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Certified Cardiometabolic Health Professional (CCHP)

# Diagnosis of NAFLD: From Non-invasive to Invasive

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# Disclosures

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National Institute of Health and industry as follows: Echosens, Inventiva, Janssen, Nordic, Novo Nordisk, Poxel, Target-NASH, Zydus.

Consultant:

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Stock/Shareholder: None

Other: None


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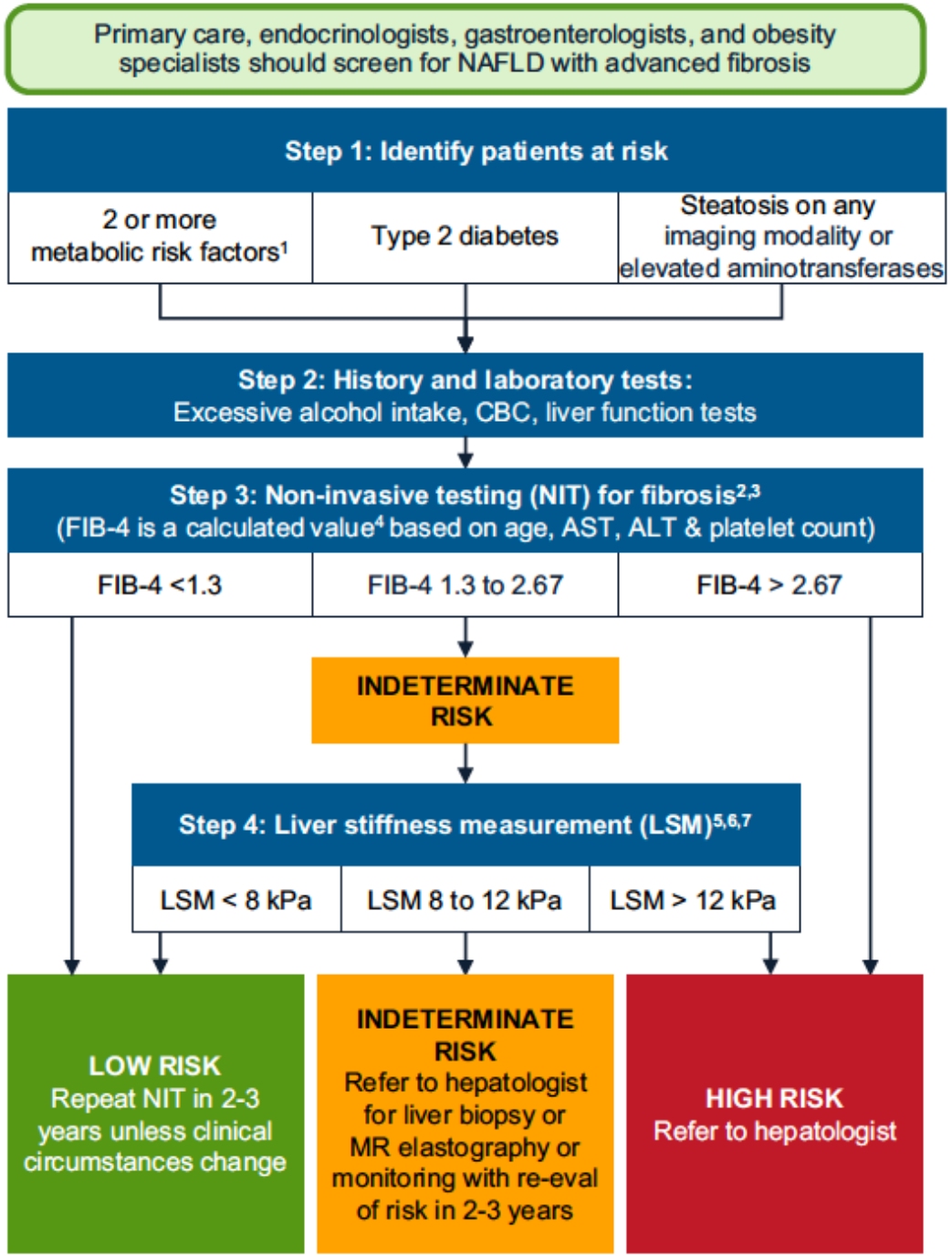
# Clinical Care Pathway for the Diagnosis of NAFLD




Kanwal et al, Gastroenterology 2021;161:1657-1669.

