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REVIEW ARTICLE

Elastography: modality-specific approaches, clinical applications, and research horizons

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Abstract Manual palpation has been used for centuries to provide a relative indication of tissue health and disease. Engineers have sought to make these assessments increasingly quantitative and accessible within daily clinical practice. Since many of the developed techniques involve image-based quantification of tissue deformation in response to an applied force (i.e., "elastography"), such approaches fall squarely within the domain of the radiologist. While commercial elastography analysis software is becoming increasingly available for clinical use, the internal workings of these packages often remain a "black box," with limited guidance on how to usefully apply the methods toward a meaningful diagnosis. The purpose of the present review article is to introduce some important approaches to elastography that have been developed for the most widely used clinical imaging modalities (e.g., ultrasound, MRI), to provide a basic sense of the underlying physical principles, and to discuss both current and potential (musculoskeletal) applications. The article also seeks to provide a perspective on emerging approaches that are rapidly developing in the research laboratory (e.g., optical coherence tomography, fibered confocal microscopy), and which may eventually gain a clinical foothold.

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Introduction

Changes in tissue mechanical properties are a well established marker of certain diseases. For example, physicians have been using palpation to detect breast and prostate tumors for centuries. This is based on the fact that tumor tissues often have a much higher compressive stiffness than normal ones [1]. In orthopedics, reduced compressive stiffness has been reported to be an early indication of cartilage degeneration [2]. Injured and diseased tendon will also exhibit aberrant biomechanical properties (e.g., stiffness, failure load) and healing tendon will progressively regain its stiffness [3]. Osteoporotic bones have lower stiffness and strength, making them more susceptible to fracture [4]. In short, a way of measuring the mechanical properties of tissue can be helpful for clinical diagnosis of existing pathologies, tracking of healing progress, or for prediction of injury risk and prognosis for the likelihood of healing.

Manual palpation is a common, albeit subjective, measure of tissue mechanical properties for diagnostic purposes. It nonetheless shares a basic operating principle with more sophisticated approaches that apply an external load to a tissue while measuring consequent tissue deformation. Recent advancements in imaging techniques have opened possibilities for accurately measuring these deformations in vivo and later extracting functional/biomechanical properties. Ophir et al. [5] first used the term "elastography" to describe the method of quantitative imaging of the distribution of biological tissue strains (a measure of tissue stretch that is normalized to

the dimensions of the undeformed tissue) and elastic modulus (a material property that describes relative tissue compliance). Ultrasound and magnetic resonance imaging were the earliest adapted modalities used for elastography and such approaches have evolved over many years. The current perspective article seeks to review newer techniques and applications that have emerged in the past 5 years using ultrasound and magnetic resonance elastography as well as other imaging modalities. The goal is to thus provide an overview of elastography methods developed for common clinical imaging modalities and their present and potential clinical applications.

Mechanical properties of tissue

Reflecting their composition, most tissues in the human body are viscoelastic, possessing the properties of both elastic (solid) and viscous (fluid-like) materials. The response of a tissue to an applied load (stress–strain curves as in Fig. 1) will vary depending on the relative elastic and viscoelastic properties of a tissue. While the viscous properties are closely related to function in some cases (such as dissipation of impact energy), in this review we will focus on the elastic properties of tissue, which are most often described by elastic modulus.

Most biological tissues are structurally complex, with accordingly complex material behaviors that complicate analytical treatment. For the purposes of conceptual (mathematical) expedience, engineers often describe material behavior in terms of a few parameters that approximately characterize a substance's tendency to deform under applied stress. Elastic modulus is most commonly used, and is defined as the slope of the stress–strain curve (how much the material stretches in response to an incremental change in applied stress). The precise definition of elastic modulus depends on how stress and strain are described. The most common definitions are Young's modulus (E), shear modulus (G), and bulk modulus (K). Young's modulus is defined as tensile (or compressive) stress over tensile (or compressive) strain, while shear modulus is defined as shear stress over shear strain. Bulk modulus is an extension of Young's modulus in three dimensions and is defined as volumetric stress over volumetric strain. The Poisson's ratio (ν) is also a commonly used parameter in biomechanics. It is defined as the ratio of transverse strain over axial strain when a sample is stretched. The relationship among E, G, K, and ν can be described by:

$$G = \frac{E}{2(1+\nu)} \tag{1}$$

and,

$$K = \frac{E}{3(1-2\nu)} \tag{2}$$

Given their high water content, most soft tissues inside the human body are nearly incompressible, which means they have a Poisson ratio close to 0.5. This gives a simplified relationship between shear modulus (G) and Young's modulus (E) of $E \approx 3G$. Since the bulk modulus does not vary much (less than 15%) for human tissues, shear modulus and Young's modulus are the most suitable parameters to measure.

