

Q&A WITH RICHARD L. EHMAN



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What are the specific biomarkers of liver disease that MRE is uniquely suited to provide for clinical trials in NASH?

NASH is typically described in histologic terms: increased fat in hepatocytes, inflammatory activity, cellular injury, and development of fibrosis. Among these processes, fibrosis is most strongly associated with mortality. Currently, the most important biomarker provided by MRE is liver stiffness, which in engineering terms is known as the magnitude of the complex shear modulus. One of the reasons why this biomarker is so useful is that it is profoundly affected by fibrosis. In advanced fibrosis, liver stiffness is increased many-fold compared with that of normal liver tissue. Multiple studies have shown that stiffness measurement by MRE has high diagnostic performance in non-invasively detecting and staging liver fibrosis⁽¹⁾. The performance of MRE is probably equal to or better than biopsy in this regard due to the much larger volume of liver evaluated.

While stiffness is the best-known biomarker provided by MRE, recent research has shown that there are other independent biomarkers that can be obtained with MRE that may be helpful in assessing NASH, as well.

For which stage of the progression of NAFLD to NASH to Cirrhosis does MRE provide the most accurate results?

Liver stiffness increases progressively with increasing stages of NASH fibrosis. There is strong evidence in the literature that MRE has the highest diagnostic

performance of all non-invasive tests for assessing the severity of fibrosis at all stages. The increase in liver stiffness accelerates for advanced stages of fibrosis, so that in stage 3 the stiffness is typically doubled compared with normal liver and in stage four it is tripled or more. Therefore, MRE is most accurate in diagnosing stage 3 and 4 fibrosis.

MRI-based measurement of proton density fat fraction (PDF) is a quick and accurate way to quantitatively assess hepatic steatosis at all grades of severity.

With this background about the sensitivity of MRE for liver disease progression, how do you envision MRE being used in clinical trials for NASH/NAFLD therapeutics?

MRE is being used in clinical trials of NASH therapeutics in several ways. The FDA has suggested that given the absence of clear diagnostic criteria for identifying patients who are likely to progress from NAFLD to NASH, they encourage drug developers to focus on treatment of NASH patients with advanced fibrosis or cirrhosis. These trials therefore need to recruit participants who have stage 3 or 4 fibrosis and this typically must be confirmed with biopsy. Therefore one of the important applications of MRE in clinical trials is to screen potential participants to accurately identify those who have stage 3 or 4 fibrosis prior to confirmatory biopsy. This will reduce the number of patients who would be excluded if biopsy shows less than stage 3 fibrosis.

Another application of MRE is to serve as an exploratory endpoint. Based on FDA guidance, the goal of many NASH trials is to demonstrate that a drug therapy will cause improvement in liver fibrosis by one stage or more. Most current trial designs require biopsy to test and prove this endpoint, but many studies are including the MRE as an additional biomarker that can be used more often and less expensively than biopsy in study participants.

As an inventor of MRE as a non-invasive liver imaging technology, what is your opinion about the best field strength of the MRI scanner for MRE?

The tissue parameters measured by MRE are not affected by field strength. MRE works well on basic

1.5T MRI systems. It works equally well on 3.0T systems if appropriate pulse sequences are used to minimize signal loss in the liver due to magnetic susceptibility effects at this higher field.

You have made major contributions to non-invasive imaging methods for estimation of liver fibrosis using MRE. Resoundant has moved the technology into the clinical arena with formal profiles by QIBA and approval by FDA supporting MRE as a reliable measure for the severity of fibrosis in the liver. Can you comment on the consistency of MRE measures of liver stiffness across different sites, MRI scanners and field strengths?

The goal of the Quantitative Imaging Biomarkers Alliance (QIBA) is to transform patient care by making radiology a more quantitative science. From long experience, we know that one of the greatest barriers to successfully applying quantitative MRI biomarkers in clinical practice is that measurement technology is not standardized, leading to systematic discrepancies in measurement of the same biomarkers on different scanners. Therefore, our objective with MRE was to convince the MRI manufacturers to implement the technology in a very consistent way across platforms. Fortunately, GE, Siemens, and Philips agreed with our goal. As a result all of the FDA-cleared implementations of MRE employ standardized acquisition techniques, driver technology, and processing algorithms that are equivalent in all important aspects.

