REVIEW

Virtual touch quantification (VTq) elastography for non-invasive assessment of liver disease and its complications: what the clinician needs to know

David Sherman,¹ Phillip Lung,² Philip Shorvon²

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¹Gastroenterology Department, Central Middlesex Hospital, London Northwest Healthcare NHS Trust, London, UK

²Department of Radiology, Central Middlesex Hospital, London Northwest Healthcare NHS Trust, London, UK

Correspondence to

Dr David Sherman, Gastroenterology Department, Central Middlesex Hospital, London Northwest Healthcare NHS Trust, Acton Lane, London NW10 7NS, UK; david.sherman@nhs.net

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ABSTRACT

Liver stiffness measurement (LSM) is the most widely used non-invasive alternative to biopsy for assessing liver fibrosis in the UK. Virtual touch quantification (VTq, also known as acoustic radiation force impulse) is the principal available alternative to transient elastography (Fibroscan) and is delivered via software enhancements to standard ultrasound (US) machines. It has recently been endorsed by National Institute for Health and Care Excellence in terms of both accuracy and cost-effectiveness for use in viral hepatitis. However, while an increasing proportion of radiologists use VTq, familiarity among gastroenterologists and trainees with LSM techniques is variable and implementation is patchy. This review considers the background, evidence for and practical use of VTq elastography in clinical practice in the UK. Potential future developments in this rapidly evolving field are also highlighted.

INTRODUCTION

The past 15 years have seen rapid advances in the evolution of non-invasive techniques to assess liver disease, providing alternatives to liver biopsy for the assessment of liver fibrosis in routine clinical practice. These can be divided into (1) shear wave or elastographic methods and (2) composite serological surrogate biomarkers (see [table 1](#)). Whereas the former is achieving widespread adoption in the UK, commercial availability of the latter is currently limited and mostly confined to tertiary centres, in contrast to Western Europe where they are more accessible.

The pioneering work on liver elastography by Echosens, in developing a free-standing platform for conducting and measuring mechanically induced shear waves in liver by vibration-controlled transient elastography (TE, Fibroscan), has been followed by the development of alternative methods for measuring the velocity of induced shear waves, integrated into modern ultrasound machines.¹ The first of these was ARFI (Acoustic Radiation Force Impulse) elastography or VTq (Virtual Touch Quantification), developed by Siemens.² Generally to date, VTq has been performed by hospital-based radiologists as a 5-min addition to routine diagnostic or surveillance scans, whereas TE has usually been adopted in the clinic setting by physicians or their hepatology nurse specialists. A further platform developed more recently by Supersonic Imagine is ShearWave elastography, which also uses real-time imaging and is able to display colour-coded areas of liver stiffness measurement (LSM).³

Whereas Fibroscan was first licensed for use in Europe in 2003, VTq was released by Siemens to all countries in 2008, apart from China where it was available from 2009. In the USA, further evidence on both technologies was required by the FDA. Fibroscan was eventually cleared for the USA market in April 2013 and VTq in December 2013. Fibroscan/TE is a hepatology dedicated 'stand-alone' product, whereas ARFI/VTq is an ultrasound imaging feature typically purchased by radiology departments as a

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Table 1 Principal available techniques for non-invasive assessment of liver fibrosis

Category	Examples
Serological biomarkers	
Composite markers of routine tests	APRI, Forns index, Lok index
Commercially available (non-routine)	Fibrotest, enhanced liver fibrosis (ELF) test
Disease specific	FIB-4, NAFLD fibrosis score, BARD score
Liver stiffness measurement (LSM)	
Shear wave-based techniques	Transient elastography (Fibroscan) Acoustic radiation force impulse (ARFI) ShearWave elastography (Supersonic)
Magnetic resonance	MR elastography

useful addition to a multipurpose US platform. The more widespread use of ultrasound by GI/hepatology clinicians may therefore explain the relative greater awareness of the ARFI technology in mainland Europe, compared with both the UK and USA where hands on familiarity with ultrasound is less common.

Since the original studies in the late 2000s, mainly in patients with hepatitis C, sufficient biopsy-controlled evidence for VTq quantification of liver fibrosis has accumulated to show that the technique is at least comparable with TE for the detection of cirrhosis. Additionally, potential advantages for VTq including lower failure rates, use in decompensated liver disease including the presence of ascites, real-time scanning allowing the selection of the optimal measurement site and integration into existing platforms have emerged.^{4–7} A comparison of the two techniques is shown in [table 2](#).

