatitis C, 30 people with liver cirrhosis, and 10 healthy controls. Mean age 65 years. 31 male, 39 female	VTq (ARFI shear-wave velocity), biochemical tests, liver biopsy. Biochemical tests done on same day as ARFI. Timing of liver biopsy unclear.	Mean shear-wave velocity values: F0–1: 1.09±0.22 m/s F2: 1.24±0.52 m/s F3: 1.61±0.79 m/s F4: 2.35±1.11 m/s. Diagnosis of liver cirrhosis using ARFI: AUROC: 0.930 (no CI). The most appropriate cut-off value for shear-wave velocity values was 1.59 (sensitivity 95%, specificity 83%).	EAC identified and included. Sensitivity and specificity not reported by liver fibrosis stage.
Liu et al. (2014)	Prospective, diagnostic accuracy	n=108 (final analysis): 92 people with chronic hepatitis B. Mean age 40 years; 71 male, 21 female 16 healthy volunteers. Mean age 42 years; 10 male, 6 female.	VTq vs liver biopsy and TE ARFI measurement within 1 day of liver biopsy. No follow-up.	AUROC values: ARFI: F≥2 0.91 (p=0.27), F4: 0.96 (p=0.04). TE: F≥2: 0.87 (p=0.04), F4: 0.96 (p=0.13).	Company identified in initial search and excluded. EAC included.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Nishikawa et al. (2014)	Prospective diagnostic accuracy (Japan)	108 people with chronic hepatitis C. Mean age 59.5 years (range 49.0–66.0). 56 male, 52 female.	VTq vs liver biopsy. ARFI measurement within 1 week of liver biopsy. Patients had liver biopsy before starting treatment with interferon. No follow-up.	Correlation: shear velocity value significantly correlated with fibrosis r=0.732 (p<0.0001). AUROC: F1: 0.81, F2: 0.9, F3: 0.86, F4: 0.88.	EAC identified and included. ARFI also correlated with BMI, gamma-glutamyltranspeptidase and hyaluronic acid blood levels in fibrosis stages F0–1, F2 and F3–4 respectively. ARFI measurements did not correlate with inflammation.
Rizzo et al. (2011)	Prospective, diagnostic accuracy (Italy)	139 people with chronic hepatitis C. Mean age 55 years, 83 male, 55 female	VTq vs liver biopsy and TE. Percutaneous liver biopsy and ARFI/TE measurements within 6 months. No follow-up.	ARFI AUROCs: F>2=0.86 (CI 0.79 to 0.91); F>3=0.94 (CI 0.89 to 0.97); F>4=0.89 (CI 0.83 to 0.94). TE AUROCs: F>2=0.78 (CI 0.70 to 0.85); F>3=0.83 (CI 0.75 to 0.89); F>4=0.80 (0.72 to 0.86). TE was unreliable in 9 (6.5%) people. ARFI results were not influenced by ALT level but TE results were.	EAC identified and included. ARFI was found to be reproducible and accurate for staging of both intermediate (F2) and advanced (F3–4) liver fibrosis.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Sporea et al. (2012a)	Retrospective cohort, multicentre study (Japan, Romania, Germany, Italy, Austria)	914 people with chronic hepatitis C. 911 valid cases	VTq vs liver biopsy: n=914. VTq vs TE vs liver biopsy: subgroup n=400	Correlation between ARFI and fibrosis stage was highly significant (r=0.654, p<0.0001). Overall correlation with histological fibrosis stage was not significantly different for ARFI and TE: ARFI r=0.689 (p<0.0001); TE r=0.728 (p<0.0001). ARFI cut-off (m/s), AUROC, sensitivity and specificity: F≥1 (>1.19): 0.779; 69.9; 80 F≥2 (>1.33): 0.792; 69.1; 79.8 F≥3 (>1.43): 0.829; 74.8; 81.5 F=4 (>1.55): 0.842; 84.3; 76.3. ARFI was inferior to TE for cirrhosis (AUROC: 0.885 vs 0.932, p=0.01) and all fibrosis (AUROC: 0.772 vs 0.857, p=0.01); and similar for predicting significant and severe fibrosis (AUROC: 0.813 vs 0.818, p=0.77; AUROC: 0.862 vs 0.866, p=0.81).	Correlation used to assess reliability, using Spearman test. No CIs. Hypothesis was not accurately tested. A subgroup of 400 people with chronic hepatitis C assessed with ARFI and TE. Full paper. Company identified and included. EAC accepted.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Yamada et al. (2014)	Diagnostic accuracy and prediction of response to treatment – prospective status not clear (Japan)	People with chronic hepatitis C (n=124) Mean age 57 years; 56 males. 61 patients had treatments. 46 had genotype 1 HCV and 15 had genotype 2 HCV.	VTq, liver biopsy. Liver fibrosis stage assessed by liver biopsy and ARFI. Response to peg-IFN plus ribavirin combination therapy treatment assessed.	ARFI measurement (Acuson S2000) was done within 1 week before liver biopsy. Follow-up was at weeks 4, 12, 24, 36, 48, end of treatment and week 24 after the treatment for genotype 1. For genotype 2 follow-up was at weeks 4, 12, 24, and week 24 after the treatment. The shear-wave velocity value increased with the progression of the histological fibrosis stage, as assessed using the Metavir scoring system, and a significant correlation was found between the 2 variables (Pearson product–moment correlation coefficient=0.764, p<0.001). The AUROCs were F≥2 (0.890) and F≥3 (0.943).	Company identified but not included; EAC included. The shear-wave velocity value measured by ARFI could not predict the treatment response for patients with genotype 2 HCV, but showed some benefit for patients with genotype 1.
Ye et al. (2012)	Prospective diagnostic accuracy (China)	204 people with chronic hepatitis B. Mean age 35.5 years (19–63). 60 healthy volunteers. Mean age 30 years (20–54) 158 male,106 female.	VTq, ultrasound-guided liver biopsy. 66 people had liver biopsy. ARFI measurement within 3 days of liver biopsy. No follow-up.	Spearman's rank CC=0.87 (p<0.001). AUROCs: F0–2 vs F3=0.99; F0–2 vs F4=0.97.	EAC identified and included. ARFI liver stiffness measurements showed good correlation with fibrosis stage and a high diagnostic accuracy between early/intermediate and advanced fibrosis stages.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Abbreviations: ARFI, acoustic radiation force impulse; AUROC, area under receiver operating characteristic; CC, correlation coefficient; CI, confidence interval; HCV, hepatitis C virus; ITD, intention to diagnose; peg-IFN, pegylated interferon; TE, transient elastography; VTq, Virtual Touch Quantification.					