Several studies⁽²⁻⁴⁾ have demonstrated reproducibility of liver stiffness measurements across different field strengths and vendor platforms.

But precision is also important in pharma trials. If MRE is performed before and after a test therapy, how do we know whether a measured stiffness difference is due to a true biologic change or simply measurement variability? The published QIBA consensus profile for MRE⁽⁵⁾ provides guidance that if the exam is done properly, a difference greater than 19% is almost certainly a true biologic change. Given the large increase in liver stiffness from stage 3 to stage 4, this is a useful level of precision. We are actively developing advanced versions of MRE technology that promise to have even better precision.

Can MRE provide imaging biomarkers for other stages of disease such as inflammation?

This is a very exciting area. MRE can provide several independent biomarkers beyond the property called stiffness. It is possible to process MRE data to calculate a quantity called loss modulus, which reflects the viscous properties of tissue. This biomarker seems to sensitively reflect changes in water distribution in tissue and our research has shown a strong relationship to the presence of inflammatory activity⁽⁵⁾. There are several other independent biomarkers that can also be derived from MRE data and we are exploring their potential to reveal other histologic changes such as hepatocyte injury.

Is MRE cost-effective?

Yes. Just recently in the U.S., the Centers for Medicare and Medicaid Services (CMS) approved a new Category I CPT code (76391) for standalone MRE. At a reimbursement level of \$240 per exam, this makes MRE much more accessible for patients. We are hopeful that MRE can often be paired with PDFF and reimbursed under this new CPT code for a rapid, highly accurate and low-cost exam for liver fat and fibrosis.

Recently published research shows that MRI scans can be enhanced with hepatocyte specific contrast agents like Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) to yield qualitative and quantitative assessments of fibrosis. Can you comment on how this type of assessment compares with MRE?

These studies have shown that measures of liver enhancement obtained during the hepatobiliary phase following administration of this hepatocyte specific contrast agent are reduced in proportion to the severity of liver fibrosis and inflammation. This makes sense because fibrosis and necroinflammation will reduce the fraction of functioning hepatocytes in a given volume of liver tissue. Most studies to date have shown that this biomarker for liver function has only moderate performance in fibrosis staging. A study with a head-to-head comparison with MRE, published in 2017, showed that the contrast technique had an AUC performance of 0.60 - 0.70 for classifying staging fibrosis, whereas the performance of MRE was above 0.90 for all fibrosis stages.



Are exogenous MRI contrast agents necessary or helpful for MRE?

Studies have shown that MRI contrast agents have no effect on liver stiffness and provide no significant advantage or disadvantage in the MRE acquisition.

We understand that a more advanced version of the technology called 3D MRE may soon become available. How does it differ from the 2D MRE method that is currently in use and what additional information does it provide about the progression of NAFLD?

The current version of MRE provided by the MRI manufacturers is called 2D MRE because wave data from individual cross sections of the liver are used to calculate stiffness. This approach is possible because the Resoundant driver system has been engineered to generate mechanical waves that propagate mainly in the transverse direction in the liver. This allows valid stiffness measurements to be obtained by imaging wave propagation in individual cross-section slices that can be easily acquired during suspended respiration. It is a simplification that made the technology easier to implement when it was first introduced.

A more advanced approach for MRE is to visualize propagating waves in the liver throughout a 3D volume and processing the data with a more advanced algorithm that can account for waves propagating in any direction. Even though much more data needs to be acquired, we can now do this within just a few breath-holds, in total acquisition times comparable to 2D MRE.