Further landmarks were reached for VTq in 2015 with the publication of a National Institute for Health

and Care Excellence (NICE) Technology Appraisal in October 2015,⁸ which recommended it as the most cost-effective option for UK units that did not already possess a Fibroscan machine. In addition, the first National VTq user group meeting was held at Central Middlesex Hospital in the same month. The comprehensive EASL Guidelines on non-invasive techniques were published by Castera *et al* last year.⁹

However, while increasing number of radiologists are familiar with the theory and practice of elastography, there is a need for UK gastroenterologists and hepatologists to embrace these techniques so that patients can benefit fully from the considerable potential advantages of LSM that adoption of elastography by all units would offer, both in the diagnosis and monitoring of liver diseases.

This review will briefly summarise the current state of knowledge of VTq in the wider context of elastography as a whole and also consider recent evidence for its use outside the traditional sphere of viral hepatitis. Emphasis will be placed on practical aspects relevant to everyday clinical practice.

Basic physics and technology

The standard VTq technique is made possible by uploading a software modification to a Siemens Acuson US machine (2000 series or above).¹⁰ The radiologist performs a routine abdominal USS and selects a suitable 10×6 mm window (region of interest (ROI)—[figure 1](#)) in the right lobe while scanning through an intercostal space. The US probe then generates a short-lived shear wave with a high-frequency (up to 600 Hz) ultrasound ‘push pulse’. The velocity of the induced shear wave, which moves at right angles to the original pulse, is transduced by the same probe ([figure 2](#)).³ Although it is also possible to analyse the left lobe of the liver with VTq, the LSM

Table 2 Comparison of transient elastography (TE) and virtual touch quantification (VTq) techniques

	TE	VTq/ARFI
Measurement units	Force in kilopascals	Velocity in metres per second
Shear wave	Low-frequency mechanical vibration	High-frequency US ‘push pulse’
Availability	Requires purchase of Fibroscan machine	Requires US machine+software modification
Setting	Mobile, outpatient clinic	Radiology department
Operator	Clinician/specialist nurse	Radiologist/sonographer
Simultaneous US assessment/surveillance	No	Yes
Region of interest	Blind 10×40 mm	Chosen by operator 10×6 mm
Reproducibility	Good	Good
Accuracy	Similar to VTq	Similar to TE
Evidence base	Well validated	Well validated, but less than TE
Failure rate	Up to 16%	1–6%
F4 detection	High >90%	High >90%
Detection of F2	Reduced accuracy, but >80%	Reduced accuracy, but >80%
Use in ascites/obesity	No/requires XL probe	Yes/yes
Liver stiffness measurement (LSM) affected by inflammation/other factors	Yes	Yes
Cost-effectiveness in UK (as assessed by NICE)	Less than VTq, greater than liver biopsy	More than both TE and liver biopsy

ARFI, acoustic radiation force impulse; NICE, National Institute for Health and Care Excellence.

Figure 1 Liver ultrasound showing region of interest (ROI) box prior to liver stiffness measurement by VTq.

results sometimes differ markedly from the standard right lobe and currently their significance is controversial and not in widespread clinical use.

Standard physical theory of deformation of elastic materials (Hooke's law) dictates that the velocity of the induced shear wave is proportional to both the magnitude of the force applied to the tissue and the deformability, or stiffness, of the tissue multiplied by a constant (figure 3).^{3 11 12} Thus, for a fixed deforming force or 'push pulse' of specific frequency, shear velocity (SV) is directly proportional to the stiffness (Young's modulus). As healthy liver tissue is composed essentially of cells and vascular spaces within a collagen-based extracellular matrix skeleton, it can be considered to fulfil most of the requirements of such a model. Furthermore, as the liver stiffens with

Figure 2 Illustration of the principle of liver stiffness measurement (LSM) by VTq. An acoustic push pulse generates shear waves through a user-defined region of interest (ROI). Multiple targeted detection pulses from the US probe calculate the velocity of the shear wave. Published by courtesy of Siemens UK.