Evidence synthesis

The company included a brief synthesis of the clinical evidence included in its submission and summarised 2 additional systematic reviews with meta-analyses (Nierhoff et al. 2013; Bota et al. 2013a). An overview of the evidence synthesis is included on pages 31–33 of the assessment report. Based on findings from the evidence synthesis, the company concluded that VTq and TE have equivalent accuracy but that results suggested TE may be slightly more accurate in diagnosing mild fibrosis (F1). The EAC felt that this conclusion was plausible, but noted that the company did not carry out a meta-analysis which would have provided a more decisive result.

The company provided an overall interpretation of the clinical evidence and concluded that VTq used in clinical practice can be a good tool to diagnose significant fibrosis (F2) and an excellent tool to diagnose severe fibrosis (F3) or cirrhosis (F4). The EAC considered that this interpretation was reasonable and that the company's assessment of the strengths and weaknesses of the studies was fair.

As a result of its concerns about the company's study selection and the subsequent identification of additional clinical evidence, the EAC did a meta-analysis of the 10 studies it selected for inclusion. A random effects approach was used to calculate pooled outcome data for correlation (between VTq, TE and liver biopsy Metavir scores), sensitivity, specificity and prevalence for each disease type (hepatitis B, C or a combination). Proportions were transformed using the logit function where necessary to overcome skewness and values of 0 were transformed to 0.5 to allow pooling of the data. Results were back-transformed to provide estimated pooled proportions and 95% confidence intervals. Nine outcome estimates were made from multiple studies and 6 from single studies. A summary of the studies and populations is shown in table 3.5 of the assessment report (page 42) and the outcome data and pooled estimates are shown in tables 3.6 and 3.7 on pages 43 and 44 of the assessment report. The pooled estimates are reproduced here in table 3.

Table 3 Pooled estimates from meta-analysis with 95% confidence intervals for prevalence and diagnostic accuracy

Hepatitis type		Comparator to liver biopsy							
		VTq				**TE**			
	Fibrosis stage	F≥1	F≥2	F≥3	F4	F≥1	F≥2	F≥3	F4
B	No. of studies	–	2	–	1	–	1	–	1
	Prevalence	–	0.43 (0.06–0.79)	–	0.27 (0.19–0.36)	–	0.61 (0.51–0.70)	–	0.27 (0.19–0.36)
	Sensitivity % (95% CI)	_	70.02 (31.59 – 92.19)	_	93.1 (77.23 – 99.15)	_	81.8 (70.39 – 90.24)	_	88.1 (72.65 – 97.81)
	Specificity % (95% CI)	_	87.01 (78.69 – 92.40)	_	76.83 (66.40 – 85.90)	_	71.24 (55.42 – 84.28)	_	86.67 (77.95 – 93.76)
C	No. of studies	2	5	5	4	–	1	1	1
	Prevalence	0.91 (0.83–0.95)	0.60 (0.48–0.71)	0.40 (0.32–0.484	0.23 (0.18–0.29)	–	0.63 (0.54–0.71)	0.39 (0.31–0.47)	0.22 (0.15–0.29)
	Sensitivity % (95% CI)	69.82 (66.82 – 72.66)	78.47 (70.04 – 85.03)	85.76 (75.94 – 91.99)	84.48 (79.78 – 88.24)	_	71.0 (60.57 – 80.46)	77.0 (64.40 – 80.46)	70.0 (50.60 – 85.27)
	Specificity % (95% CI)	80.95 (70.44 – 88.34)	78.96 (73.49 – 83.55)	84.36 (80.69 – 87.45)	81.45 (75.43 – 86.27)	_	71.0 (56.92 – 82.87)	85.0 (75.27 – 91.60)	82.0 (73.09 – 88.42)
B & C	No. of studies	–	7	–	5	–	2	–	2
	Prevalence	–	0.55 (0.42–0.67)	–	0.23 (0.18–0.29)	–	0.62 (0.53–0.70)	–	0.23 (00.14 –0.36)
	Sensitivity % (95% CI)	_	77.01 (68.88 – 83.52)	_	85.03 (80.59 – 88.60)	_	76.16 (63.89 – 85.22)	_	79.43 (55.69 – 92.22)
	Specificity % (95% CI)	_	81.07 (75.83 – 85.39)	_	80.44 (75.57 – 84.54)	_	71.11 (61.17 – 79.36)	_	83.82 (77.81 – 88.45)