Young's modulus and shear modulus are terms that describe "material quality," and are constructed to be independent of the shape or size of the tissue. This makes comparison among different tissues possible. When one is less directly concerned with the tissue, but rather with the functional anatomical unit (e.g., the Achilles tendon) itself, "structural properties" are usually described. For instance, the engineering term "stiffness" is defined as the ratio of the applied force on a structure over the length change induced by that force. While structural "stiffness" and material "modulus" are related, they have distinct biomechanical meanings with regard to the dimension of the tissues being considered.

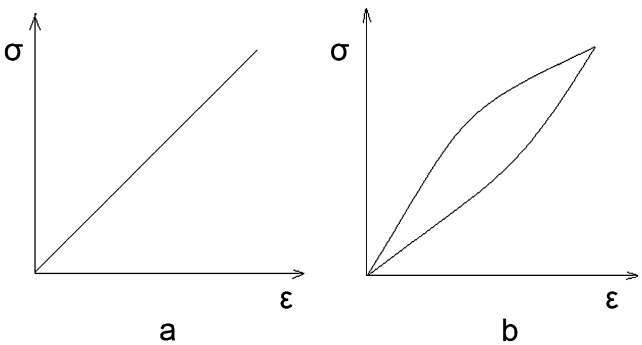

Fig. 1 Stress vs strain curves for **a** purely elastic material and **b** a viscoelastic material. The viscous nature of biological materials dissipates energy as a tissue is loaded and unloaded, as reflected in the non-linear loop of the material curve. More elastic tissues (like tendon) behave like a spring, loading and unloading with minimal energy loss. Highly viscoelastic tissues like cartilage have inherent dissipative properties that are useful for absorbing shock

Imaging modalities

Almost all elastography approaches involve some method of tissue excitation to apply mechanical stress to a region of interest, then use imaging methods to measure the displacement prior to and immediately following the applied stress. Several imaging modalities have been employed to measure these displacements. In this regard, ultrasound and MR elastography have been under very active development for the past 20 years. They infer displacements using ultra-

sound or MR signals directly, or by tracking changes in the distance between anatomical landmarks. With recent advancements in image registration, feature tracking and computational power, displacements can now be obtained by comparing pre- and post-stress images using many other imaging modalities, often in real-time. The following sections of the paper will address these imaging modalities separately.

Ultrasound elastography

Ultrasound elastography was the first and most widely researched method. Various approaches to ultrasound elastography have been proposed over the years. According to tissue excitation and displacement detection methods, they can be further classified into four subcategories: compression elastography, sonoelastography, transient elastography, and acoustic radiation force elastography.

Compression elastography

Compression elastography, also known as the static method or quasi-static method, refers to lower frequency (less than 10 Hz) compressions during tissue excitation. It is normally performed using manual manipulation or sometimes even relying on natural internal movements, such as respiration, heartbeat, etc. The study of ultrasound elasticity imaging began with Dickinson and Hill [6] and Wilson and Robinson [7]. They used the correlation between successive A-scans and M-scans respectively to measure low velocity motions in liver tissues caused by aortic pulsation. Displacement was calculated from the time integral of velocity. This method had been further extended to two dimensions with the advancement of ultrasound technology [8, 9]. In 1991, Ophir et al. [5] applied external compression to measure the resultant strain field and first referred to the method as elastography. It was assumed that the applied stress was uniform. Thus, the derived elastic moduli were inversely proportional to the measured strain (higher modulus tissues were indicated by less tissue stretch). Here, the term "elastogram" was coined to describe the resultant elastic modulus distribution. For visualization purposes, elastograms are often color-coded so that lesions with different elastic moduli can be clearly identified. This method has been developed, with oversampling (quasistatic cyclic compression) to improve signal to noise and help eliminate artifacts [10].

Compression elastography has been shown to be helpful in breast and prostate tumor detection [11, 12], thyroid tumor diagnosis [13], intravascular plaque characterization [14], and assessment of tendinosis [15–18], among other clinical applications.

