

MRI:

Diagnostic Application of cT1 & Elastography Through the Lens of Regulatory Science

Session V: Diagnostic Context of Use Friday April 22, 2022

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Research grants from industry

(Money paid to institution)

Bayer, GE, Gilead, Pfizer, Philips, Siemens

Lab service agreements (Money paid to institution)

Enanta, Gilead, ICON, Intercept, Nusirt, Shire, Synageva, Takeda

Institutional consulting (Money paid to institution)

AMRA, BMS, Exact Sciences, IBM-Watson, Pfizer

Personal consulting (Money paid to me)

Blade, Boehringer, Epigenomics

Position in company (Own stock options)

Livivos (Chief Medical Officer, pending)

Member of advisory board Quantix Bio (Unpaid)

Royalties and educational

(Money paid to me)

Medscape, Wolters Kluwer







Diagnostic biomarkers in NAFLD clinical trials

MultiScan: iron-corrected T1 (cT1) as a diagnostic enrichment biomarker in NAFLD clinical trials

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MR elastography: magnitude of complex modulus (|G*|), "shear stiffness" as a diagnostic biomarker in NAFLD clinical trials

MultiScan-cT1 and MRE-stiffness friend or foe?





Diagnostic biomarkers in NAFLD clinical trials

Outline

MultiScan: iron-corrected T1 (cT1) as a diagnostic enrichment biomarker in NAFLD clinical trials

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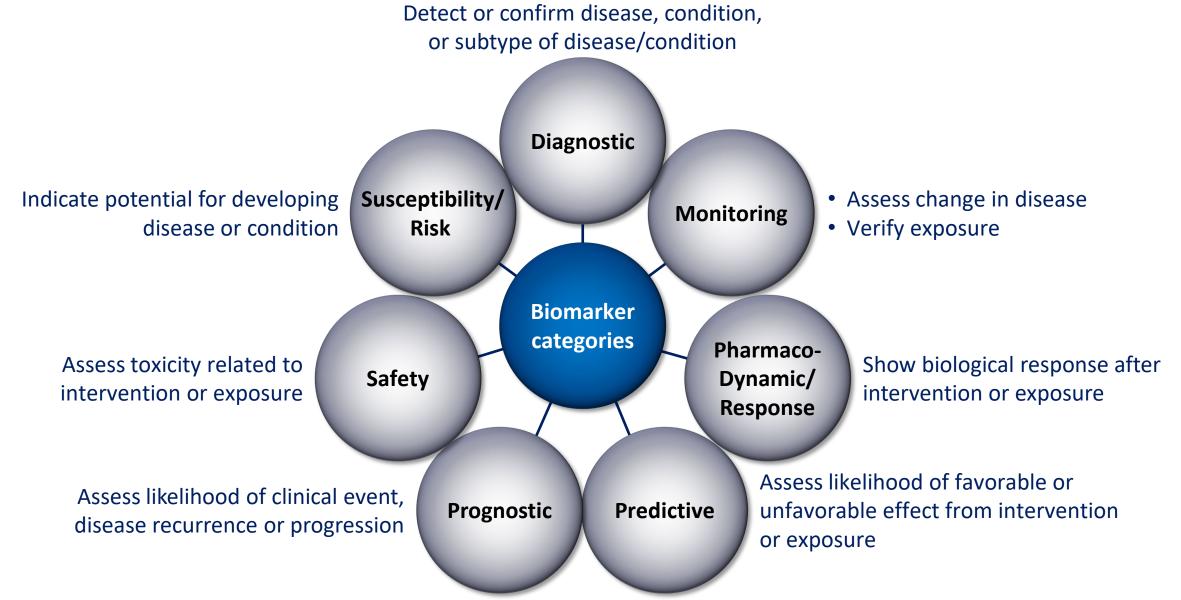
MR elastography: magnitude of complex modulus (|G*|), "shear stiffness" as a diagnostic biomarker in NAFLD clinical trials

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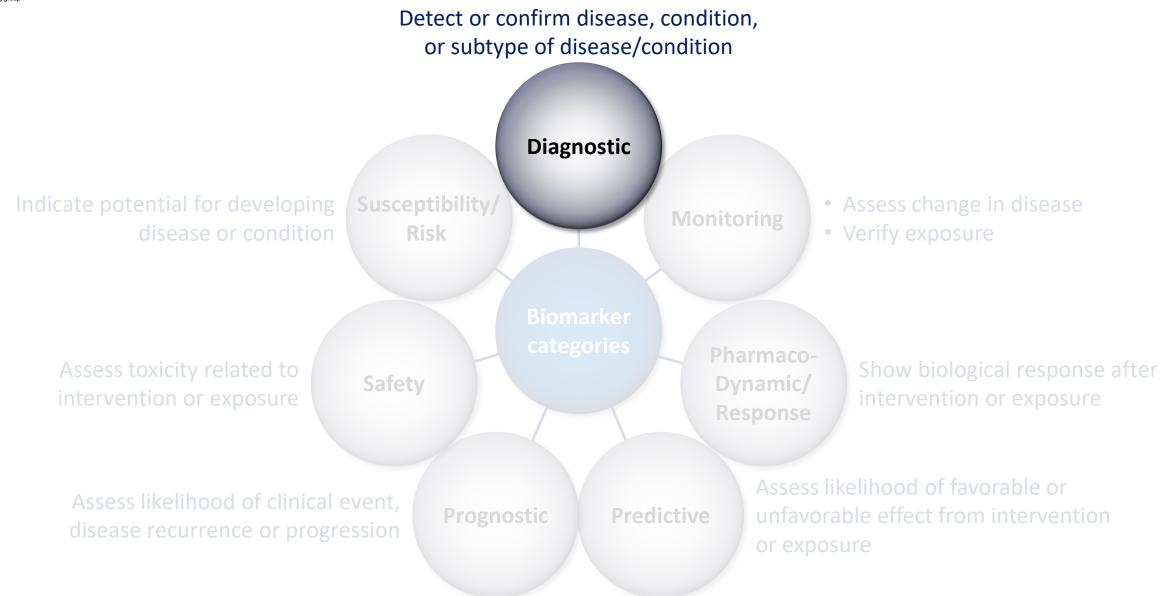
The FDA defines **seven biomarker categories**















Diagnostic biomarkers in NAFLD clinical trials

Outline

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MultiScan: iron-corrected T1 (cT1) as a diagnostic enrichment biomarker in NAFLD clinical trials

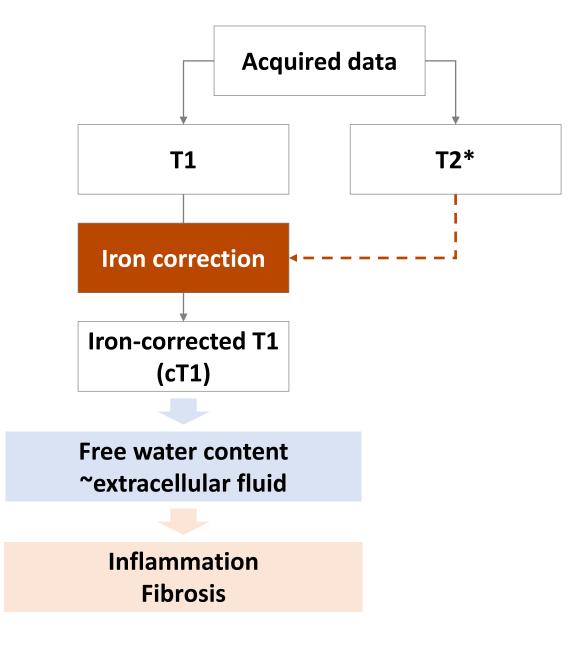
MR elastography: magnitude of complex modulus (|G*|), "shear stiffness" as a diagnostic biomarker in NAFLD clinical trials

MultiScan-cT1 and MRE-stiffness friend or foe?



MultiScan Iron-corrected T1 (cT1)







MultiScan Iron-corrected T1 (cT1)

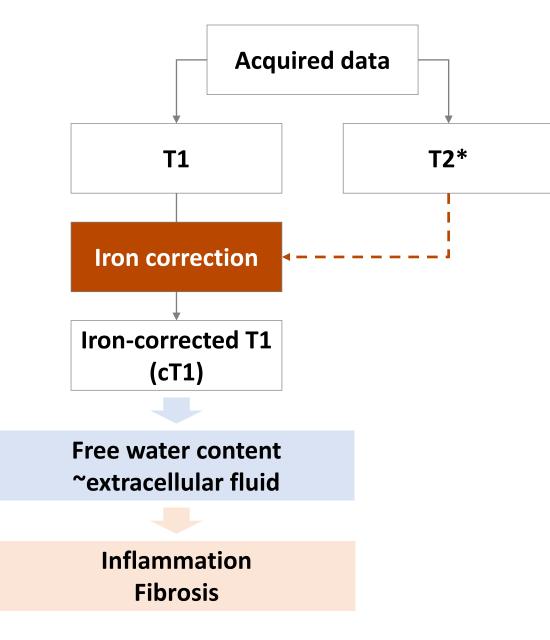


Standardized across

- Feld strength
- Scanner

Analyzed offline by PD

- Quality control
- Results reporting
- Rapid turn around







Type of biomarker:

Diagnostic enrichment biomarker

Context of use

Diagnostic enrichment biomarker that can be used, in conjunction with clinical risk factors, to identify patients who are more likely to have **liver histopathologic findings appropriate for inclusion in nonalcoholic steatohepatitis (NASH) clinical trials**



MultiScan cT1 Regulatory Status



Letter of Intent (LOI)	Initiates the qualification process of a biomarker for a proposed context of use (COU) in drug development	
Qualification Plan (QP)	Defines the intended development to generate the necessary supportive data to qualify the biomarker for the proposed COU	
Full Qualification Package (FQP)	Contains all accumulated data to support the qualification of the biomarker for the proposed COU	
Qualification Recommendation	Contains FDA's determination on whether the biomarker is qualified for the proposed COU based on a comprehensive review of the FQP	



MultiScan cT1 Evidence



EVIDENCE?

