NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review Decision

Review of MTG27: Virtual Touch Quantification to diagnose and monitor liver fibrosis in chronic hepatitis B and C

This guidance was issued in September 2015

NICE proposes an amendment of published guidance if there are no changes to the technology, clinical environment or evidence base which are likely to result in a change to the recommendations. However, the recommendations may need revision to correct any inaccuracies, usually in relation to providing a more accurate estimate of the results of the cost modelling. The decision to consult on an amendment of published guidance depends on the impact of the proposed amendments and on NICE's perception of their likely acceptance with stakeholders. NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance.

1. Review decision

Amend the guidance and do not consult on the review proposal, because the factual changes proposed have no material effect on the recommendations.

2. Original objective of guidance

To assess the case for adoption of Virtual Touch Quantification for diagnosing and monitoring liver fibrosis in chronic hepatitis B and C.

3. Current guidance

1.1 The case for adopting Virtual Touch Quantification (VTq) software to diagnose and monitor liver fibrosis is supported by the evidence. VTq is as accurate as transient elastography in diagnosing and staging liver fibrosis, and may offer other benefits in terms of imaging the liver and sampling selected areas to assess fibrosis and identify associated pathologies. By avoiding liver biopsies, it may also benefit people whose liver fibrosis needs monitoring. Cost savings through adopting VTq will be greater in hospitals in which liver biopsy is the primary method for diagnosing and monitoring liver fibrosis.

1.2 VTq should be considered as an option for people with chronic hepatitis B or C who need assessment of liver fibrosis.

1.3 Cost modelling suggests that using VTq is cost saving compared with transient elastography and liver biopsy, whether or not a compatible Siemens ultrasound machine needs to be purchased. Compared with transient elastography, the estimated overall cost saving for VTq is around £53 per person. This saving assumes that 10% of the ultrasound machine capacity would be used for VTq measurements, leaving 90% to be applied to other uses. Compared with liver biopsy, the corresponding saving is around £434 per person.

4. Rationale

VTq is still in use in the NHS. Expert advisers stated that the clinical pathway has not changed. According to the company there has been no change in the cost of VTq. There is only a minor difference in the pooled estimates of diagnostic accuracy from new evidence compared to pooled estimates in the original guidance.

5. New evidence

The search strategy from the original assessment report was re-run. References from November 2013 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5.1 Technology availability and changes

The VTq software on ACUSON S2000 and S3000 assessed in MTG27 is still available in the UK. The company has added VTq to the ACUSON Juniper system for liver indications. The cost of VTq on the ACUSON Juniper is slightly lower than VTq on the ACUSON S2000 and ACUSON S3000.

Other related new developments by the company include the point shear wave elastography (pSWE) on the ACUSON Sequoia system. pSWE has an identical function to VTq on the ACUSON S2000 and S3000 ultrasound systems. Two new functionalities used for quantitative liver elastography have also been added to the ACUSON Sequoia system. These are a deep abdominal transducer (DAX) which extends the depth range of shear wave

measurement from 8 cm to 12 cm, for people with a high body mass index (BMI) and a two-dimensional shear wave elastography (SWE) which provides a two-dimensional colour coded map of tissue stiffness. The company notes that the ACUSON Redwood which supports liver assessment using pSWE will be released shortly.

5.2 Clinical practice

The NICE pathways are Hepatitis B (chronic) and Hepatitis B and C testing. NICE guidance on VTq is referenced in the "assessment in adults" section of the Hepatitis B (chronic) pathway. Two of the 4 experts contacted noted that there has been no change to the care pathway since the guidance was published. One expert suggested that VTq technology will be used increasingly in follow up and another expert noted that it offered a good model for centres planning to start a programme from scratch. Another expert noted that the technology can be used for other clinical indications (e.g. assessment of breast lesion stiffness or thyroid nodules) if made available in primary and secondary care. This expert also noted that VTq lessens the need for liver biopsy and is more reliable and cost-effective when compared with fibroscan and transient elastography.

Liver biopsy is considered gold standard for the assessment of liver fibrosis for both Hepatitis B and Hepatitis C. The METAVIR scoring system, based on an assessment of fibrosis classifies the severity of liver disease from none (F0), through mild, moderate and severe (F1–F3), to cirrhosis (F4). Important distinctions are identifying people a) with moderate (F2) or greater fibrosis (F≥2), or b) with cirrhosis (F=4).

NICE's Hepatitis B (chronic) guideline recommends transient elastography as the initial test for chronic liver disease and that antiviral treatment be offered (without a liver biopsy) to patients with a transient elastography score ≥11kPa. Transient elastography scores below 10kPa may mean the patient will be considered for or offered a biopsy.

5.3 NICE facilitated research

None.

5.4 New studies

The EAC included 22 papers in the analysis. Five studies compared VTq with transient elastography and 17 compared VTq with liver biopsy. Fifteen papers assessed VTq in adults with hepatitis C only (one of which, was a systematic review including a further 6 studies), 4 in adults with hepatitis B only, 2 in

mixed populations of hepatitis B and C and 1 in mixed hepatitis B and C (analysed together).