Sonoelastography

In 1987, Krouskop et al. [19] proposed a one-dimensional (1-D) method to measure the mechanical properties of soft tissue at desired points. External low frequency (10 Hz) vibrations were applied to the tissue and wave velocity was measured using a gated Doppler ultrasound motion sensing system. Yamakoshi et al. [20] used higher frequency (several hundred Hertz) vibrations in a similar manner. Both the amplitude and phase of internal vibration were measured from Doppler frequency modulation of simultaneously transmitted probing ultrasound waves.

The first actual image of an elastic modulus using this approach was created by Lerner et al. [21], who introduced the term "sonoelasticity imaging." This method was further developed by Parker et al. [22–25] and has subsequently been referred to as "sonoelastography." Here, Doppler shift was used to detect the shear velocity of soft tissues induced by external vibrations. Then, Young's modulus (E) could be calculated as a function of shear velocity C_s) and material density (ρ) by:

$$E = 3\rho C_s^2 \tag{3}$$

Another shear wave source was added to the system so that the pattern of interference between the two waves could be imaged and correlated with shear velocity in the medium (Fig. 2). This approach slowed the resultant shear wave such that a commercially available ultrasound system could be used for imaging [26–28]. Three-dimensional sonoelastography was developed by acquiring a sequence ("stack") of 2D images then registering them to form a volume [29–31].

Sonoelastography has been mainly applied in prostate tumor detection [28, 29, 32] and liver disease [33], among other applications.

Transient elastography

One of the drawbacks of sonoelastography is a bias related to reflected waves created at tissue boundaries. To avoid this problem, transient elastography was proposed. The method utilized a short tone burst of vibration so that forward propagating waves could be separated from reflected waves using a pulse-echo system [34, 35].

Transient elastography has shown great promise for the detection of liver disease, especially fibrosis [36]. Other applications include breast tumor detection [37] and muscle stiffness measurement [38, 39].

Acoustic radiation force elastography

In contrast to all the above-described methods by which tissues are excited externally, acoustic radiation force