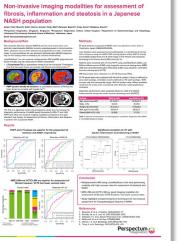
Can cT1 identify patients more likely to have liver histopathologic findings appropriate for inclusion in NASH clinical trials?



MultiScan cT1 Evidence: at least 4 relevant articles since 2020



	www.nature.com/scientificreports	
	SCIENTIFIC	
	REPORTS	
	natureresearch	
	Could for adults.	
OPEN	A an anno a star blann a duan a star	
OFEN	A composite biomarker using	
	multiparametric magnetic	
	resonance imaging and blood	
	analytes accurately identifies	
	patients with non-alcoholic	
	steatohepatitis and significant	
	fibrosis	
	Andrea Dennis ¹²¹ , Sofia Moucht ¹ , Matt Kelly ¹ , Jonathan A. Fallowfield ² , Gideon Hirschfield ³ ,	
	Michael Pavlides" & Rajarshi Banerjee'	
	Non-alcoholic steatohepatitis (NASH) is major health burden lacking effective pharmacological therapies. Clinical trials errol patients with histologically-defined NAFLD (non-alcoholic fitty liver	
	disease) activity score (NAS) = 4 and Kleiner-Brunt fibrosis stage (F) = 2; however, screen failure rates are often high following biogoy. This study evaluated a non-invasive MRI biomarker, iron-corrected	
	T1 mapping (rT1), as a diagnostic pre-screening biomarker for NASH. In a retrospective analysis of 85 biopsy confirmed NAFLD patients we explored the potential of blood and imaging biomarkers,	
	both in isolation and incombination, to discriminate those who have NAS 2.4 and F 2.2 from those without. Stepsite legitic regression was performed to select the optimal conducation of biomarkers,	
	diagnostic accuracy was determined using area under the receiver operator curve and model validated conformed with and freefold costs validation. Results showed that levels of (12, AST, 6GT and facting	
	glucose were all prod predictors of NAS 2 4 and F 22, and the model identified the combination of c11-AST-farting plucose (TAG) as fir species to any individual biomarker (AUC 0.99 30.84–0.97). This	
	highlights the patential utility of the composite cTAG scare for screening patients prior to biopoy to	1
	identify those suitable for NASH clinical trial enrolment.	
	Non-alcoholic fatty liver disease (NAFLD), is one of the most common forms of chronic liver disease, and a component of the metabolic orndrome, affecting 60% to 70% of patients with type 2 diabetes?", Non-alcoholic	
	component of the metanone systemete, anothing form to revise patients with type 2 canabeles Non-anotheness meanshepatria (NASH) is a more programme subcype of NAFLD with a 3-12% prevalence", and is possicion to become the leading activity for liver transplantation", NASH is characterised histologically by the presence of	
	hepatocyte hallocozing degeneration, hepatic lobalie inflammation and prosence of hepatic stratosis with patients at increased rak of forcess and progression to circlinesic, hepatocellular cancinoma, candornaecular disease, and	
	death'. The first pharmacological treatment for NASH, the FXR agonist obsticholic acid, is expected to receive resolutors approach in 2020', but there are a further 5 draws in phase III closed trials with approximately 130	
	active trials in total. The NAFLD Activity Score (NAS), proposed by the NASH Clinical Research Network. (NASH-CRN) is one of the most frequently used himilarical scoring ovnews in NASH disical trials. NAS is	
	derived by summing the histological staging for liver fat (stage 0-3), fobular inflammation (stage 0-3), and	1
	Perspecture, Gernini Ore, 5522 John Smith Drive, Ceford 0X4 2U, UK. 'Centre for Inflammation Research,	
	University of Edinburgh, Edinburgh, UK. "Taronto Centre for Liver Disease, University Health Network, Taronto, Canada. "Radcliffe Department of Medicine, University of Oxford, Oxford, UK. "Iemail: andrea.dennis@	1
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WJY	World Journal of Gastroenterology
Submits Manuscript https://www	05
DOI: 10.3749/wjg.=27.07409	1880/3007/907 (print) 1880/2007/2016
	ORIGINAL ARTICL
Clinical and Translational Re	arametric magnetic resonance imaging can aid
	tohepatitis diagnosis in a Japanese cohort
Eve Fryer, Shopi Yamanaka, 1	Indrea Dennis, Elizabeth Shumbayawonda, Sofa Mouchti, Timothy J Kendall, Yasushi Norcki, Takaoni Kesoku, Yuji Ogawa, Masato Yoneda, Satoru Salto, Rajarshi Benerjee, Atsushi Nakajima
OfICD number: Konse Insjo 1000- 0002-1931-6336; Louise Tetlaw 0000- 0011 6220-0175; Andrea Dennis	Kesta Imaja, Yasushi Honda, Takaoni Kessaka, Yaji Ogawa, Satora Saito, Atsushi Nakajim Department of Gazzoratorology and Hopoloogy. Yekshama City University School Medicite, Yokshama 256-0004, Japan
0006-0002-0112-4528; Elizabath Shumharuwenda 2006-0006-0111- 2003; Sofia Menatul 0000-0002-3168- 5342; Timority J Kendall 0008-0003-	Louise Tellow, Andrea Dennis, Elizabeth Shumbeyawonda, Sofa Mouchti, Catherine Kally, Batt Kally, Rajanshi Banejes, Inservation, Perspectum, Oxford 0004 21.1., United Kingdom
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0000-0042-1x24-5042; Talaomi Kanoku 9000-0042-5597-1390; Yiqi Ogawa 0000-0041-7013-0002; Manato Yoneda 1000-0041-7015-	Eve Fryst, Department of Cellular Pathology, Oxford University Hospitals NHS Freedati Tran, Oxford OX3 HOU, United Kingdom Bregi Yamania, Acatomic and Clinical Pathology Department, Valubarus City Universi
5478; Satura Salto-2008-0002-5004- 5218; Calherine Kelly 100C-2002- 9234, 2214; Mart D Kelly-2008-0002	Bogi Yamanka, Anatomic and Clinical Pathology Department, Yukubama City Universi Hospital, Yikohoma 236-0056, Japan Humin Youwin, Department of Garroemenology, Yokohama City University Graduam Scho
5034-6233; Rajanhi Bunenjor 1000- 0003-2023-5234; Assushi Nakajima 0000-0023-6243-1456.	 Sense Vesse, Department of Obsteinering, Patronine Cay Certainly Obsteine Patro of Medicine, Veshatara 20:0004, Apar. Sensescoffera author: Andrea Deanis, PhD. Research Scientific, Internation, Perspectu
Aather contributions: Imajo K and Nakajima A developed the study	Gemini One, 5520 John Smith Drive, Oxford OX4 211, United Kingdom, andrea dentric@perspectum.com
concept, protocols and initiated the project, Kelly MD and Baserjee R	Abstract
assisted in the further development of the protocol and drafting the	BACKGROUND Non-invasive assessment of non-alcoholic stratoberatitis (NASH) is increasing
	desirability due to the invasive nature and costs associated with the current for of assessment; liver biopsy, Quantitative multiparametric magnetic resonan
clinical study protocol, Israjo K, Nakajima A, Fryer E, Kendall TJ, Vamanda S, Honda V, Konceles T.	
Nakajima A, Fryer E, Kendall TJ, Yamaruka S, Horda Y, Kosoku T, Ogawa T, Toneca M and Salto S	imaging (mpMRI) to measure liver fat (preten density fat fraction) an
Nakajima A, Fryer F, Kendell TJ, Yamaraka S, Horda Y, Konsika T, Ogawa T, Tomeca M and Salto S contributed to the data collection; Terfow L, Deretis AM.	imaging (mpMII) to measure liver fat (proton density fat fraction) an ilbroinflammatory disease [inon-corrected TI (cTI)], as well as elastograph techniques [vibration-controlled transient elastography (VCTE) liver stiffler measure1, magnetic resonance elastography (MRE) and 20 Shear-War
Nakajima A, Fryer E, Kendull TJ, Yamaruka S, Honda Y, Kenoka T, Ogama T, Toneca M and Salto S contributed to the data collection	imaging (mpMRI) to measure liver fat (preten density fat fraction) at fibroinflammatory disease liton-corrected Ti (cTi)], as well as elastograph techniques (vibration-controlled transient elastograph) (VCTB) liver stiffle





2020





2021



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2021



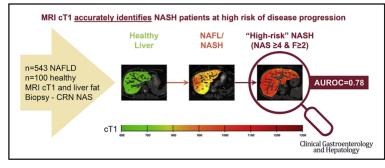
ARTICLE IN PRESS

Clinical Gastroenterology and Hepatology 2021;:===

Clinical Utility of Magnetic Resonance Imaging Biomarkers for Identifying Nonalcoholic Steatohepatitis Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis

Anneli Andersson,* Matt Kelly,* Kento Imajo,[‡] Atsushi Nakajima,[‡] Jonathan A. Fallowfield,[§] Gideon Hirschfield,[∥] Michael Pavlides,^{¶,#,**} Arun J. Sanyal,^{‡‡} Mazen Noureddin,^{§§} Rajarshi Banerjee,* Andrea Dennis,* and Stephen Harrison[¶]