Hepatitis C - The EAC included 17 studies (Alem 2019, Bota 2015, Elhosary 2016, Friedrich-Rust 2015, Frulio 2014, Gandy 2016, Joo 2015, LazAr 2018, Lopez 2018, Lupusoru 2016, Nierhoff 2013, Nishimura 2016, Paranagua-Vezozzo 2017, Ragazzo 2017, Sporea 2016, Tai 2015, Tsukano 2018) which provided cross-sectional data for the number of patients identified as having significant fibrosis (F≥2) or cirrhosis (F=4) by the VTq method versus a reference standard (usually liver biopsy).

The systematic review identified (Nierhoff 2013) included 6 studies (Fierbinteanu-Braticevici 2009, Lupsor 2009, Song 2010, Fierbinteanu-Braticevici 2011, Rizzo 2011, Sporea 2011b) of patients with hepatitis C and used liver biopsy as the gold standard. Three studies, all set in Romania, included overlapping populations (Fierbinteanu-Braticevici [2009,] n=74; Lupsor [2009], n = 112 and Sporea [2011b] n = 543). Hence the two smaller studies were removed from the analysis.

The Nishimura 2016 and Tai 2015 included patients with hepatitis B or C but reported results separately, so these studies are included separately in this section and in the section below.

Only 12 studies provided enough information to be included in a metanalysis. A bivariate mixed effect model (gives summary of receiver operating characteristic curve [SROC]) was used to calculate the pooled estimate for sensitivity and specificity. Results showed a sensitivity of 77% and a specificity of 80% for significant fibrosis (F≥2) and sensitivity of 85% and a specificity of 85% for cirrhosis (F=4). AUC reached 0.853 for both fibrosis stages. The summary estimates for diagnostic testing of hepatitis C suggests that diagnostic testing for F = 4 is more accurate than for F≥2.

Evidence from other studies comparing VTq versus liver biopsy or TE have shown high predictive accuracy of VTq in the detection of cirrhosis (F4) in hepatitis C, with AUROC >80%, although some of these studies did not present data to allow calculation of sensitivity and specificity (Friedrich-Rust 2015, Gandy 2016, Ragazzo 2017, Sporea 2016).

Hepatitis B – The EAC noted that evidence is more limited for hepatitis B. Six studies (Cano 2014, Dong 2015, Dong 2016, Nishimura 2016, Su 2018, Tai 2015) providing cross-sectional data comparing the number of patients identified as having fibrosis by the VTq method versus a reference standard (usually liver biopsy) were identified. The EAC included one meta-analysis (Cano 2014 - published only as an abstract). This meta-analysis included 4

studies which were not listed in the abstract with a total of 476 patients. Pooled sensitivity was 67% (95% CI 0.62 to 0.73) and pooled specificity was 87% (95% CI 0.82 to 0.92). The ROC showed a significant diagnostic value of ARFI in assessing liver fibrosis with an AUC of 0.9359. Of the 5 subsequent studies only 2 had data that could be pooled for F≥2. The sensitivity and specificity for the two studies were 82.9% and 65.0%; and 83.6% and 90.1%; respectively. Three studies had data for F=4. The sensitivity was 66.7%, 90.7% and 62.8%, respectively; specificity was 85.5%, 92.2% and 70.5%, respectively. Due to the between-study heterogeneity, especially with unbalanced study sizes, SROC analysis was not conducted, hence there was no updated pooled estimate for hepatitis B.

Mixed population of Hepatitis B and C

The EAC included one study (Jain 2016) providing cross-sectional data comparing the number of patients identified as having significant fibrosis (F≥2) or cirrhosis (F=4) by the VTq method versus liver biopsy. The study had 69 patients, mean age 34.5 years, 49 (71%) male, of whom 51 (74%) had HCV infection, 16 (23%) had HBV infection and 2 (3%) had combined HBV and HCV infection. Diagnostic accuracy was assessed using the Ishak scoring system which comprises a seven-point (F0-F6) scale. ARFI liver propagation velocity was positively correlated to histology with Spearman's correlation coefficient rho = 0.789 ($p<0.0001$). Thus, the mean shear-wave velocity (SWV) showed an increasing trend with increasing grade of fibrosis.

The EAC notes that no studies in children were identified and that there was significant heterogeneity in studies identified above due to differing cut-offs for shear wave velocities for the various stages of liver disease by different manufacturers. The main limitation to this evidence update was that only publications which described the technology as 'virtual touch' were included. This means publications that have described the technology differently may have been missed out.

5.5 Cost update

The VTq costs have not changed from those used in the cost model informing the NICE guidance. The company advises that the initial purchase price and maintenance costs have been aligned across several models and these are same as the cost in the original guidance.