Figure 3 Basic physics of tissue deformation in relation to elastography. (A) Hooke's law, (B) equation converting shear velocity in m/s to stiffness (Young's modulus) in kPa, using the constant tissue mass density ρ (almost constant at 1000 kg/m³).

fibrosis the velocity of the shear wave increases, providing a numerical representation against which fibrosis stage can be measured.

Whereas TE records shear wave results in kilopascals, VTq records SV in metres per second. Although in theory velocity in m/s can be converted into shear force in kPa (see equation in figure 3), TE and VTq readings are not readily interchangeable due to the differing physical properties of the shear force produced by the physical and ultrasonic transducers employed in each technique, respectively.

The scan technique, quality control and interpretation

The VTq procedure is based upon a standard 10 observations technique, after selection of a ROI (figure 1) following a routine initial US scan. The patient is fasted for 6 hours, important as LSM changes with increased portal blood flow following a meal. The latest version of the Siemens software records each LSM on the screen interface, and at completion mean, median and IQR are generated automatically. Agreed quality standards dictate that a set of LSM results should have a greater than 60% success rate, with 10 successful observations whose IQR/median ratio is less than 0.3, that is, a narrow range of variation.¹³ However, with VTq the radiologist has discretion in reporting results, whereas the TE software requires 10 successful LSMs to generate a mean liver stiffness reading in kPa from its 'elastogram'.¹²

Mean LSMs are usually reported against the reference calibration for Metavir fibrosis stage originally published by Friedrich-Rust *et al*,⁵ measured on a cohort of patients with hepatitis C who had been biopsied within 6 months of ARFI. Reference ranges have also been established for normal subjects.¹⁴ With respect to clinical evaluation of fibrosis in different patient populations, a strong argument is emerging

for both disease-specific and population-specific validation of LSMs, for viral as well as other non-viral liver diseases.

Unlike TE, VTq is able to detect accurate LSM in the presence of ascites and decompensated CLD, as the latter's push pulse is not attenuated and the optimal area of interest can be detected with real-time imaging. The impulse produced by TE is attenuated by fat, requiring a modification in the form of the XL probe, whereas VTq appears less affected by obesity.^{15 16}

Interestingly, the correlation of biopsy fibrosis stage with that predicted by elastography is least accurate in the intermediate stages (Metavir F2–3), where the interobserver error between histopathologists is also greatest. However, when one considers that histological staging systems such as Ishak and Metavir reflect mainly liver architectural features, chosen arbitrarily, rather than quantification of fibrosis, this phenomenon is not surprising. In contrast, validated quantitative measures such as Collagen Proportionate Area may perform better in disease staging.¹⁷ Since the area measured by VTq is approximately 200× larger than that sampled by a standard 18G liver biopsy needle, those experienced in using VTq increasingly appreciate that measured variations in LSM are real phenomena, which require close clinical correlation and explanation. As a result, the new 'clinical science' of elastography has also shed further light on the previously recognised fallibility of liver biopsy as the putative 'Gold standard'.¹⁸

From the clinician's perspective, LSM is mainly used for (1) exclusion of F2 fibrosis and (2) confirmation of advanced fibrosis or cirrhosis (F3/F4). The former is employed to exclude serious liver disease in referrals from primary care, whereas the latter confirms a pivotal stage in the development of CLD, with profound implications for treatment and monitoring, as well as future surveillance for both varices and hepatocellular carcinoma. Serial measurements at 1–3 yearly intervals are increasingly employed, frequently providing additional information to clinical signs as well as routine biochemical and serological tests.

Factors determining accuracy in the prediction of liver fibrosis stage

The clinician must interpret the elastography results combined with the standard US liver report in light of clinical history and examination findings, as well as available biochemical and serological tests. However, this requires detailed knowledge and experience of elastography technique, potential effect of confounding factors and also being prepared to consider the result unreliable, particularly if it does not fit with the clinical picture. This may occur in as many as 20–30% of cases (Sherman D, Sangwaiya MJ, Tadrous P, *et al.* Factors contributing to variance between ARFI elastography and liver histology: results of a large

unselected consecutive series with simultaneous biopsy of ARFI measurement site. submitted for publication).