*Perspectum Ltd, Gemini One, Oxford, United Kingdom; *Department of Gastroenterology and Hepatology, Yokohama City School of Medicine, Yokohama, Japan; *Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom; "Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada; "Division of Carcilovascular Medicine, Radcliffe Department of Medicine, John Radcliffe Hospital, Oxford, United Kingdom; "Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, United Kingdom; "*Department of Internal Medicine, Virginia Commodia Research Centre, University of Oxford, Oxford, United Kingdom; *Tepartment of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virgina; ⁵⁵Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center, Sinai Medicia Center, Los Angeles, California



BACKGROUND & AIMS: Nonalcoholic fatty liver disease (NAFLD) is increasing in prevalence worldwide. NAFLD is associated with excess risk of all-cause mortality, and its progression to nonalcoholic steatohepatitis (NASH) and fibrosis accounts for a growing proportion of cirrhosis and hepatocellular cancer and thus is a leading cause of liver transplant worldwide. Noninvasive precise methods to identify patients with NASH and NASH with significant disease activity and fibrosis are crucial when the disease is still modifiable. The aim of this study was to examine the clinical

Abbreviations used in this paper. AST, asparate aminotransferase; AUROC, area under the receiver operating characteristic; CAP, controlled attenuation parameter; c11, corrected 11; F, fibrosis; FAST, FibroScan-AST; FID4, fibrosis+(IQ6), interquirile range; MRE, magnetic resonance

Ad 1, To 2, Thousand, And T, Interducture tange, Int.C., Integrated resultative elaisography RATL, nonaciocholic fatty liver disease; NAS, nonalicoholic fatty liver disease activity score; NASH, nonaciocholic stateses; NAS, nonalicoholic fatty liver disease activity score; NASH, nonaciocholic state thothepatitis; NISE, a bloodbased diagnostic multivariate index test that is specifically designed to rule-in and rule-out at-risk NASH, NPV, negative predictive value; PDFF,

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Ν

- 543 NAFLD
- 100 normal controls

5 sites

- UK
- US
- Japan

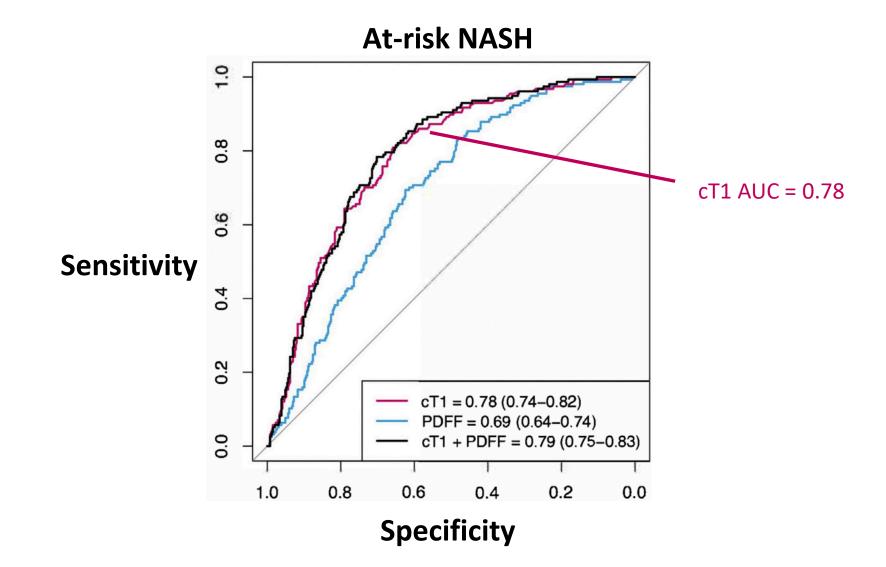
2 MR biomarkers

- cT1
- PDFF

Biopsy reference







5 center-study: Anderson 2021 Clin Gastro Hepatol 34626833





Cutoff	Sens	Spec	Youden
≥ 800 ms	86	56	142
≥ 825 ms	78	67	145
≥ 875 ms	59	81	140
≥ 900 ms	48	86	134
≥ 925 ms	39	90	129

5 center-study: Anderson 2021 Clin Gastro Hepatol 34626833



Cut-off of \geq 875 ms has 59% sens. and 81% spec. for at-risk NASH



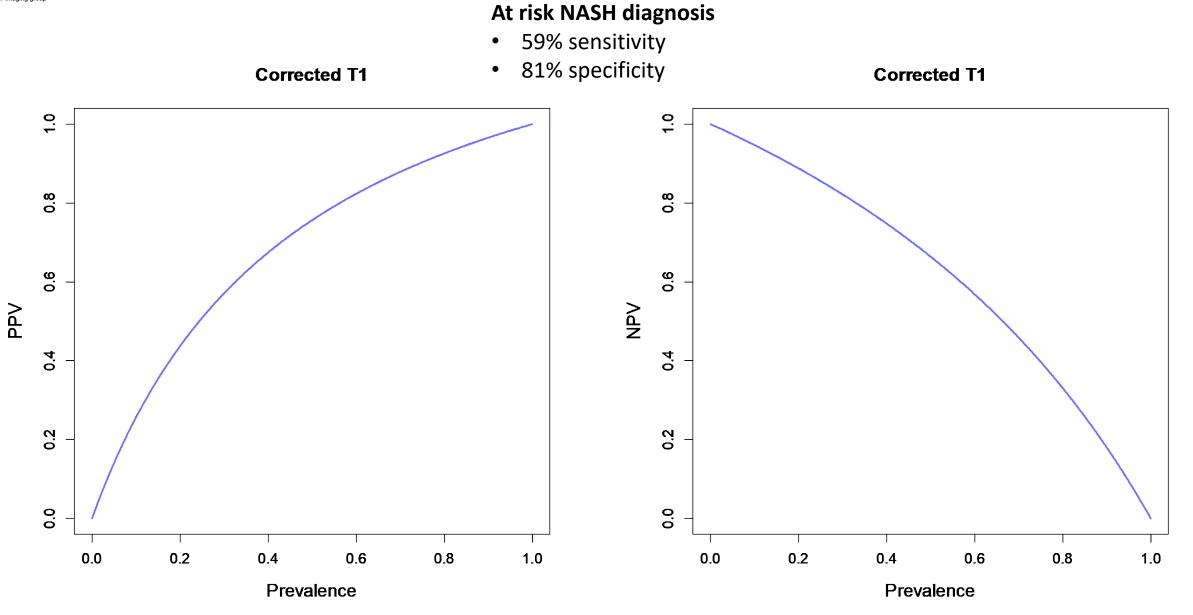
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MultiScan cT1 PPV and NPV simulation curves

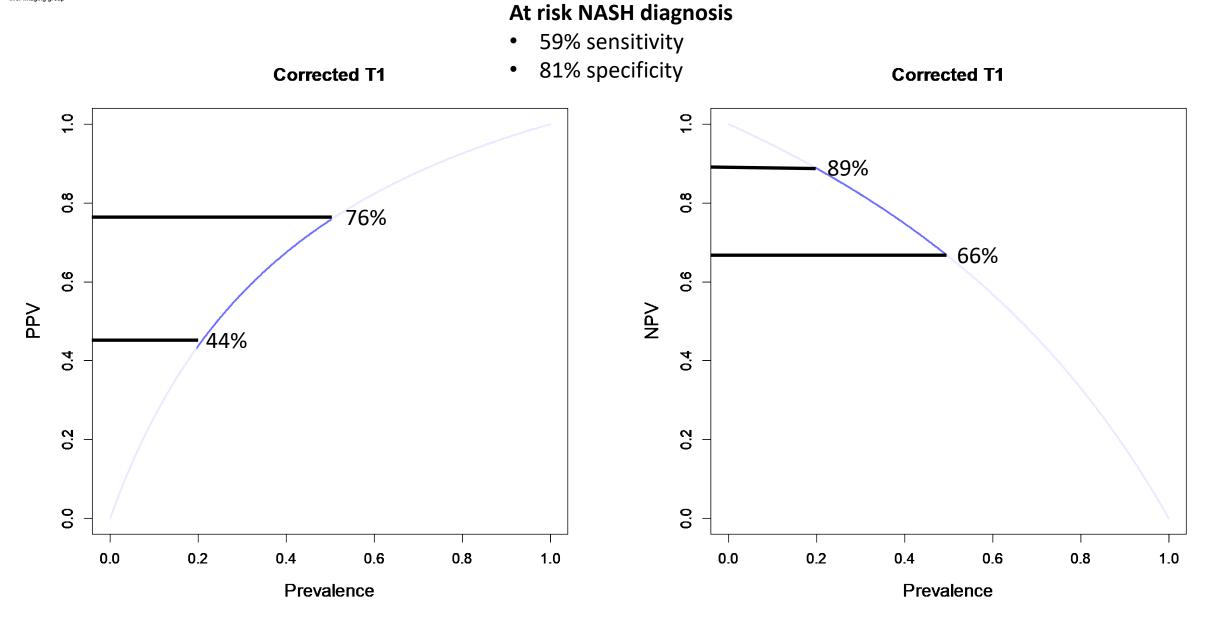






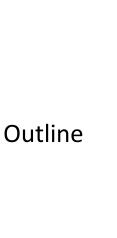
For prevalence between 20-50%: PPVs 44-76%; NPVs 60-94%