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# NAFLD and T2DM


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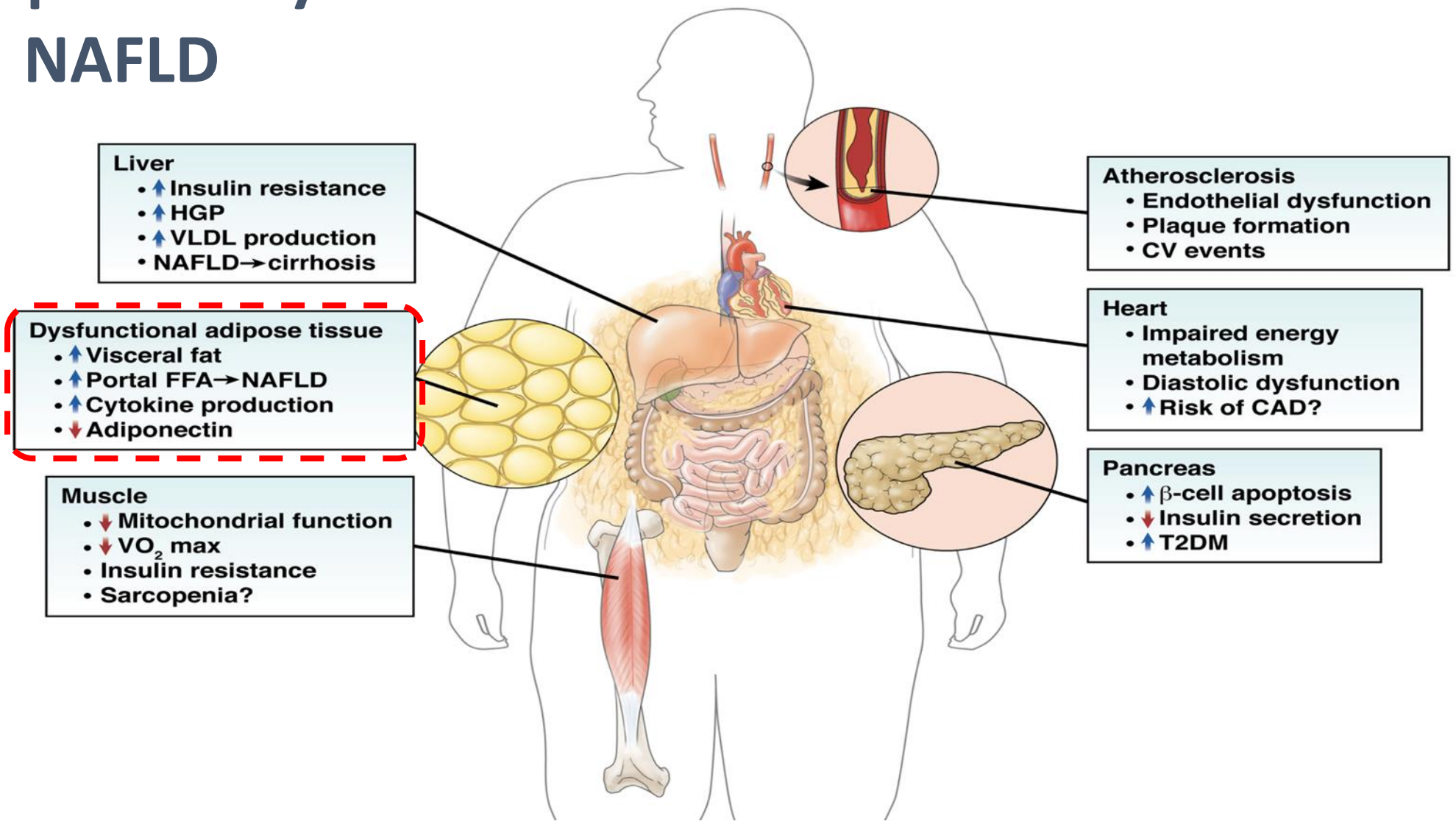