The results of the meta-analysis showed that the prevalence of significant fibrosis (F2) for both hepatitis B and C was lower with VTq (0.55) than TE (0.62). However, the techniques had similar scores for cirrhosis (F4; 0.23 for VTq and 0.23 for TE). Sensitivity and specificity values were similar for hepatitis B and C. VTq had slightly higher values for both sensitivity and specificity in diagnosing significant fibrosis (F2; 77% and 81% respectively) than TE (76% and 71% respectively) in people with hepatitis B and C.

Sensitivity was greater than specificity for cirrhosis (F4) in the combined study population for VTq (85% and 80% respectively), and the opposite was found for TE (79% and 84% respectively). However, the values were similar for both VTq and TE. Pooled correlation coefficients were similar for VTq and TE in the combined study population (0.68 to 0.69).

The EAC noted that no adjustment could be made for patient characteristics other than disease type, study design and location because there was insufficient information in the papers.

Adverse events

In its submission, the company stated that no adverse events have been reported for VTq and none were identified in the literature, from the MHRA's website or MAUDE databases. The EAC repeated the literature and other searches to confirm this statement, and concluded that no adverse events related to VTq were identified.

5.2 Summary of economic evidence

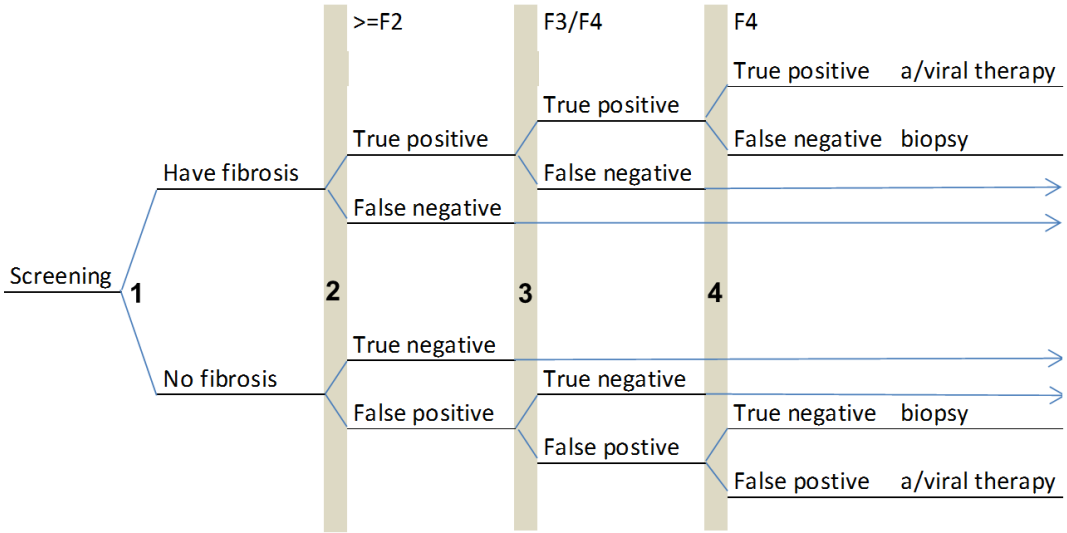
The company carried out a literature search for economic studies related to VTq, TE or liver biopsy and hepatitis and identified 61 potentially relevant publications, of which 10 were considered suitable for full text review. After applying inclusion and exclusion criteria, the company did not identify any relevant economic studies for VTq. However, 5 studies were presented relating to the comparators (TE and liver biopsy) and critically appraised.

The EAC considered that the company's search strategy and inclusion/exclusion criteria were appropriate, but noted that the date range and search terms could have been broader and 2 further databases could have been searched. The EAC carried out a revised search addressing these issues and did not find any relevant publications, confirming the company's conclusion that there was no published economic evidence relating to VTq (see pages 49–50 of the assessment report). The EAC considered that the 5 papers identified by the company relating to the comparators were useful for modelling purposes, and found 1 additional comparator paper.

De novo analysis

The company submitted a de novo cost analysis evaluating VTq and liver biopsy (where needed) against TE and liver biopsy (where needed) and liver biopsy alone. Costs were modelled from an NHS and personal social services perspective using 2013 prices. The population included in the model was people with chronic hepatitis B or C needing assessment of liver fibrosis. The model structure was a decision tree based on a cohort of 1000 people referred by a GP and stratified according to the presence or absence of fibrosis, then sequentially across 3 groups according to stage of fibrosis determined by Metavir score (F2, F3 or 4, or F4; see figure 1). The EAC validated the model and noted that the variables in the executable Microsoft Excel file were accurately defined, whereas some variables were not clearly described in the submission document.