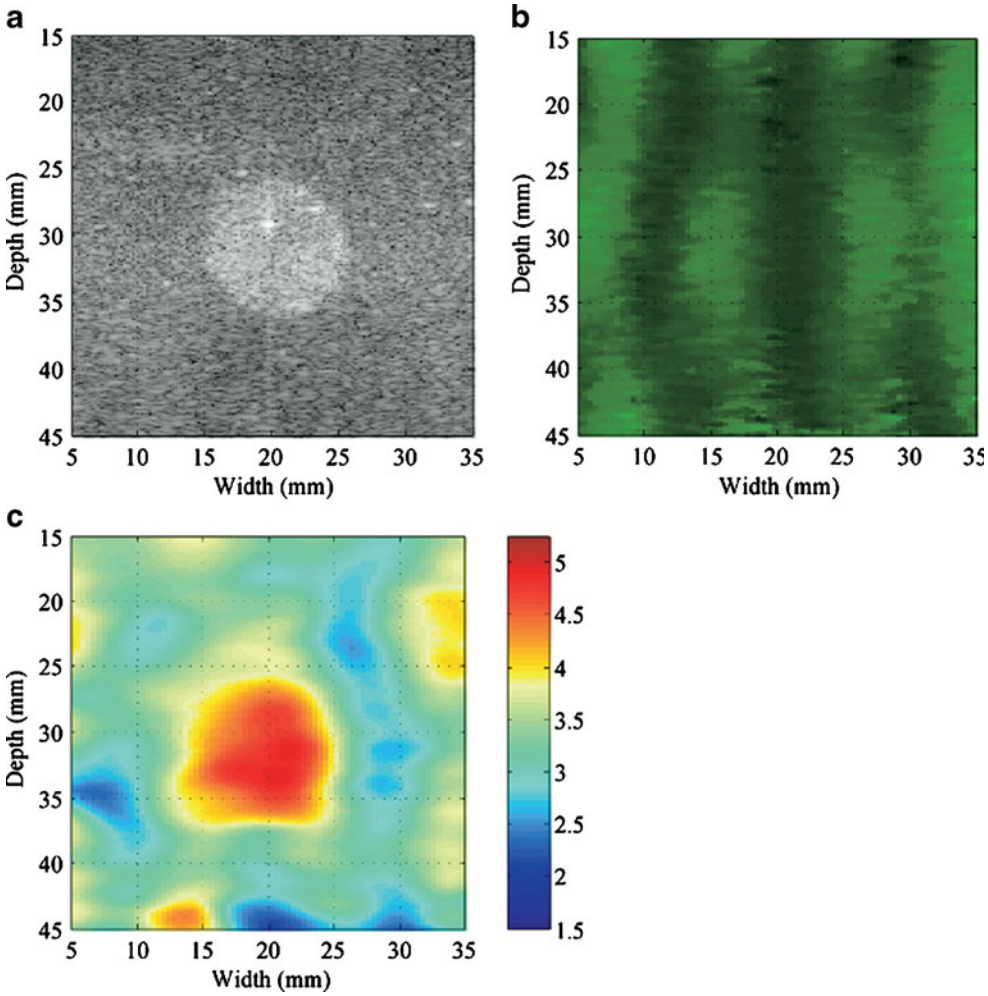

Fig. 2 Results reprinted from Hoyt et al. [24]. The images represent sonoelastographic techniques applied to a phantom intended to mimick heterogeneous tissue (13×13×8 cm) containing a 1 cm diameter stiff circular inclusion. Results depict the matched **a** B-mode ultrasound image, **b** sonoelastogram and **c** shear velocity images (units m/s)

elastography uses internal tissue excitation through a focused ultrasound pulse [40–42]. The force induced by the pulse can be calculated according to:

$$F = 2\alpha I/c \tag{4}$$

where α is the absorption coefficient of the medium, c is the speed of sound in the propagation medium, and I is the intensity of the acoustic beam [42]. After excitation, displacements can be measured using pulse echo techniques with normal pulses at a diagnostic level.

Acoustic radiation force elastography has been applied to breast lesion imaging [43], abdominal imaging [44], as well as providing guidance for cardiac and liver tissue ablation [45, 46].

Magnetic resonance elastography

Compared with ultrasound imaging, magnetic resonance imaging (MRI) offers advantages for elastographic imaging in terms of a larger field of view and the potential to more easily incorporate a three-dimensional analysis. Muthupillai et al. [47] proposed the magnetic resonance elastography (MRE) method using phase-sensitive magnetic resonance to measure shear modulus. The tissue excitation method was similar to that of sonoelastography by which high-frequency (200 to 400 Hz) vibrations were applied externally to the tissue surface to induce shear waves within the tissue. Tissue displacements were then correlated with the phase shifts of the magnetic resonance signals (e.g., Fig. 3) [47–49]. Various data processing techniques have been proposed to relate these displacements to mechanical properties. More comprehensive summaries of this technique can be found elsewhere [50].

It has been reported that several factors can affect results obtained using MRE including the frequency of tissue excitation, tissue temperature, and the direction of wave propagation and polarization [51]. While these factors do influence quantitative measurements, relative assessments based on qualitative tissue stiffness measurements in applications like tumor lesion detection are less sensitive.

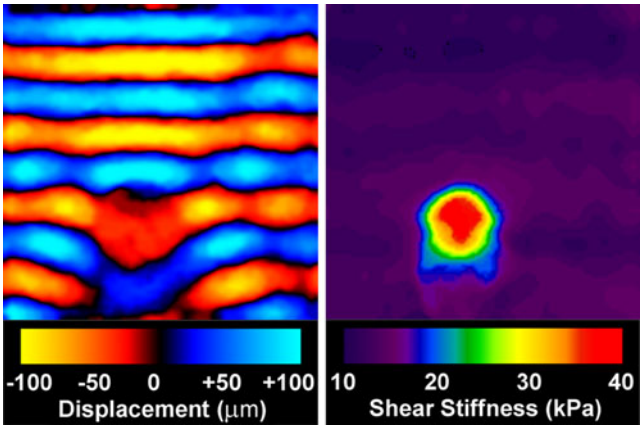

Fig. 3 Magnetic resonance elastogram showing the typical spatial resolution and measurable tissue stiffness range achievable with a clinical grade MRI. **a** Shear waves propagating in a homogeneous phantom with an embedded 1.5 cm diameter cylinder of stiffer gel. **b** The elastogram depiction of the object. Reprinted with permission from Manduca et al. [50]

Magnetic resonance elastography has been used in a wide variety of applications spanning breast cancer detection [52], liver disease detection [53], brain tissue stiffness measurement [54], lung mechanical properties measurement [55], and muscle tissue characterization [56–58].

Optical elastography

Optical elastography (e.g., clinical endoscopy) is also a well-established concept that has many methodological forms. White light elastography has been used to replace strain gauges in the measurement of tissue mechanical properties in the laboratory [59]. Because of the limited penetration of white light, in vivo application of white light elastography has been mainly limited to skin disease detection [60]. We describe below two other forms of optical elastography that have been developed in recent years that take advantage of advancements in optical imaging.