Diagnostic biomarkers in NAFLD clinical trials

MultiScan: iron-corrected T1 (cT1) as a diagnostic enrichment biomarker in NAFLD clinical trials

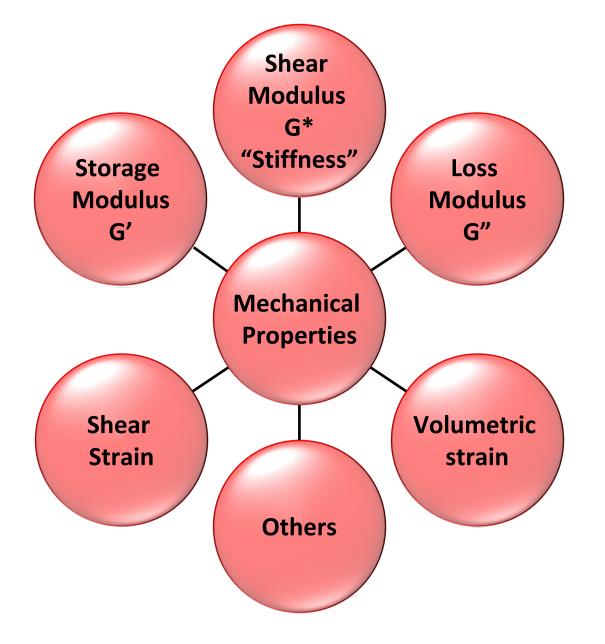
MR elastography: magnitude of complex modulus (|G*|), "shear stiffness" as a diagnostic biomarker in NAFLD clinical trials

MultiScan-cT1 and MRE-stiffness friend or foe?



MR elastography = noninvasive assessment of mechanical properties

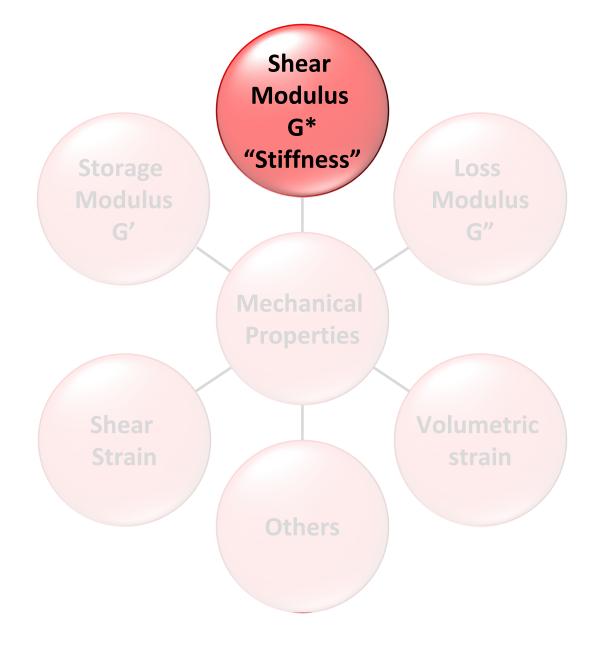






Current context of use and regulatory approval pathway

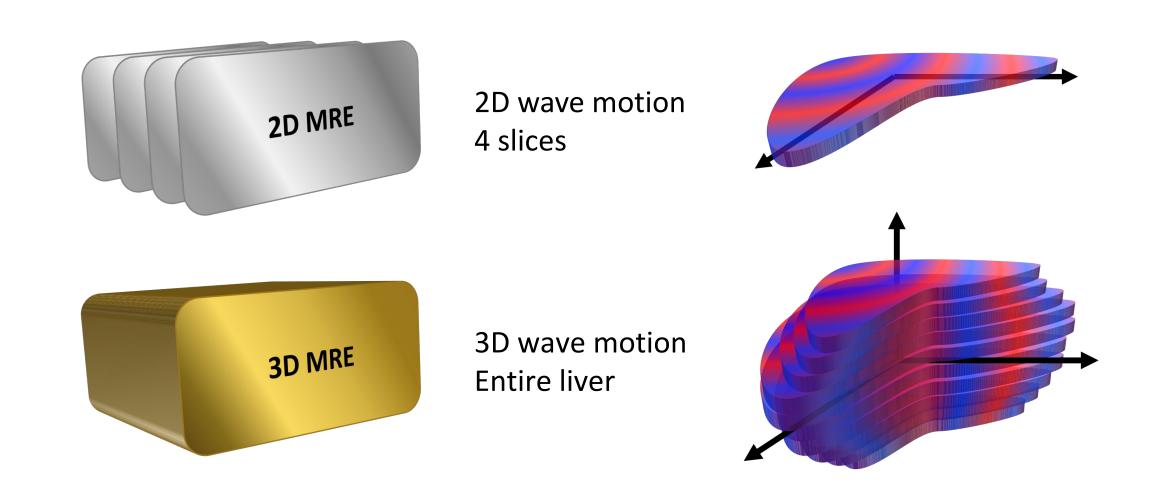






Two main flavors of MRE







Current regulatory pathway





Image acquisition and reconstruction standardized across

- Feld strength
- Scanner

Soon: Optional automated cloudbased analysis by Resoundant

- Results reporting
- Rapid turn around



3D wave motion Entire liver





Type of biomarker: Diagnostic biomarker

Context of use

A diagnostic biomarker to **pre-screen patients** with clinical risk factors for nonalcoholic fatty liver disease (NAFLD) or fibrotic nonalcoholic steatohepatitis (NASH) for enrollment in clinical trials to identify those at high risk of having histopathologic findings on liver biopsy of

- significant fibrosis (≥F2) or
- advanced fibrosis (≥F3) or
- cirrhosis (F4)



2D MRE |G*| Regulatory Status



Letter of Intent (LOI)	Initiates the qualification process of a biomarker for a proposed context of use (COU) in drug development	
Qualification Plan (QP)	Defines the intended development to generate the necessary supportive data to qualify the biomarker for the proposed COU	
Full Qualification Package (FQP)	Contains all accumulated data to support the qualification of the biomarker for the proposed COU	
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2D MRE |G*| Regulatory Status



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ification n (QP)	Defines the intended development to generate he data to qualify the biomarker for the proposed (OU	PAR-21-178 (Drug Development Tools
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alification ge (FQP)	Contains all accumulated data to support the qualific for the proposed COU	cation of the biomarker
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2D MRE |G*| Evidence



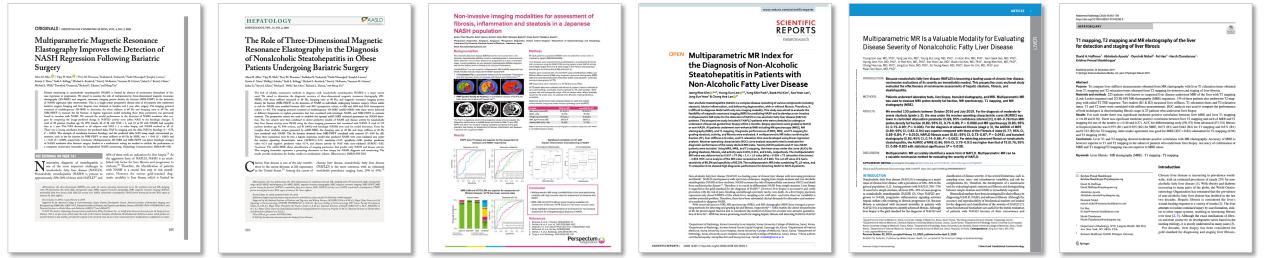
EVIDENCE?

Can MRE identify patients at high risk of having significant fibrosis ($F \ge 2$), advanced fibrosis ($F \ge 3$), or cirrhosis?



2D MRE |G*| Evidence: at least 12 relevant articles since 2020





raphical abstract	Authors
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stography may help in fibrosis evaluation in those with NAFLD Valid readings. Lical vality of these tests cannot be assessed fully as intention-to- prose analyses and validation of pre-specified cut-offs are sing.	accounting these liver filterois and inflammation, using liver biopsy as the reference. We found that some techniques that measure liver stiff- ness had a good performance for the diagnosis of severe liver scarring.

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2D MRE |G*| Evidence: at least 12 relevant articles since 2020



			SCIENTIFIC REPORTS		
Multiparametric Magnetic Resonance Elastography Improves the Detection of			OPEN Multiparametric MR Index for		T1 mapping, T2 mapping and MR elastography of the liver for detection and staging of liver fibrosis
			the Diagnosis of Non-Alcoholic		
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NAFLD and Alcohol-Related Liver Diseases	OF HEPATOLOGY			
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 Elastography may help in fibrosis evaluation in those with NARLE and valid readings. Clinical utility of these tests cannot be assessed fully as intention-to- 	inflammation, using liver biopsy as the reference. We found that some			
diapose analyses and validation of pre-specified cut-offs are lacking.	techniques that measure live stiff- ners had a good performance for the dagnois of severe liver scarring.		Notice that the second SWITS of the second s	



2020

2D MRE |G*| Eviden

Research Article NAFLD and Alcohol-Related Liver Diseases

JOURNAL OF HEPATOLOGY



Meta-analysis

pSWE

20





2D SWE

2D MRE

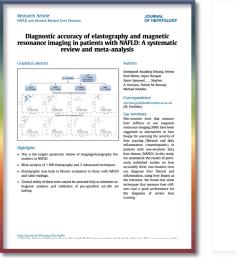
11 studies

4 studies

Biopsy reference



2021



Highlights

Graphical abstract

VCTE N = 53 studi

- · This is the largest systematic review of imaging/elastography biomarkers in NAFLD.
- Meta-analysis of 1 MR elastography and 3 ultrasound techniques.
- Elastography may help in fibrosis evaluation in those with NAFLD and valid readings.
- · Clinical utility of these tests cannot be assessed fully as intention-todiagnose analyses and validation of pre-specified cut-offs are lacking.

resonance imaging (MRI) have been suggested as alternatives to liver biopsy for assessing the severity of liver scarring (fibrosis) and fatty inflammation (steatohepatitis) in patients with non-alcoholic fatty liver disease (NAFLD). In this study, we summarise the results of previously published studies on how accurately these non-invasive tests can diagnose liver fibrosis and inflammation, using liver biopsy as the reference. We found that some

scarring.