Figure 1 Company's de novo cost model



Model parameters

The company used the estimated prevalence of fibrosis to stratify the cohort into the 3 stages, and applied the sensitivity and specificity of each treatment strategy (VTq, TE or liver biopsy) for each stage, creating estimated numbers of true or false negatives or positives. The EAC generally agreed with this approach.

The model was based mainly on fibrosis assessment and did not include any treatment or monitoring costs for people in the F≥2 and F3 or 4 groups. For F4 fibrosis (cirrhosis), the true-positive group had antiviral therapy and the false-negative group had liver biopsy. False positives had antiviral therapy. According to figure 1, true negatives had a biopsy. The EAC questioned the rationale for this approach and whether this assumption was actually included in the model calculations.

The company did not state the time horizon for the model, but the EAC considered that the outcomes were likely to be realised using a 1-year horizon, based on the duration of antiviral therapy.

The company's estimates of fibrosis prevalence at each stage were based mainly on clinical expert advice and on 1 study in people with cirrhosis (see page 101 of the sponsor's submission), because exact figures were difficult to determine. The EAC sought additional clinical expert advice to validate these assumptions but the experts consulted were not able to provide any further certainty.

The diagnostic accuracy figures for VTq and TE were taken from the available literature and liver biopsy was assumed to have 100% sensitivity and specificity. The EAC agreed with the approach taken for liver biopsy and TE (figures taken from a meta-analysis), but felt that the figures used for VTq were not sufficiently robust. The EAC addressed this issue in its own meta-analysis of the clinical evidence.

Costs and resource use

The company included direct costs for VTq, TE and liver biopsy, calculating the costs of VTq and TE using a bottom-up approach. The cost for TE was based on a report published by the Centre for Evidence-based Purchasing (Stamuli et al. 2009) and revised slightly in light of annual variation in patient throughput to £25.33. The cost for VTq was estimated as £15.02, based on capital (VTq and Acuson S2000 machine), staffing, maintenance and

infrastructure costs. The cost for liver biopsy was estimated from the 2013–14 payment by results tariff to be £615, based on a mix of procedures.

The EAC agreed with the estimates for these costs but felt that they could be further explored in sensitivity analyses; the capital costs for VTq and TE were not estimated using the annuity method, and the company did not describe the exact mix of procedures used to calculate the biopsy cost. The cost of antiviral therapy was estimated to be £10,000 per patient in the executable model; the EAC was unsure as to the rationale behind this figure.

The company carried out deterministic one-way and multi-way sensitivity analyses varying the prevalence of liver fibrosis (from 10% to 45%), the diagnostic accuracy of VTq, technology and treatment costs and whether or not biopsy was done. The EAC generally agreed with the company's approach but commented that the company did not explain the rationale for the variations in prevalence it considered.

Results

Findings from the company's base case and sensitivity analyses are described on pages 60–62 of the assessment report. The results of the base case indicated that VTq could result in a cost saving of £10.31 per patient when compared with TE and £599.08 per patient when compared with liver biopsy (table C12, page 122 of the submission).

The EAC noted that the findings from the company's sensitivity analysis may have been incorrectly reported in the submission, with results from the one-way analysis not presented and the results from the multi-way analysis presented in section 9.5.6 (page 124 of the submission). Further findings based on changing the proportion of people having liver biopsy from 100% to 20% are shown in tables C16a and C16b (pages 128–129) in the submission, although the EAC noted that this variable is not listed in the description of the sensitivity analyses and could not determine the rationale for the figure of 20%. Varying the overall prevalence of liver fibrosis (described as incidence in the company's submission) and the diagnostic accuracy of VTq lowered the

cost saving per person in the best- and worst-case scenarios from £527 to £419 if all patients had a biopsy. If only 20% of people had a biopsy, the cost savings for VTq could be considerably reduced, and at higher prevalence levels VTq could be cost-incurring. The cost of antiviral therapy was also varied from the base case of £10,000 to £6500, and at this level the cost savings for VTq ranged from £8 to around £60 (see tables C16a, C16b and C16c on pages 128–130 of the company's submission).

The EAC considered that the model addressed the decision problem in the scope, but that the structure did not accurately reflect current clinical pathways for people with liver fibrosis and did not include all the relevant costs and outcomes for diagnosing and treating the condition. No monitoring or treatment costs were included for people in the F≥2 or F3 or 4 fibrosis groups. The EAC felt that this was erroneous, as people with less severe fibrosis may benefit from treatment. The EAC also questioned the assumption that people falsely classified as negative for fibrosis would not incur any treatment costs and would re-enter the model as new patients. It felt that this was a misleading approach, because misdiagnosis may incur additional costs (from further diagnostic tests, inpatient or emergency episodes and treatment). The EAC considered that a mortality arm would have been useful to account for the small increased risk associated with liver biopsy, but acknowledged that this was likely to have been incorporated in the chosen tariff cost. The EAC also noted that the company had used a cohort approach rather than a per-patient approach as specified in NICE's methodology.