The stiffness measurements obtained with 3D MRE are somewhat more accurate than those obtained with 2D MRE. But the main advantage of 3D MRE is that the precision is higher: smaller longitudinal changes in liver stiffness can be reliably identified in therapeutic trials. In addition, 3D MRE permits even more reliable calculation of the new biomarkers that I mentioned earlier. We are finding that a multiparametric approach, using measurements of stiffness, loss modulus, and proton density fat fraction (PDFF), is showing great promise for non-invasively predicting the NAFLD activity score (NAS), which is a biopsy-based system for grading the severity of the NAFLD/NASH continuum⁽⁶⁾.

What advances do you anticipate in the future of quantitative diagnostic imaging with MRE for NAFLD and other liver diseases?

Evidence is accumulating that MRE-based biomarkers are strongly correlated with clinically-significant outcomes such as progression from fibrosis to cirrhosis and progression from compensated to decompensated cirrhosis. Studies are also examining the significance of the rate of change in these biomarkers over time as a predictor of subsequent clinical outcome. It seems likely that in the future, the longstanding emphasis on subjective histologic classifications of liver disease will be increasingly supplanted by guidance from quantitative biomarkers such as provided by MRE in diagnosis, treatment, and ongoing surveillance of patients with liver disease.

Tell us a little bit about your background and the academic pathway that led you to become interested in imaging of the mechanical properties of tissue and applications in liver disease?

At the beginning of my career, I originally planned to pursue a PhD in physics. But I found myself fascinated by seemingly endless opportunities at the intersection of biomedical and physical science. When I finished my residency in radiology, early prototype MRI systems were first becoming available. As a young radiologist at the Mayo Clinic I was thrilled to be in the right place and time to be involved in the early exploration of this new modality.

The current focus of my research program began more than 20 years ago when I became interested in finding some way to use imaging technology to noninvasively assess the mechanical properties of tissue. Many diseases cause large changes in these properties but none of the conventional imaging techniques were able to assess them. My team developed a technology in which mechanical vibrations are applied to tissue and the resulting propagating waves are imaged using a special MRI technique that we developed. The acquired data are processed to create cross-sectional images that quantitatively depict the stiffness of tissue. We called the technique Magnetic Resonance Elastography (MRE).



We published that discovery in the journal SCIENCE⁽⁷⁾, aware that there could be many potential applications, from assessing brain disease to detecting cancer. After a decade of focused effort, we developed a way to apply MRE to assess the stiffness of the liver in vivo. Our initial testing showed that the technology was well-suited for detecting and staging liver fibrosis, offering many patients a safer, more comfortable, and less expensive alternative to liver biopsy.

It's unusual for a physician with the academic and clinical responsibilities you have at the Mayo Clinic, to develop a new technology in a highly competitive field like medical imaging and radiology, create a company around it and bring the technology to market. Can you tell us a little bit about your role in founding Resoundant and what you hoped to accomplish with it?

In 2006, we realized that MRE had extraordinary capabilities as a tool for non-invasively assessing liver fibrosis. We developed improved versions of the pulse sequences, processing software, and the devices used to generate shear waves in the liver. In response to demand from our clinicians, in 2007 we implemented MRE as a standard diagnostic test for Mayo Clinic patients.

As it emerged that MRE could serve as a reliable non-invasive alternative to biopsy for detecting liver fibrosis, we wanted to make the test available to patients everywhere by working with the MRI manufacturers to implement the technology. However, we found that because MRE required special hardware in addition to software, the manufacturers were reluctant to make the investment required to implement the technology as a product. To overcome this problem, the Mayo Clinic founded a company, Resoundant Inc., to design and manufacture MRE driver systems and to assist MRI manufacturers in implementing MRE as a product.

In 2009, GE Healthcare introduced MRE as an FDA-cleared technology, making it available worldwide. Since then Resoundant also has worked with Siemens and Philips to introduce MRE for their systems, as well, making MRE widely available across most health systems and regions. By the end of 2019, we project

that MRE will be available on more than 1500 MRI systems around the world, using technology developed at the Mayo Clinic and driver systems manufactured by Resoundant.

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Disclosure

RLE and the Mayo Clinic have a financial interest related to magnetic resonance imaging technology.