Although various factors such as biliary obstruction or cholestasis, venous outflow blockage or congestive heart failure, and meals or exercise may have a significant effect on LSM,¹² in the clinical setting these features are almost always excluded by clinical history, VTq protocol or the initial abdominal USS. Studies in VTq, by both our group and others, suggest that there is no evidence that adjustments need to be made for age, gender and depth of subcutaneous fat layer or the chosen ROI measurement point (Sherman *et al* submitted for publication).¹⁴ In contrast, TE requires the use of the XL probe in patients with a BMI of 30 or more.

Despite increasing evidence that liver biopsy's status as a 'Gold Standard' may be overrated, information from many biopsy-controlled studies has given insight into the limitations of elastographic techniques. Recent data, including those from our own large unselected biopsy series, show that the most important confounding factors in routine use affecting predictive accuracy of VTq are (1) fatty change (either as the primary disease or as a comorbidity); (2) inflammation; and (3) a scan with high variability, expressed as a high IQR/median >0.3 (Sherman *et al*, submitted for publication).¹⁹ In addition, evidence shows that other non-viral aetiologies of liver disease such as alcoholic (ALD) and autoimmune (AILD) liver diseases may have reduced predictive value as they are subject to greater variation, part of which is due to intense inflammation in the active phase.

Of course, the presence of increased variation between LSMs obtained by ARFI, shown as a high IQR/median of 10 values, may not always be an indicator of an unreliable scan but simply a true reflection of liver disease with uneven distribution. Studies of whole explanted livers have given an insight into this variation.²⁰ However, whereas TE may register a 'failure' in this situation, VTq provides more discretion to the operator to report the results while advising caution in interpretation.

In summary, careful reporting and clinical interpretation of LSMs are important and clinical management decisions based on LSM alone, such as the initiation of antiviral therapy, must be made with the awareness of these and other potential pitfalls. Close collaboration with radiological and histopathological colleagues within an multidisciplinary team setting is therefore recommended.

Usefulness in the assessment of viral hepatitis

Not surprisingly, the strongest body of evidence for elastography has been accumulated for viral hepatitis, in particular for HCV where fibrosis progression is predictable and slow, with inflammation usually mild. As a result of this and the advent of highly effective

new therapies, very few patients with HCV infection now undergo liver biopsy during assessment in the UK.

Evidence from both biopsy-controlled studies, and also comparative studies between TE and VTq, have shown similarly high predictive accuracy of both techniques in the detection of cirrhosis in hepatitis C, expressed by both AUROC and positive predictive values in excess of 90%.^{9 21} Performance for intermediate fibrosis stages and F2 exclusion is less consistent between techniques and across trials, although still with predictive parameters well above 80%, but this may be for a number of reasons including both methodological and population heterogeneity between studies.

The forthcoming licensing of newer highly effective pan-genotypic directly acting antiviral agents for HCV is likely to almost completely eliminate the need for liver biopsy in straightforward situations, whereas LSM will continue to be of some use in defining and following-up those with advanced fibrosis or cirrhosis.

In contrast, the position is less clear for hepatitis B, where fibrosis progression is unpredictable and the degree of inflammation highly variable. A recent meta-analysis suggested that VTq is at least non-inferior to TE for F4 cirrhosis estimation.²² It is likely that exclusion of F2 fibrosis is more accurate when inflammation is less active, but liver biopsy is still often required when initiating antiviral therapy as histological inflammatory grade may be crucial and LSM readings cannot distinguish contributions from fibrosis and necroinflammation.

The 2013 NICE guidelines for HBV, which predated those for VTq use in both HCV and HBV published in 2015, recommend initial assessment with elastography and yearly monitoring thereafter.²³ The independent analysis of high-quality randomised studies contained in the 2015 NICE guidance has confirmed the lower cost per test of VTq compared with either TE or biopsy, and non-inferiority of accuracy. Furthermore, VTq can be used to measure the stiffness of a variety of other tissues, including breast, salivary glands, prostate, etc.⁶

NAFLD and screening in primary care

As stated above, the inherent variability and technical difficulties associated with the assessment of fatty liver diseases by elastography techniques have reflected lower reliability of fibrosis detection in published studies. There are more data for TE, and poor initial results prompted the development of the Fibroscan XL probe in addition to the standard M version, which generates a mechanical signal of lower frequency and higher amplitude, to compensate in those with a BMI of 30 or greater.²⁴ However, high-quality data for its efficacy are lacking to date, and it is possible that the optimal cut-offs for fibrosis stages differ from the original M probe.^{8 25} Data for VTq are also sparse compared with viral hepatitis but might be

expected to yield higher accuracy, given the greater penetration and reduced attenuation of the ARFI shear wave.