Additional work carried out by the External Assessment Centre

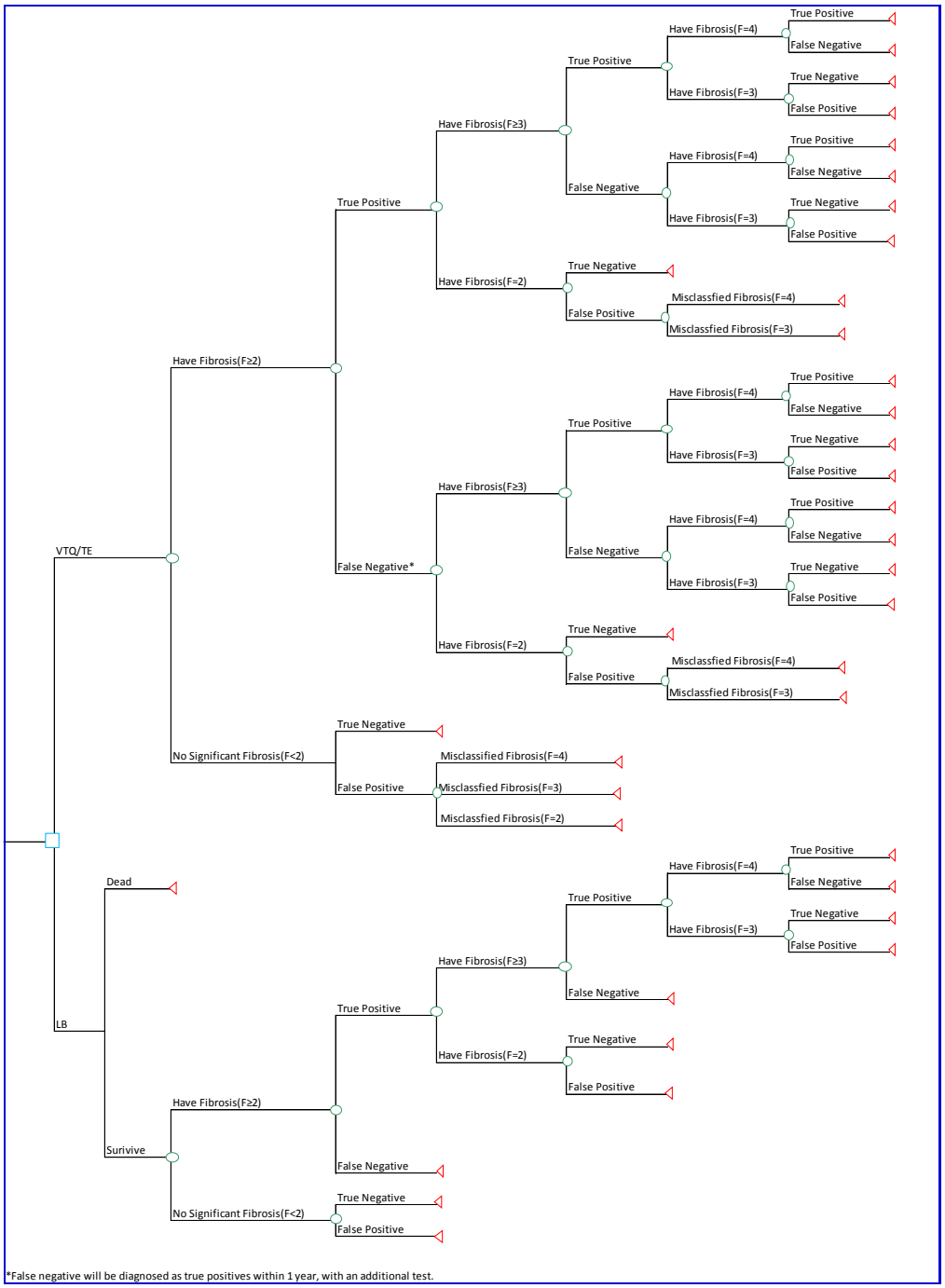
The EAC revised some parameters and re-ran the company's model to address these issues, including treatment and monitoring costs for people diagnosed with less severe fibrosis (F<2) and those initially classed as false negative, and a mortality arm. The revised model was a sequential decision tree incorporating outcomes for F≥2, F≥3 and F4 fibrosis using VTq, TE and liver biopsy over a 1-year time horizon for adults or children with chronic hepatitis B or C. Each stage included true positives, false positives, true

negatives and false negatives. A diagram of the model structure is shown in figure 2.

Model parameters

Revised prevalence and diagnostic accuracy parameters for the model were taken mainly from the EAC's meta-analysis and applied at each sequential stage for VTq, TE and liver biopsy. As in the company's model, liver biopsy was treated as the reference standard with 100% sensitivity and specificity.

Figure 2 EAC's revised model



The EAC made several assumptions for the model which are described in detail on pages 64–69 and in tables 4.1 and 4.2 (pages 71–72) of the assessment report. Key assumptions were as follows:

- People categorised as false negative for fibrosis would return and be re-diagnosed as true positive within 1 year.