Authors

Michael Pavlides Correspondence

(M. Pavlides).

Lay summary

Emmanuel Anandraj Selvaraj, Ferenc Emil Mózes, Arjun Narayan Ajmer Jayaswal, ..., Stephen

A. Harrison, Patrick M. Bossuyt,

michael.pavlides@cardiov.ox.ac.uk

Non-invasive tests that measure liver stiffness or use magnetic

techniques that measure liver stiff-

ness had a good performance for

the diagnosis of severe liver

https://doi.org/10.1016/j.jhep.2021.04.044

Diagnostic accuracy of elastography and magnetic

resonance imaging in patients with NAFLD: A systematic review and meta-analysis

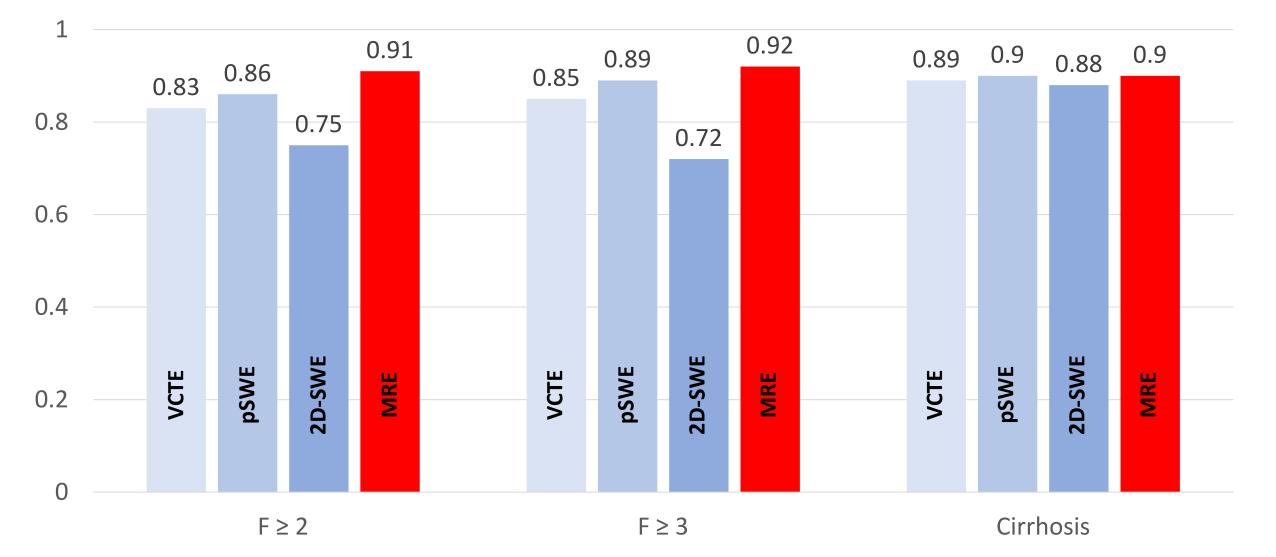
MRE = 11 studie



2D MRE-|G*| has higher AUC for F≥2 and F≥3, not cirrhosis @



AUC





2D MRE-|G*| has higher AUC for F≥2 and F≥3, not cirrhosis @



AUC

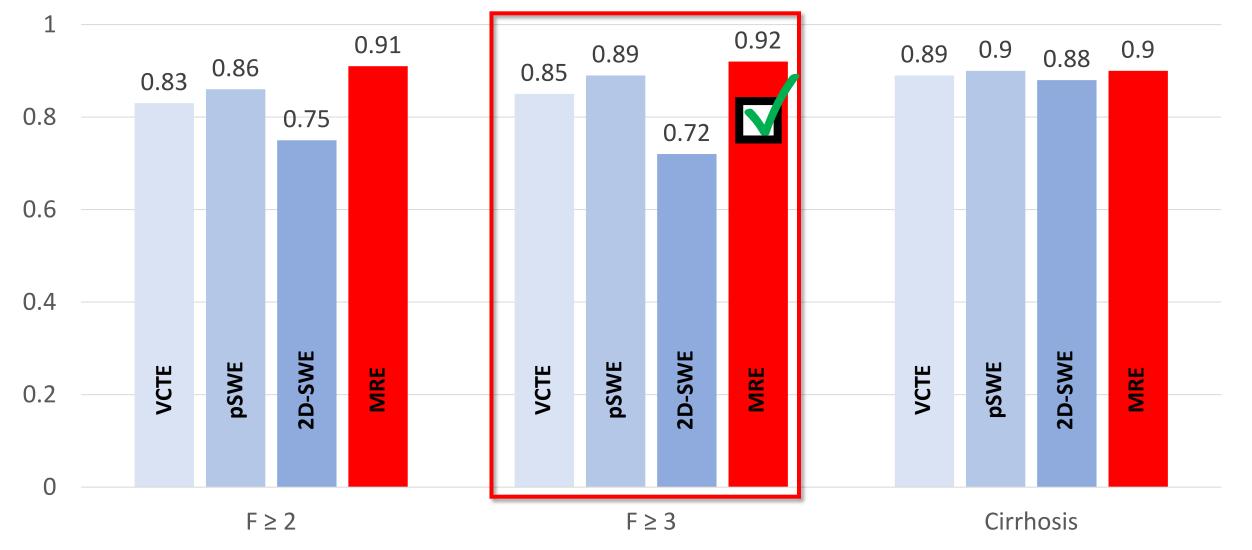




2D MRE- $|G^*|$ has higher AUC for F≥2 and F≥3, not cirrhosis i



AUC

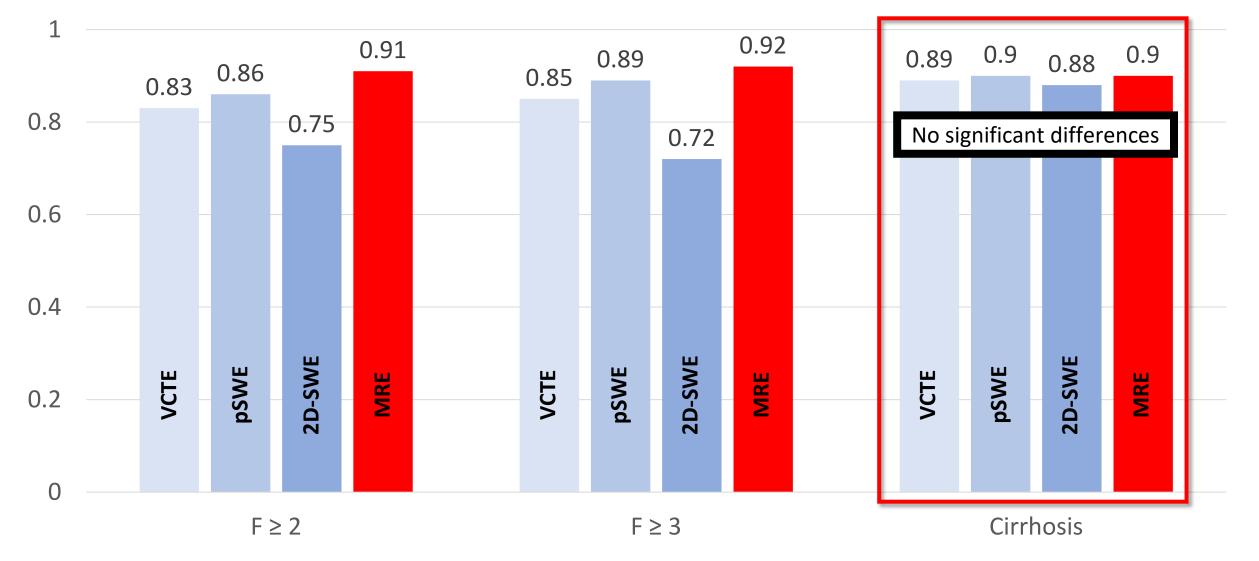




2D MRE-|G*| has higher AUC for F≥2 and F≥3, not cirrhosis @



AUC







Modality	Fibrosis Stage	Sens	Spec	Youden
VCTE	F ≥ 2	80	73	153
	F ≥ 3	80	77	157
	Cirrhosis	76	88	164
pSWE	F ≥ 2	69	85	154
	F ≥ 3	80	86	166
	Cirrhosis	76	88	164
2D SWE	F ≥ 2	71	67	138
	F ≥ 3	72	72	144
	Cirrhosis	78	84	162
MRE	F ≥ 2	78	89	167
	F ≥ 3	83	89	172
	Cirrhosis	81	90	171