At present, the precise diagnosis of NASH still requires liver histology, but there will continue to be increased focus on non-invasive methods, particularly if future randomised trials show longer term benefit from potential therapeutic agents such as liraglutide or obeticholic acid, over and above weight reduction, lifestyle modification and attention to risk factors. Given that NAFLD makes up approximately 50% of referrals from primary care with abnormal LFTs, the use of non-invasive methods to excluded F2 fibrosis (and perhaps NASH also) will become increasingly important in triage.

At present, current data suggest that elastography alone is not sufficient and will need to be used in conjunction with validated clinical screening tests, such as the NAFLD fibrosis score, and serological markers such as the enhanced liver fibrosis test.^{9 26} Further high-quality studies in populations with high prevalence of both NAFLD and NASH will be required, in addition to comparative studies of VTq versus TE using the XL probe.

Other conditions and patient groups

Detailed consideration of other conditions is beyond the scope of this review but inevitably, where available, elastography is increasingly used across the whole spectrum of liver disease by clinicians. However, data on alcohol-induced, autoimmune liver disease, iron overload and others are accumulating but there are few large series with the exception of ALD. NICE also recommended the use of VTq in paediatric viral liver disease in 2015,⁸ in view of the obvious potential benefits and not least because of the practical difficulties of performing liver biopsy. Ultimately, a greater understanding of the effect of inflammation and other confounding variables on LSM is likely to improve the accuracy and utility of non-invasive techniques in these conditions in future.

Portal hypertension

Portal hypertension (PHT) is another area where elastography, in the form of both LSM as well as the comparatively recent technique of spleen stiffness measurement (SSM), has provided further pathophysiological understanding as well as a non-invasive detection method likely to prove invaluable in the future.

The physiology of PHT in cirrhosis would suggest that LSM would correlate well with the increases in portal pressure seen in early cirrhosis, as the resistance to portal blood flow would be proportional to the reduced compliance (effectively inversely proportional to stiffness) of liver tissue resulting from the fibrotic and other processes occurring in CLD. However, initial studies of elastography with TE demonstrated a

less good correlation with the occurrence of varices on endoscopy and hepatic venous pressure gradient (HVPG) than expected. This finding is explained by the circulatory changes that evolve in later stages of PHT, with increased portal inflow and vasodilatation of the splanchnic circulation becoming more important in determining the rise in HVPG and the development of oesophagogastric varices, over and above increased hepatic sinusoidal resistance.²⁷

Of course, these processes can be detected by existing routine US techniques such as measurement of longitudinal spleen length, combined with Doppler measurement of portal vein diameter, flow pattern direction and the presence of portosystemic collaterals. Alternatively, SSM can be used either alone or, more commonly, in conjunction with these parameters as well as platelet count. A number of scoring systems have been studied, revealing high levels of accuracy in initial studies,^{28–30} although these have not yet been extensively compared with other scoring systems, for example, platelet/spleen ratio.

The emphasis advocated by the Baveno group has focused mainly on the detection of clinically significant portal hypertension (CSPH) as a pivotal stage of prognostic significance in compensated cirrhosis, predicting the development of varices and future decompensation. In this area, VTq has a distinct advantage in allowing simultaneous conventional and Doppler US, combined with LSM and potentially SSM, although the widespread applicability and usefulness of the latter technique have yet to be demonstrated.

While combinations of these modalities have yielded high predictive values for endoscopic PHT of over 90%, no single scoring system is in general use, to some extent reflecting limitations in local expertise. Recently, the Baveno VI conference in 2015 recommended the use of platelet count above 150 and LSM by TE below 20 kPa as thresholds where surveillance endoscopy could be avoided, due to the low likelihood of varices requiring treatment. A decision was reached by a consensus of experts reflecting the high NPV for CSPH demonstrated in trials.³¹ It is likely that an equivalent threshold for LSM by VTq will be developed in the near future, although further validation of this approach in longer term studies is required.