- Prevalence rates for stages of fibrosis were different for VTq and TE based on the EAC's meta-analysis. The combined hepatitis B and C prevalence rates for VTq were used for TE and liver biopsy in the model to ensure compatibility.
- Combined hepatitis B and C prevalence and diagnostic accuracy figures for F≥3 fibrosis were not available from the meta-analysis. The EAC therefore used figures for hepatitis C across the model for this stage.
- Treatment delay resulting from misdiagnosis was unlikely to have a clinical impact and so long-term modelling of disease progression was not needed. According to published clinical evidence and expert advice gathered by the EAC, progression in both hepatitis B and C is relatively slow.
- People diagnosed as being at stage F≥2 had fibrosis and those at stage F≤1 did not.
- The majority of misclassified (false-positive) cases for VTq and TE would be diagnosed as having F2 fibrosis. A proportion of those with F2 fibrosis would be misclassified as having F3 or 4 fibrosis. These proportions were chosen arbitrarily and subjected to sensitivity analyses.
- People diagnosed with F3 or 4 fibrosis would have antiviral therapy.
- A mortality risk of 0.003 would apply to liver biopsy, based on available literature.

The unit costs for VTq and TE were estimated using an annuity method and discounted at 3%, to give a per-test figure of £15.24 for VTq and £25.90 for TE. The cost for liver biopsy was estimated from tariff costs to be £622. The costs for antiviral therapy were taken as £2808 for those at stage F3 and £5680 for those at stage F4, based on duration of treatment with peginterferon alfa and ribavirin. Costs for a compatible Siemens ultrasound machine were modelled in 2 scenarios, 1 including purchase costs and 1 assuming a machine was already available.

Results of incorporating the EAC's revised parameters in the company's model

Findings from the revised base case are shown in tables 3 and 4. In a scenario where a compatible Siemens ultrasound machine would be purchased along with the VTq software, using VTq would generate cost savings of £53 per person compared with TE and £434 compared with liver biopsy. If a compatible ultrasound machine was already available, the cost savings for VTq increased slightly to £57 compared with TE and £438 compared with liver biopsy.

Table 3 Costs for VTq and comparators if ultrasound machine purchased

	Expected cost (base case)
VTq	£1971
Transient elastography	£2025
Liver biopsy	£2405
VTq cost savings against transient elastography	**£53**
VTq cost savings against liver biopsy	**£434**

Table 4 Costs of VTq and comparators if ultrasound machine not purchased

	Expected cost (base case)
VTq	£1968
Transient elastography	£2025
Liver biopsy	£2405
VTq cost savings against transient elastography	**£57**
VTq cost savings against liver biopsy	**£438**

The EAC carried out deterministic sensitivity analyses varying prevalence rates, sensitivity and specificity for VTq and TE, distribution of false positives between stages F2 and F3, unit costs of VTq and TE, usage levels of TE and antiviral therapy costs. The rationale for the variations chosen is described on page 70 of the assessment report and results of the sensitivity analyses are presented in tables 4.5 to 4.12 on pages 74–79.

Findings from the sensitivity analyses showed that VTq remained cost-saving across all scenarios. The key drivers affecting the cost savings per person were prevalence of liver fibrosis, the distribution of false positives to other fibrosis stages, the specificity of VTq and TE for stages F≥2 and F≥3, unit costs of VTq and TE and anti-viral treatment costs.

The EAC acknowledged some limitations of its revised parameters. Due to the lack of clear data available on prevalence and diagnostic accuracy at each stage of fibrosis, figures were extrapolated for the stages in a sequential model rather than each stage being presented separately. Figures for hepatitis C at stage F≥3 fibrosis were applied to the whole population because combined data were not available. Several assumptions were made to calculate technology and comparator costs, but the EAC varied these parameters in sensitivity analyses to address uncertainty.

6 Ongoing research

The company did not identify any ongoing studies evaluating VTq. The EAC searched the clinical trials database (www.clinicaltrials.gov) and found 3 trials which it considered might be relevant. Details of the trials are shown in table 2.1 on pages 11–12 of the assessment report.

7 Issues for consideration by the Committee

Clinical evidence

The EAC considered that the evidence submitted by the company was in keeping with the scope, but many papers reported findings for overlapping study cohorts. The EAC's literature search found 5 additional papers and included 2 that the company had excluded. One paper was a conference abstract and so may not have been peer-reviewed.

The evidence base was weighted more heavily towards hepatitis C than hepatitis B, with 7 of the 10 included studies evaluating use of VTq in hepatitis C. This may not be a significant concern as the mechanism of liver fibrosis

may be similar between the 2 conditions. Prevalence, sensitivity and specificity were assessed in the EAC's meta-analysis but estimates could only be pooled for those with F≥2 fibrosis. Findings from the meta-analysis showed the range of sensitivity and specificity to be similar for hepatitis B and C. When comparing VTq and TE, the EAC found that the correlation coefficients were similar for the combined hepatitis population. VTq had slightly higher diagnostic accuracy than TE for F≥2 fibrosis and results for the 2 technologies were similar for cirrhosis (F4). From these findings, it is possible to assume that VTq has equivalent diagnostic accuracy to TE for stage F≥2 fibrosis. The diagnostic accuracy of VTq compared with that of TE in cases of mild or no fibrosis is not clear, but this has been addressed through the EAC's revised parameters applied to the company's economic model.