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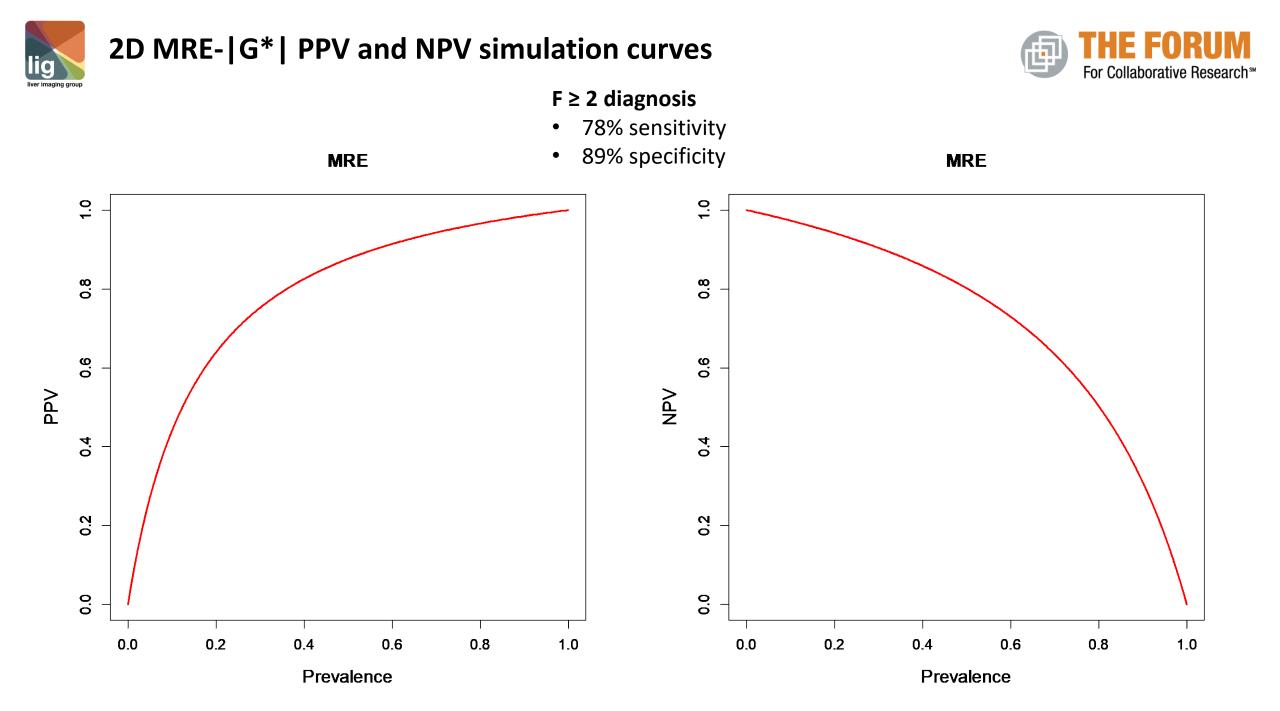
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MRE-stiffness = 78% sens. and 89% spec. for $F \ge 2$



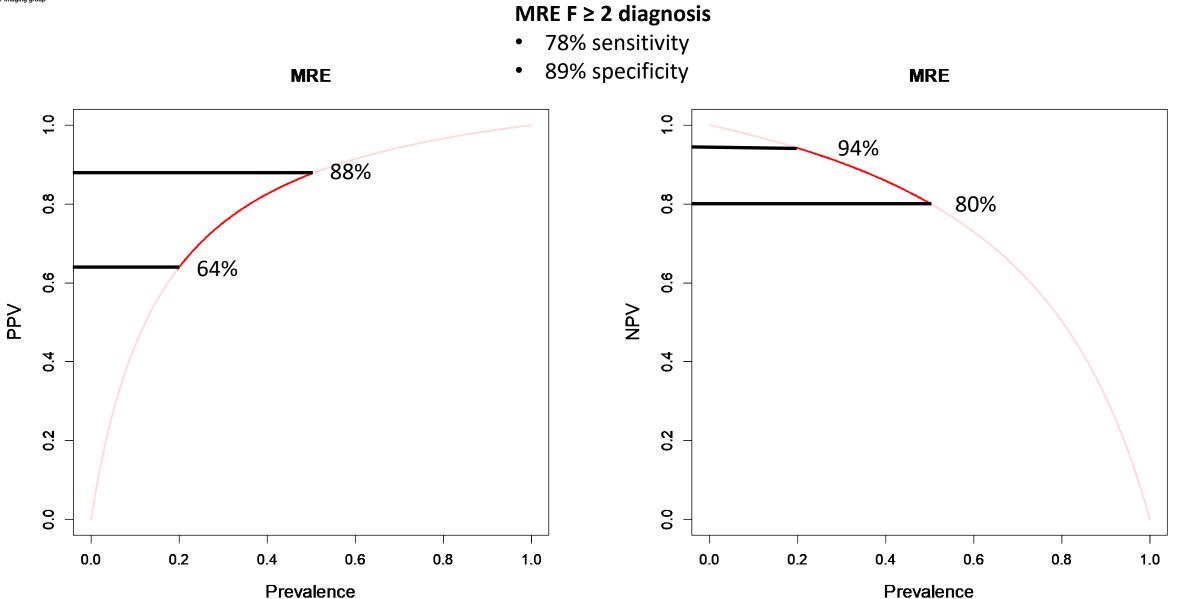
Modality	Fibrosis Stage	Sens	Spec	Youden
VCTE	$F \ge 2$	80	73	153
	$F \ge 3$	80	77	157
	F = 4	76	88	164
	F ≥ 2	69	85	154
pSWE	$F \ge 3$	80	86	166
	F = 4	76	88	164
2D SWE	$F \ge 2$	71	67	138
	$F \ge 3$	72	72	144
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For prevalence between 20-50%: PPVs 64-88%; NPVs 80-94%











Diagnostic biomarkers in NAFLD clinical trials

MultiScan: iron-corrected T1 (cT1) as a diagnostic enrichment biomarker in NAFLD clinical trials

MR elastography: magnitude of complex modulus (|G*|), "shear stiffness" as a diagnostic biomarker in NAFLD clinical trials

MultiScan-cT1 and MRE-|G*| friend or foe?