Clearly, further research is needed in this area, providing the prospect of an initial screening test to select patients with compensated cirrhosis who require endoscopic screening for varices, as well as potentially reducing the need for follow up surveillance. Such a test would depend partly on proven evidence of reliability, local expertise, as well as ease of use and widespread applicability.³² As yet, the ‘Holy Grail’ of a non-invasive test for PHT remains elusive, although these new developments suggest that it may soon be within reach.

Prediction of outcome—risk of progression and prognosis

One of the most interesting aspects of elastography research is that long-term follow-up studies, particularly with Fibroscan, have shown that LSM correlates with a variety of prognostic outcome measures, beyond that indicated by liver biopsy stage alone. This phenomenon may be partly explained by the fact that (1) patients with cirrhosis will show a continuum of values above the diagnostic threshold of 12.5 kPa by TE or 1.75 m/s by VTq, up to potential maxima of 75 kPa and 5 m/s, respectively, which reflect a spectrum of severity of liver damage in cirrhotics in greater detail and (2) further increases in LSM may indicate the presence of other disease processes such as inflammation, continued alcohol intake, etc super-added to fibrosis.

Thus, in addition to information on PHT, there is evidence that a single LSM in compensated cirrhotics gives prognostic information on future risk of decompensation, and the risk of developing hepatocellular carcinoma.^{33–34} In decompensated cirrhotics, VTq shear velocities show a high level of correlation with widely used clinical prognostic scoring systems such as MELD, Child Pugh and Maddrey,^{35–36} and LSM by TE has shown correlation with a range of liver outcomes and also mortality or need for transplantation.^{34–37} Interestingly, a further study showed that in a cohort of ICU patients higher LSMs on admission was correlated with a significantly greater risk of mortality, even in those without liver disease.³⁸ This raises the possibility of a wider significance of LSM in the critically ill, including situations beyond primary liver disease.

Furthermore, serial LSMs are likely to provide information on improvements in liver damage in response to antiviral therapy in HCV/HBV, immunosuppressive therapy in AILD and abstinence from alcohol in ALD. However, further research is needed, particularly with VTq, to confirm the clinical utility of these observations and conduct direct comparisons with commonly used prognostic scores. VTq may have advantages in this area in view of increased accuracy and a lower failure rate in decompensated CLD.

Summary and conclusion

The advent of new non-invasive technologies for assessing liver damage is timely, given the recent rise in incidence in chronic liver disease seen in the UK (Lancet commission). The new clinical science of LSM by elastography has provided an invaluable non-invasive tool with which hepatologists can both assess and monitor the degree of liver damage in their patients. At the same time that the limitations, sampling and observer errors of the hitherto ‘Gold standard’ of liver biopsy have also been revealed, a new window through which liver disease can be viewed has been opened. In practice, future use of both VTq and TE is likely to be complementary to both a

reduced volume of liver biopsies, and the use of serological markers in certain situations.⁹

In the near future, LSM is set to become as fundamental a part of the clinical assessment of liver disease as abdominal palpation, LFTs, endoscopy or biopsy, and is already an indispensable tool in the armamentarium of the physician treating liver disease. If the observed correlations between LSM and prognosis are confirmed by further studies, it may complement or even replace existing scoring systems such as Child-Pugh and MELD.

The future will also see evolution of this technology and developments including wider availability in both secondary and the primary care interface via rapid access referral pathways, facilitated in the case of VTq by training of both radiographers and specialist nurses. VTq elastography, or comparable techniques depending upon local preference, will become a mandatory technique in assessment and monitoring of liver diseases, and potentially allow rationalisation of both variceal and HCC surveillance frequency.

Despite a reduced role in HCV diagnosis following the advent of highly effective pan-genotypic therapies, its use in HBV, NAFLD, ALD and probably AILD will increase. Although the initial implementation of VTq within a hepatology service presents challenges, it is likely that shared experience and further guidelines will make this task considerably easier.³⁹

Physicians using these techniques in every day practice will need to acquire a detailed understanding of this new clinical science, with an understanding of its limitations as well as the potentially greater insight that LSM provides in some clinical situations. In turn, more research in a variety of disease groups and populations, as well as dedicated training of gastroenterology trainees will be needed in this area. Looking further ahead, it is the prediction of this review that a better insight into elastography and allied techniques may even revolutionise our understanding of liver disease itself.

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