The company concluded that VTq is a good tool for diagnosing fibrosis at stage F2 or higher and an excellent tool for diagnosing fibrosis at stage F3 or higher, which is when antiviral therapy is initiated. The EAC agreed with this conclusion. Several studies examined the combination of elastography with serum markers. Expert clinical advice indicated that this combination may increase diagnostic accuracy for both VTq and TE.

The included studies did not evaluate using VTq in children and the EAC concluded that the evidence for use in children is limited, although a clinical trial in a paediatric population is ongoing.

The clinical evidence did not include outcomes for length of hospital stay and bed usage, quality of life, need for liver biopsy and use of antiviral therapy (subsequent diagnosis), which were outcomes identified in the decision problem. The EAC agreed with the company that the majority of these were secondary outcomes not investigated specifically in any of the studies.

The decision problem included considering the use of VTq in primary care, and the company's submission stated that VTq could be requested in primary care or done in an outpatient setting. However, no evidence was presented for VTq used in a primary care setting.

The EAC noted that no adjustment for confounding variables such as study location or patient characteristics was made in the meta-analysis, because this information was poorly reported in the included studies. None of the studies was done in the UK but 4 took place in Europe. This may limit the generalisability of the findings to the UK. The company noted that the ethnicity of the study populations was not clear and that this may influence the accuracy of VTq. Differences in fibrosis stage cut-off points between European and Asian patients was reported in 1 study (Sporea et al. 2012a), but the criteria for each subgroup were poorly reported and the number of people with each stage of fibrosis was different between the 2 groups.

None of the studies assessed the use of VTq in monitoring response to treatment, although the study by Yamada et al. (2014) evaluated the ability of ARFI to predict response to antiviral therapy based on hepatitis genotype.

The economic modelling has taken into account the resource consequences of false-negative and false-positive diagnoses. The clinical impact of these is unclear, but the EAC considered that treatment delay resulting from false-negative misdiagnosis was unlikely to have a clinical impact because disease progression in both hepatitis B and C is relatively slow. The clinical impact of a false-positive diagnosis may involve unnecessary treatment and distress for the patient.

Cost evidence

Both the EAC and the company concluded that no economic evidence had been published for VTq, and so the cost evidence relied on de novo modelling. The company's model compared VTq with TE and liver biopsy at each stage of fibrosis sequentially. The EAC felt that the model parameters should be revised because they did not fully take into account the diagnostic pathways for hepatitis B or C, and did not include all relevant costs. The EAC re-ran the company's model with revised parameters to address these issues and to include a mortality arm to encompass the risk associated with liver biopsy. Parameters were varied in sensitivity analyses to address

uncertainties. Findings from the revised model were similar to the company's original model, in that use of VTq generated cost savings when compared with TE and liver biopsy in particular. Savings were achieved in the EAC's base case and across all the scenarios explored in sensitivity analyses. The main drivers of costs were found to be the prevalence of fibrosis, distribution of false-positive results to different fibrosis stages, specificity of VTq and TE, and costs of the technology and antiviral therapy.

The EAC acknowledged some limitations in its development of revised parameters. Figures for the prevalence of fibrosis, sensitivity and specificity were only available for F≥2 and F4 fibrosis for hepatitis B and C combined, and for stage F3 for hepatitis C. Because of this, each stage could not be modelled separately and a sequential approach was necessary. The model also included adults and children, given the lack of specific clinical data relating to children as a separate subgroup. The risk of mortality associated with liver biopsy was included in the model, but the resource impact of treating complications from liver biopsy was not modelled. This could be assumed to be incorporated in the tariff cost for liver biopsy.

8 Authors

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NICE Medical Technologies Evaluation Programme

November 2014

Appendix A: Sources of evidence considered in the preparation of the overview

Details of assessment report:

- Morris E, Summers J, Peacock J et al., Virtual Touch Quantification to diagnose and monitor liver fibrosis, August 2014

Submissions from the following sponsors:

- Siemens

Related NICE guidance

- Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults. NICE clinical guideline 165 (June 2013). Available from www.nice.org.uk/guidance/cg165
- SonoVue (sulphur hexafluoride microbubbles) – contrast agent for contrast-enhanced ultrasound imaging of the liver. NICE diagnostics guidance 5 (August 2012). Available from: www.nice.org.uk/guidance/dg5
- Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. NICE public health guidance 43 (December 2012). Available from: www.nice.org.uk/guidance/ph43
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (April 2012). Available from: www.nice.org.uk/guidance/ta253
- Extracorporeal albumin dialysis for acute liver failure. NICE interventional procedure guidance 316 (September 2009). Available from: www.nice.org.uk/guidance/IPG316
- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance 153 (August 2008). Available from: www.nice.org.uk/guidance/TA153

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Kuroda H, Kakisaka K, Tatemichi Y et al. (2010) Non-invasive evaluation of liver fibrosis using acoustic radiation force impulse imaging in chronic hepatitis patients with hepatitis C virus infection. Hepato Gastroenterology 57 (102–103): 1203–7

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their specialist society, royal college or professional body. The advice received is their individual opinion and does not represent the view of the society.