PPV and NPV simulation curves: cT1 vs. MRE

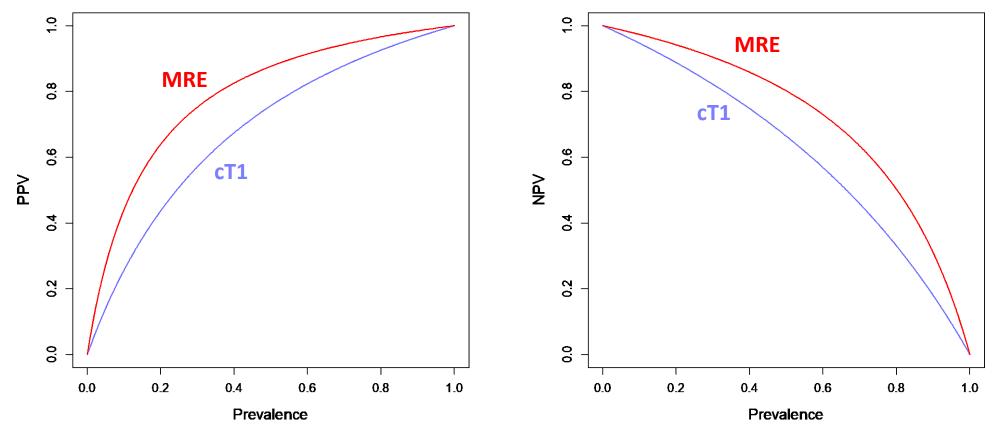


cT1 at risk NASH diagnosis

- 59% sensitivity
- 81% specificity

MRE F ≥ 2 diagnosis

- 78% sensitivity
- 89% specificity





PPV and NPV simulation curves: 20-50% prevalence cT1 vs. MRE

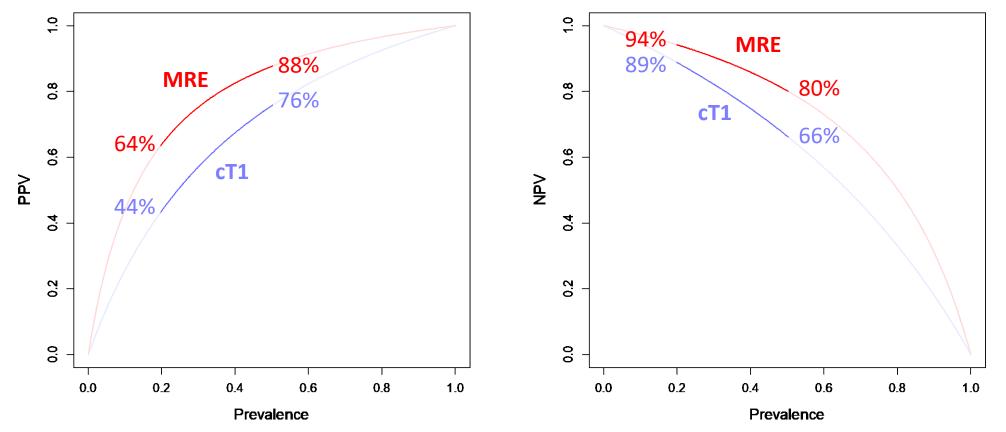


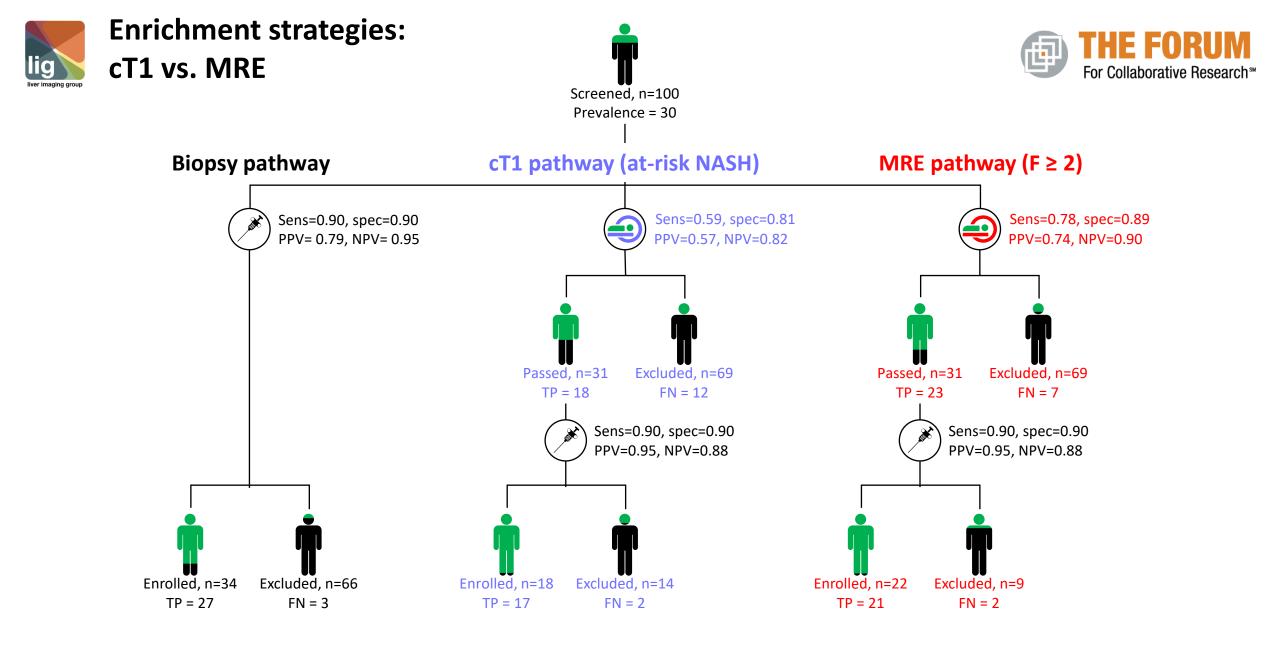
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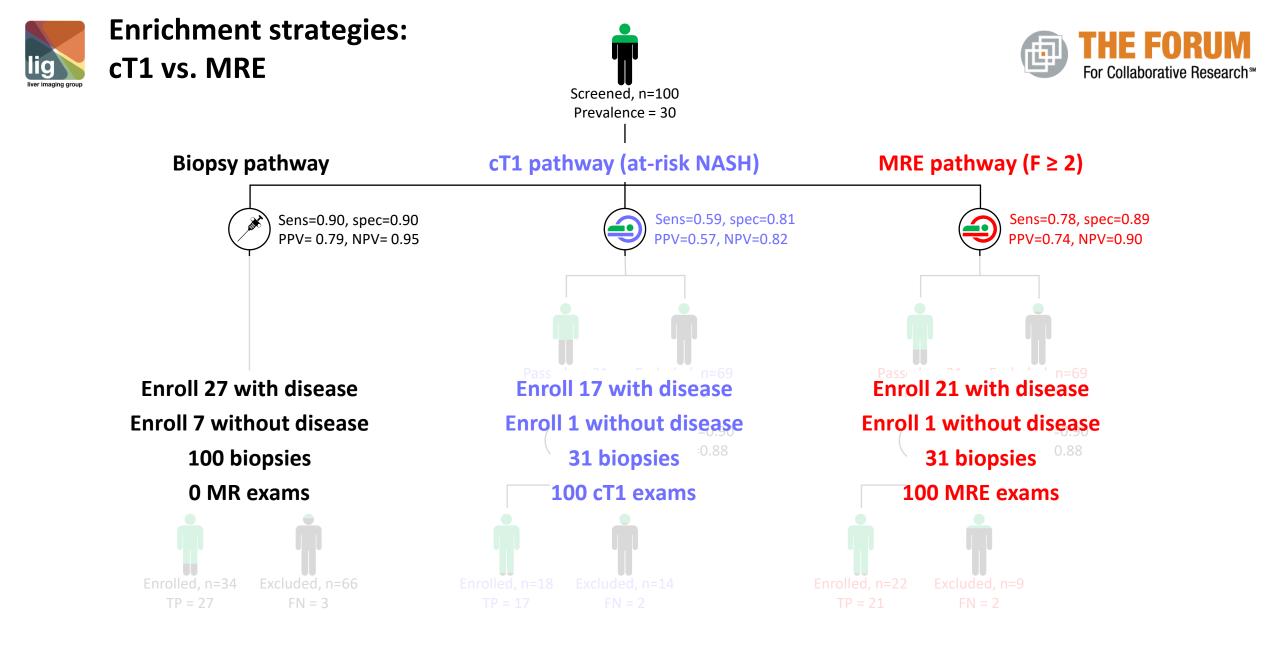
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Modified from Kay Pepin and Michael Kalutkiewicz



Modified from Kay Pepin and Michael Kalutkiewicz



2D MRE |G*| Evidence

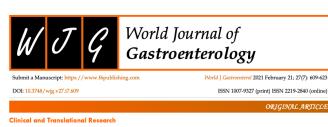


DIRE **COMPARISON?**



cT1 versus MRE in NAFLD





Quantitative multiparametric magnetic resonance imaging can aid non-alcoholic steatohepatitis diagnosis in a Japanese cohort

Kento Imajo, Louise Tetlow, Andrea Dennis, Elizabeth Shumbayawonda, Sofia Mouchti, Timothy J Kendall, Eve Frver, Shogi Yamanaka, Yasushi Honda, Takaomi Kessoku, Yuji Ogawa, Masato Yoneda, Satoru Saito, Catherine Kelly, Matt D Kelly, Rajarshi Banerjee, Atsushi Nakajima

Kento Imajo, Yasushi Honda, Takaomi Kessoku, Yuji Ogawa, Satoru Saito, Atsushi Nakajima, ORCID number: Kento Imajo 0000-0002-1931-6326; Louise Tetlow 0000-Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, Yokohama 236-0004, Japan 0001-6285-4878; Andrea Dennis 0000-0002-0152-6528; Elizabeth

Shumbayawonda 0000-0003-0351-Louise Tetlow, Andrea Dennis, Elizabeth Shumbayawonda, Sofia Mouchti, Catherine Kelly, Matt D 2063; Sofia Mouchti 0000-0002-3169-Kelly, Rajarshi Banerjee, Innovation, Perspectum, Oxford OX4 2LL, United Kingdom 5242; Timothy J Kendall 0000-0002-

4174-2786; Eve Fryer 0000-0003-Timothy J Kendall, Centre for Inflammation Research, University of Edinburgh, Edinburgh, 1385-6433; Shogi Yamanaka 0000-United Kingdom, Edinburgh EH16 4TJ, United Kingdom 0001-8882-3981; Yasushi Honda

Eve Fryer, Department of Cellular Pathology, Oxford University Hospitals NHS Foundation Kessoku 0000-0002-5587-1386; Yuji Trust, Oxford OX3 9DU, United Kingdom

Shogi Yamanaka, Anatomic and Clinical Pathology Department, Yokohoma City University 549X: Satoru Saito 0000-0002-5666 Hospital, Yokohoma 236-0004, Japan

5834-1234; Matt D Kelly 0000-0002-Masato Yoneda, Department of Gastroenterology, Yokohama City University Graduate School 5834-635X; Rajarshi Banerjee 0000of Medicine, Yokohama 236-0004, Japan 0003-2022-5218; Atsushi Nakajima

> Corresponding author: Andrea Dennis, PhD, Research Scientist, Innovation, Perspectum, Gemini One, 5520 John Smith Drive, Oxford OX4 2LL, United Kingdom andrea.dennis@perspectum.com

Nakajima A developed the study concept, protocols and initiated the

project: Kelly MD and Baneriee R Abstract assisted in the further development

of the protocol and drafting the BACKGROUND

Non-invasive assessment of non-alcoholic steatohepatitis (NASH) is increasing in clinical study protocol; Imajo K, desirability due to the invasive nature and costs associated with the current form Nakajima A, Fryer E, Kendall TJ, of assessment; liver biopsy. Quantitative multiparametric magnetic resonance Yamanaka S, Honda Y, Kessoku T, imaging (mpMRI) to measure liver fat (proton density fat fraction) and Ogawa Y, Yoneda M and Saito S fibroinflammatory disease [iron-corrected T1 (cT1)], as well as elastography contributed to the data collection: techniques [vibration-controlled transient elastography (VCTE) liver stiffness Shumbayawonda E to the data measure], magnetic resonance elastography (MRE) and 2D Shear-Wave elastography (SWE) to measure stiffness and fat (controlled attenuated parameter, analysis; Imajo K, Tetlow L, CAP) are emerging alternatives which could be utilised as safe surrogates to liver biopsy Shumbayawonda E, Kelly C, Kelly

609



0000-0002-1624-5462; Takaomi

Ogawa 0000-0001-7033-088X; Masato Yoneda 0000-0001-7815-

5218: Catherine Kelly 0000-0002-

Author contributions: Imajo K and

0000-0002-6263-1436.