Optical coherence tomography (OCT) is a relatively new optical imaging modality for imaging internal tissue structures [61]. It is similar to ultrasound imaging except that it uses infrared light waves instead of acoustic waves. OCT allows tissue imaging at a microscopic level (spatial resolutions around 10 μm) and it is relatively inexpensive and portable [62]. OCT elastography was proposed to image micrometer-level displacements and strain distributions induced by compression in 1998 [63]. The tissue excitation method used in this case was a small step-wise increase in compressive force on external tissue surfaces. The displacements were tracked using speckle tracking algorithms, and tissue strain maps were then calculated. In this modality, feature tracking in the images is of utmost importance, and various tracking algorithms have been compared for performance and accuracy [64–66]. Clinically, OCT has been mainly applied on extracardiac arteries and veins for coronary disease detection [67]. Other applications include quantification of the mechanical properties of developing tissues [68] and imaging of the stiffness of skin lesions [69].

In 2004, fibered confocal fluorescence microscopy (FCFM) was first described [70]. FCFM combines the advantages of a confocal microscope and endoscope to allow in vivo measurement of targeted tissues at the tissue and cell levels. The technique was later applied to measure soft tissue material properties in vivo using fluorescently labeled cell nuclei as markers of tissue displacement [71–73]. The method has been shown to be able to detect very small mechanical tissue defects, while simultaneously monitoring the key biological aspects of cell behaviors.

Improved elastogram analysis using the inverse finite element method

The finite element method (FEM) has been used in the medical field to predict tissue deformations (for instance related to injury and failure) given the anatomy, mechanical properties, and applied loads. If the tissue deformations are already known (e.g. from the clinical imaging data of a mechanically loaded tissue), finite element methods can be used in an "inverse" approach to extract the tissue mechanical properties. Here, the geometry and deformation are obtained by taking images before and after deformation. A finite element model is then reconstructed from the images and material properties are obtained by iteratively adjusting the parameters in the model until the predicted strains most closely match the measured strains. Such an approach is being increasingly used, and offers great potential for improved extraction of functional biomechanical information from clinical imaging data [74]. For elastography methods that only provide relative measures of tissue stiffness because of difficulties in accurately measuring local strain distributions, inverse FEM can be used as a supplementary method to quantitatively derive material properties [75].

An advantage of inverse FEM is that it is modality-independent. Images from all modalities can be applied as long as they provide enough data for model construction and deformation calculation. Miga et al. [76, 77] helped pioneer this approach and have coined it "modality-independent elastography." This flexibility with regard to imaging modality has resulted in its use in a wide range of clinical applications including cardiovascular diseases [74], mammography [77], dermoscopy [76], atherosclerotic coronary plaques [78], myometrium modeling [79], and liver hemangioma [75].

Application to musculoskeletal tissues

While the primary clinical application of elastography remains for tumor detection, its potential application to musculoskeletal tissues has increasingly driven research activity around the development of new approaches and the translation of existing approaches to clinical devices. Until now, the most plausible clinical application of functional imaging of skeletal tissues has been with regard to the early diagnosis of tissue and joint degeneration [80], and the assessment of osteoporosis-related fracture risk [81, 82]. Also possible, but less developed, is the potential for imaging-based assessment of healing, and the use of this information in modulating a particular therapy (or rehabilitative protocol) based on functional readouts.

Muscle is the mostly widely researched musculoskeletal tissue for elastography. Dresner et al. [56] demonstrated the applicability of MR elastography to measure skeletal muscle stiffness. The same method has been applied to quantify differences in muscle stiffness between normal and dysfunctional (lower-extremity neuromuscular dysfunction) groups [83] and for identifying taut bands with higher stiffness than normal muscles [84]. Bensamoun et al. [85, 86] quantitatively measured the stiffness of thigh muscle and compared the results before and after treatment for hyperthyroid activity. MR elastography measurements of skeletal muscles have been verified against mathematical models and correlated with electromyographic data [87]. The effects of aging on muscle stiffness have been examined by MRE [88]. As a competing method, sono-elastography has also been applied to measure skeletal muscle elasticity [89–91].