Ms Sophie Auld
Superintendent Radiographer, Society and College of Radiographers

Dr Simon Elliot
Consultant Radiologist, Royal College of Radiologists

Dr Edmund Godfrey
Consultant Radiologist, Royal College of Radiologists

Mr Colin Griffin
Ultrasound Lead, British Medical Ultrasound Society

Dr Michael Heneghan
Consultant Hepatologist, British Association for the Study of the Liver

Dr Priya Narayanan
Consultant Radiologist, Royal College of Radiologists

Dr David Sherman
Consultant Physician & Gastroenterologist, Royal College of Physicians

Dr Philp Shorvon
Consultant Radiologist, Royal College of Radiologists

Professor Paul Sidhu
Consultant Radiologist, Royal College of Radiologists

Professor Roger Williams
Director of the Institute of Hepatology, Foundation for Liver Research, Royal College of Physicians

- Of the 10 expert advisers, 7 have had direct involvement with VTq and 3 would like to use the technology but it is not currently available to them. Five experts have been involved in research on this technology.
- Seven experts thought that VTq was a significant modification of an existing technology and 2 thought it was thoroughly novel. Four experts stated that similar technology exists. One commented that VTq differs from other technologies in that it enables targeted sampling of liver stiffness.
- Nine experts commented that the most appropriate use for VTq is the assessment of the severity of liver fibrosis or the presence of cirrhosis in people with liver disease. One expert commented that VTq could be used to asses patients referred with liver enzyme abnormalities.
- Seven experts stated that the FibroScan would be the main comparator and 3 felt that it would be liver biopsy. Two stated that serum markers can also be used.
- Three experts identified the FibroScan as a competing product. Other products identified were the ShearWave (manufactured by Philips) and Supersonic.
- Five experts felt that the opportunity for non-invasive assessment and avoidance of liver biopsy will be the main benefit to patients. Three experts commented that using VTq could allow better or more informative results. One expert felt that the ability to assess fibrosis at the same time as ultrasound would be of benefit.
- Five experts believed that the additional patient benefits of VTq are likely to be realised in practice. The main obstacles identified were the cost and availability of the ultrasound machines and software. Six experts believed that a reduced rate of liver biopsies would be useful in measuring the benefits of VTq.
- Six experts felt that using VTq instead of liver biopsies would be cost-saving. One commented that using VTq would enhance liver services in line with the National Liver Plan 2010. Seven experts believed that the system benefits are likely to be realised in practice.

- Seven experts stated that appropriate ultrasound equipment (Siemens Acuson) would be needed to use the VTq software. Eight experts believed that training would be needed to use the device but 3 felt that its use is relatively simple. One commented that clinical input from a hepatologist was important.
- The main costs identified were for the acquisition of the software and an appropriate ultrasound machine if it were not already available. Four experts anticipate that VTq would overall reduced costs. One commented that the technology could be used for the diagnosis of other conditions which would mitigate the acquisition costs.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

- Addaction
- Adfam
- Al-Anon Family Groups
- Alcohol Concern
- Alcohol Research UK
- Alcoholics Anonymous (AA)
- British Liver Trust
- Children's Liver Disease Foundation
- Compass UK
- Cystic Fibrosis Trust
- Drinkaware
- Drug and Alcohol Action Programme
- European Association for the Treatment of Addiction UK (eATA)
- Focus 12
- Foundation 66
- Hepatitis A-Z
- Hepatitis B Foundation
- Hepatitis C Trust
- Joseph Rowntree Foundation
- Lifeline Project
- Mentor UK
- Rehabilitation for Addicted Prisoners Trust (RAPt)
- Turning Point
- UK Harm Reduction Alliance

- Two questionnaires were received, 1 from the British Liver Trust and 1 from the Hepatitis B Foundation.

- The British Liver Foundation felt that VTq could be useful for all diagnosed patients but particularly in the early diagnosis of new patients, avoiding invasive tests and providing a rapid outcome.
- The Hepatitis B Foundation UK was not clear on the benefits but considered that a pain-free option for assessment would be advantageous to people with hepatitis B and C.
- The British Liver Foundation stated that social stigma is associated with liver disease because there is a common misconception that all disease is caused by alcohol. Easier and quicker diagnosis can only be beneficial to the patient. The Hepatitis B Foundation UK also voiced concern over the amount of stigma hepatitis B and C attracts.
- The British Liver Foundation stated that there were no disadvantages to using this technology for patients.
- According to the British Liver Foundation, VTq may be advantageous for people with mental health issues and people with alcohol and drug problems as their lifestyle requires quicker and less invasive diagnosis for the best compliance with treatment.
- The British Liver Foundation stated that NICE guidance would encourage more clinicians to use non-invasive technology. The Hepatitis B Foundation UK felt that guidance would improve access to VTq for patients, but cost may be an issue.
- The British Liver Foundation felt that some clinicians need to increase their understanding and confidence in ultrasound testing.
- The British Liver Foundation stated that guidance would be useful on all of the non-invasive markers for liver disease.

A statement was also received from the Children's Liver Disease Foundation, which reflected on the experiences of children and their families having liver biopsy as an ongoing feature of their liver disease. The foundation stated that it would support any effective technology that aided the diagnosis or ongoing management of children affected by any type of liver disease in childhood, and that limited the number of liver biopsies needed.