Tetlow L, Dennis AM,

Nakajima A, Dennis AM,

February 21, 2021 Volume 27 Issue 7

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145 suspected NASH •

1 site

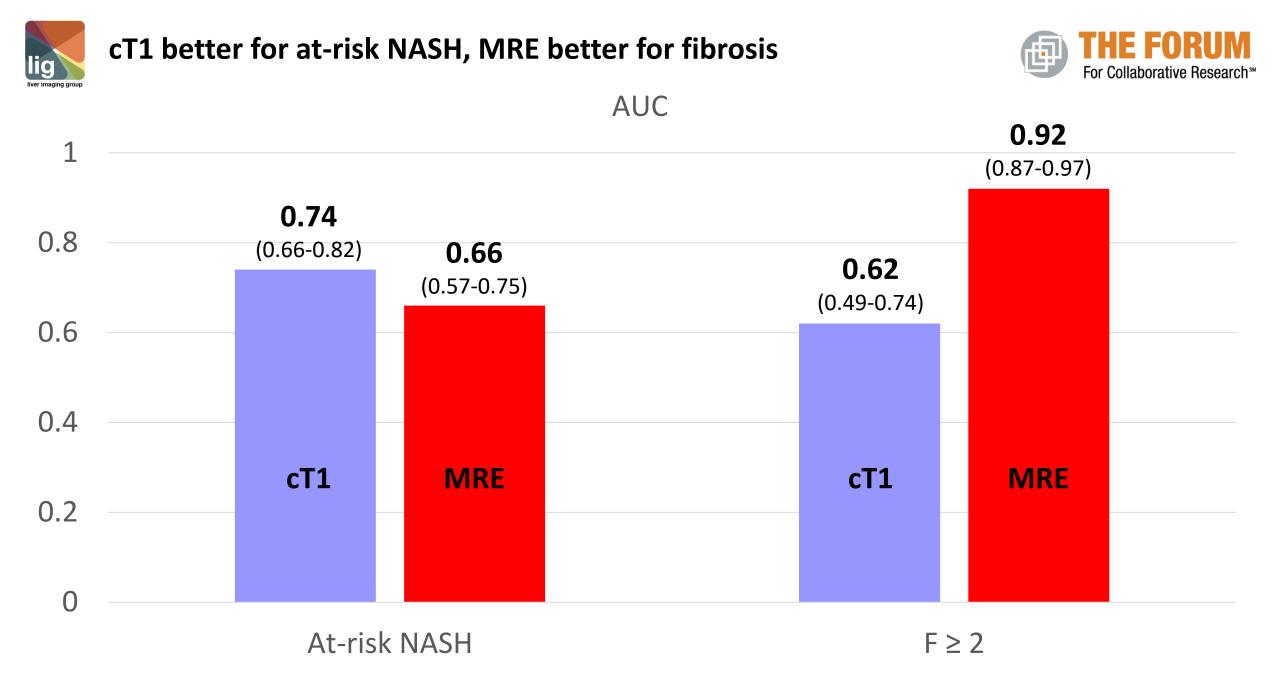
Japan

3 MR Biomarkers

- cT1
- PDFF •
- 2D MRE-|G*| •

(Also VCTE, CAP)

Biopsy reference



Imajo 2021 WJG 33642832



Complementarity?



- 20 NASH
- 27 non-NASH

1 site

• Korea

3 MR Biomarkers

- T1 (no iron correction)
- MRS-FF
- 2D MRE-|G*|

(Also VCTE, CAP)

Biopsy reference

OPEN Multiparametric MR Index for the Diagnosis of Non-Alcoholic Steatohepatitis in Patients with Non-Alcoholic Fatty Liver Disease

www.nature.com/scientificreports

Non-alcoholic steatohepatitis (NASH) is a complex disease consisting of various components including steatosis, lobular inflammation, and ballooning degeneration, with or without fibrosis. Therefore, it is difficult to diagnose NASH with only one imaging modality. This study was aimed to evaluate the feasibility of magnetic resonance imaging (MRI) for predicting NASH and to develop a non-invasive multiparametric MR index for the detection of NASH in non-alcoholic fatty liver disease (NAFLD) patients. This prospective study included 47 NAFLD patients who were scheduled to undergo or underwent ultrasound-guided liver biopsy within 2 months. Biopsy specimens were graded as NASH or non-NASH. All patients underwent non-enhanced MRI including MR spectroscopy (MRS), MR elastography (MRE), and T1 mapping. Diagnostic performances of MRS, MRE, and T1 mapping for grading steatosis, activity, and fibrosis were evaluated. A multiparametric MR index combining fat fraction (FF), liver stiffness (LS) value, and T1 relaxation time was developed using linear regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the newly devised MR index. Twenty NASH patients and 27 non-NASH patients were included. Using MRS, MRE, and T1 mapping, the mean areas under the curve (AUCs) for grading steatosis, fibrosis, and activity were 0.870, 0.951, and 0.664, respectively. The multiparametric MR index was determined as 0.037 × FF (%) + 1.4 × LS value (kPa) + 0.004 × T1 relaxation time (msec) -3.819. ROC curve analysis of the MR index revealed an AUC of 0.883. The cut-off value of 6 had a sensitivity of 80.0% and specificity of 85.2%. The multiparametric MR index combining FF, LS value, and T1 relaxation time showed high diagnostic performance for detecting NASH in NAFLD patients.

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease with increasing prevalence worldwide¹. NAFLD encompasses a wide spectrum of diseases, ranging from simple statosis and non-alcoholic statohopatitis (NASH) to liver cirrhosis. NASH increases the risk of hepatocellular carcinoma (HCC) and death from cardiovascular disease²⁴. Therefore, it is crucial to differentiate NASH from simple statosis. Liver biopsis is regarded as the gold standard for the diagnosis of NASH⁴⁴. However, liver biopsy is an invasive and costly procedure with the risk of pain, bleeding, and although extremely rarely, even death. As a liver biopsy specimen represents only about 0.0002% of the whole liver, sampling error with inter- and intra-observer variability is another potential problem. Therefore, there have been substantial clinical demands for alternative and noninvasive methods to diagnose NASH.

With recent advances in MRI, MR spectroscopy (MRS), and MR elastography (MRE) have emerged as promising methods for detecting and grading fat and fibrosis, respectively^{6,4}. MRS enables the direct measurement of the fat proton signal fraction and is considered the method of choice for a courate non-invasive quantification of liver fat¹⁰. MRE has shown promising results for staging hepatic fibrosis and detecting NASH in NAFLD

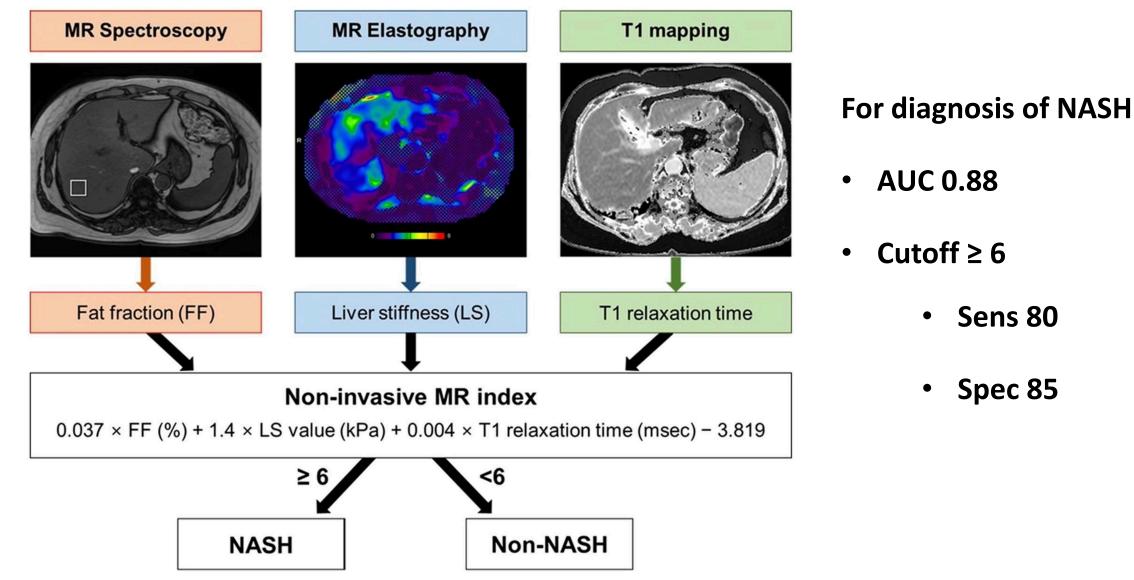
¹Department of Radiology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea. ²Department of Radiology, Korea Anrmed Forces Capital Hospital, Gyeonggi-do, Korea. ³Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea. ³Department of Pathology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea. ³These authors contributed equely: Jeong Woo Kim and Young-Sou Lee. ⁴ email: LeeBe6@korea.ac.kr

SCIENTIFIC REPORTS | (2020) 10:2671 | https://doi.org/10.1038/s41598-020-59601-3



Complementarity?





Kim 2020 Scientific Reports 32060386

NIMBLE – Non-Invasive BioMarkers for MetaBolic Liver DiseasE

Team Science: The Key to Non Invasive Biomarkers Development for NASH

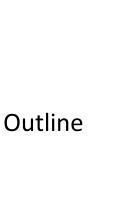


IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS









Diagnostic biomarkers in NAFLD clinical trials

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MultiScan-cT1 and MRE-stiffness friend or foe?

For Collaborative Research Diagnostic Applicatic Through the left f Regulatory Science Diagnostic Context of Use Friday April 22, 2022

Claude B. Sirlin, MD csirlin@health.ucsd.edu