Assessing joint tissue mechanics presents another potentially important application of elastography. MR elastography has been applied to measure cartilage deformation in an attempt to link mechanics to disease [92–94]. Tendon and ligament strain measurements have been performed by ultrasound elastography (Fig. 4) [17, 95, 96], and the sensitivity, specificity, accuracy, and reproducibility of the method have been explored in the imaging of symptomatic Achilles tendons [15, 17, 18] and for the detection of lateral epicondylitis [16]. Optical methods with fibered confocal fluorescence microscopy have also been developed for relating tendon stretch to tissue health [71–73]. A recent review of ultrasound elastography for musculoskeletal applications can be found by Klauser and Peetrons [97].

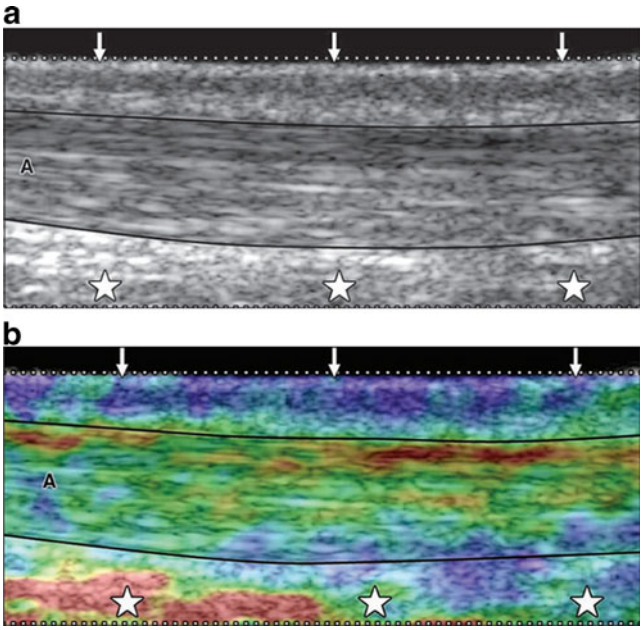

Fig. 4 Application of ultrasound elastography for the diagnosis of Achilles tendinopathy. **a** The tendon is located between *lines*, *arrows* indicate the skin, and *stars* show anterior peritendinous tissue. **b** Real-time sonoelastography image corresponding to **a** shows changes in tissue elasticity. Distinct softening can be seen in the dorsal part of the Achilles tendon. *Red* represents soft tissue; *blue and green*, hard tissue; and *yellow*, tissues of intermediate stiffness. Reprinted with permission from De Zordo et al. [17]

Conclusion and future outlook

Elastography provides a non-invasive way to measure tissue mechanical properties in vivo. It provides additional functional information that cannot otherwise be seen using traditional imaging methods. Its application has been expanding rapidly over the past few years. New methods for different clinical applications are emerging, but need to be carefully characterized before meaningful clinical application is possible.

The available methods each have their own merits and drawbacks. For example, ultrasound elastography has the benefits of low cost and short acquisition time, but suffers from generally poor spatial resolution (e.g., compression elastography has a spatial resolution of 1.5 mm at its theoretical limit [98]). MRE has a better potential resolution (35 μm at an extremely high magnetic field of 11.7 T [99]) and a larger field of view with a capacity for 3D measurement, but it is relatively more expensive and long acquisition times complicate the acquisition of images of loaded tissues. Optical elastography has very good resolution (5–10 μm [62, 72]), but a limited field of view and depth of tissue penetration. Most of the post-processing methods used to extract meaningful functional information (such as inverse FEM) are far from automatic and may require specialized computational infrastructure. In any case, the method, or even a combination of several methods, that is most suitable will depend on the underlying pathology, clinical utility, and cost–benefit of the assessment.

Several steps are required for a new method to progress from the laboratory to the bedside, including system development, feasibility testing, limited trials, and multicenter trials before eventually becoming commercialization and implementation within a standard of care [100]. Only ultrasound elastography is commercially available at the moment. Siemens (Munich, Germany) offers two elastography platforms: eSie Touch™ (compression elastography) and Virtual Touch™ (acoustic radiation force elastography) for their ultrasound systems. Hitachi (Tokyo, Japan) includes an E-mode for elastography measurement in their HI VISION™ 900 system. SuperSonic (SuperSonic Imagine, Aix-en-Provence, France) produces machines equipped with ShearWave™ elastography (acoustic radiation force elastography) for quantitative tissue elasticity measurements. Fibroscan (Echosens, Paris, France) uses transient elastography designed specifically for measuring the degree of liver fibrosis. Most other elastography modalities are still in pilot studies or clinical trials, but it is to be expected that additional commercial products will become increasingly available in the near future.

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