6. Summary of new information and implications for review

The EAC notes that the differences between the updated pooled estimates for sensitivity and specificity of hepatitis C versus the pooled estimates used in the original model are minor as seen in the table below

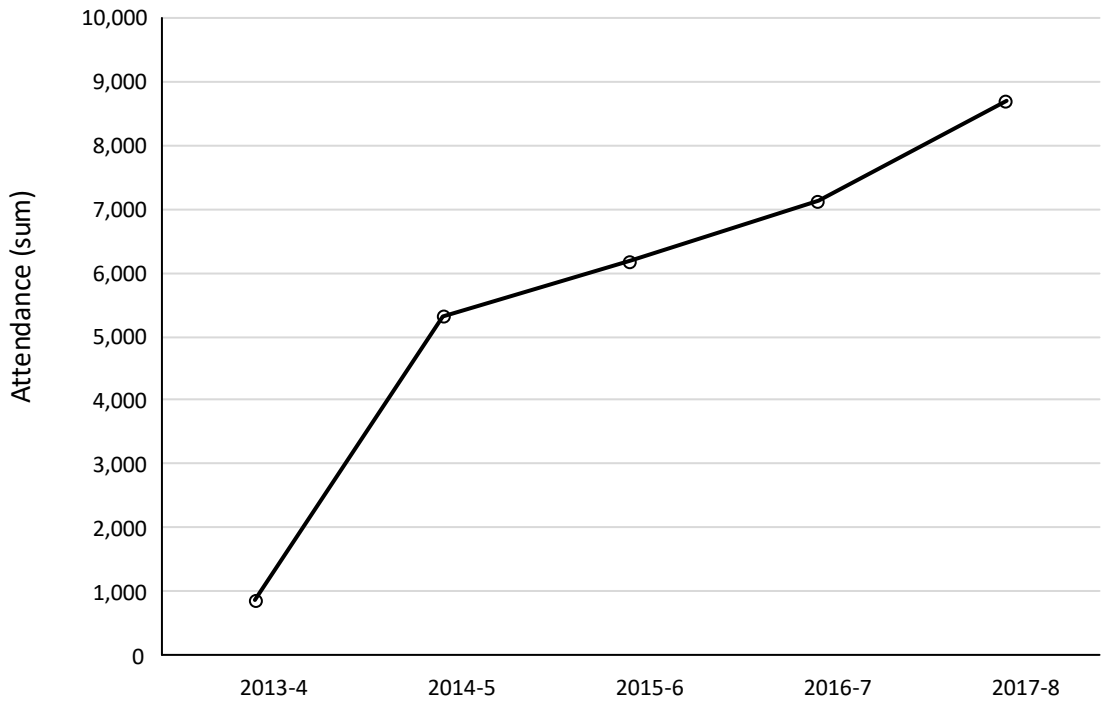
Comparison of original and updated measures of accuracy by disease

Disease	Sensitivity		Specificity	
	Update	Original	Update	Original
Hep C F≥2	77%	79%	80%	79%
Hep C F=4	85%	85%	85%	82%

There is no pooled estimate for hepatitis B due to limited evidence available. The updated values will provide robust data of diagnostic accuracy but given the wide range of values reported in the studies included in this evidence update for sensitivity and specificity their implications for modelling difficult to predict.

7. Implementation

The company noted that ACUSON S2000, S3000 or Sequoia are being used across thirty-seven NHS organisations. The adoption and impact team provided HES data for procedures with any mention of U36.4 Ultrasound elastography with Y98.- Radiology procedures and Z30.1 Liver for 2013/4 to 2017/8



8. Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No potential equality issues have been identified.

Contributors to this paper:

Technical analyst:	Tosin Oladapo
Technical adviser:	Chris Pomfrett
Associate director:	Joanne Holden
Programme director:	Mirella Marlow
Project Manager:	Sharon Wright
Coordinator:	Jo Heaney

Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	Yes
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

In progress

NICE quality standard on hepatitis C

Registered and unpublished trials

Trial name and registration number	Details
Ultrasound Based Acoustic Radiation Force Impulse Imaging NCT01781208	An interventional open label study of 62 children undergoing liver biopsy for known or suspected non-neoplastic liver disease, to assess liver fibrosis and inflammation Completed
Acoustic Radiation Force Impulse (ARFI)Technology in Prediction of Liver Fibrosis (ARFI) NCT01268865	An observational study of HBV or HCV-infected patients about to undergo liver biopsy to assist in clinical decision making. Recruitment status. Unknown

Appendix 3 – changes to guidance

<table>
<tr><th>Section of MTG</th><th>Original MTG</th><th>Proposed amendment</th></tr>
<tr><td>5.26</td><td></td><td>For the guidance review, the external assessment centre noted that the differences between the updated pooled estimates for sensitivity and specificity of hepatitis C versus the pooled estimates used in the original model are minor, as seen in table 2.

Table 2 Updated pooled estimates for sensitivity and specificity of hepatitis C

<table>
<tr><th>Disease</th><th colspan="2">Sensitivity</th><th colspan="2">Specificity</th></tr>
<tr><th></th><th>Update</th><th>Original</th><th>Update</th><th>Original</th></tr>
<tr><td>Hep C F≥2</td><td>77%</td><td>79%</td><td>80%</td><td>79%</td></tr>
<tr><td>Hep C F=4</td><td>85%</td><td>85%</td><td>85%</td><td>82%</td></tr>
</table>

[2019]</td></tr>
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