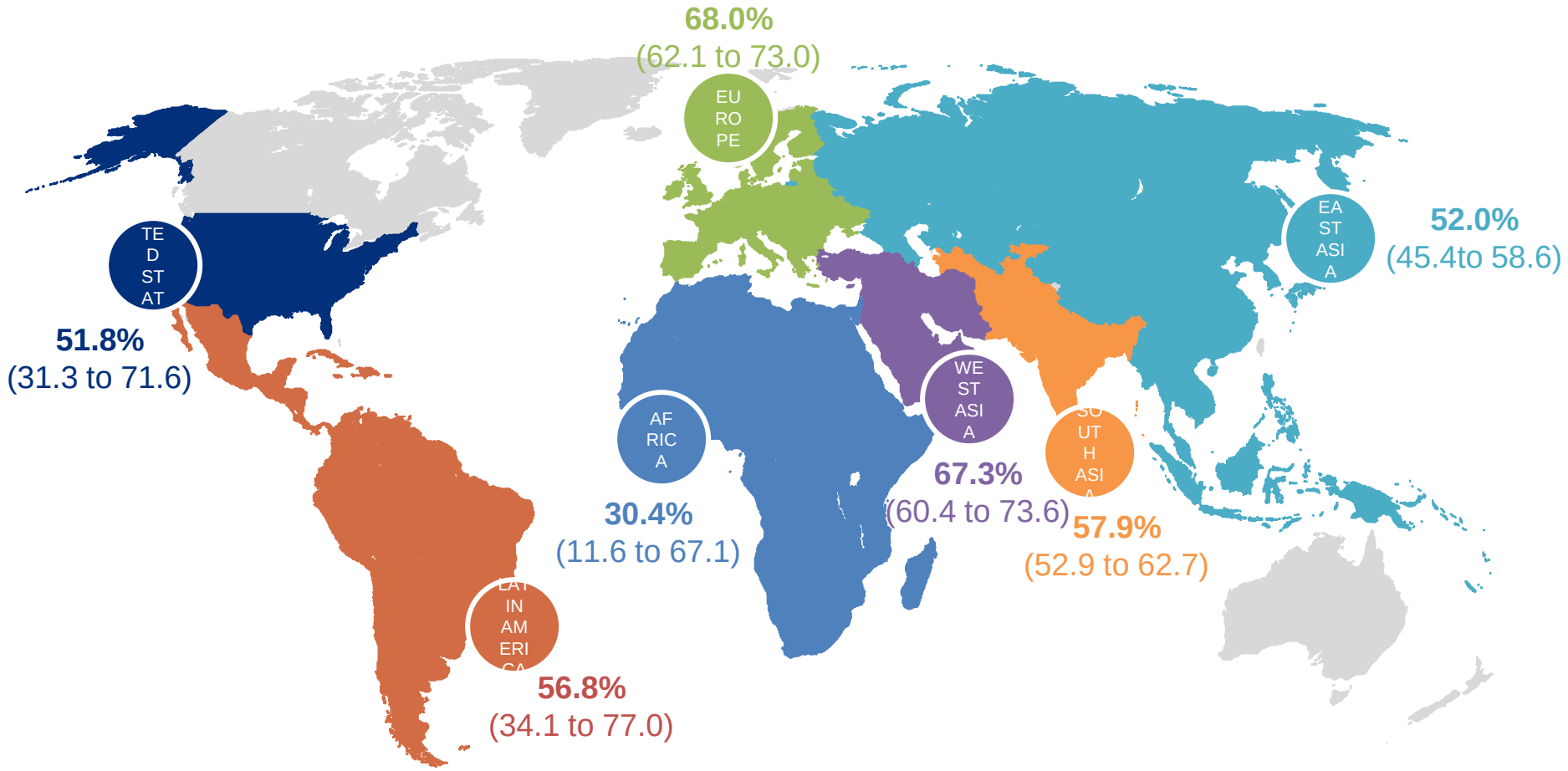
# Insulin Resistance and Lipotoxicity in NAFLD




Cusi K, Gastroenterology, April 2012, 142:711-725

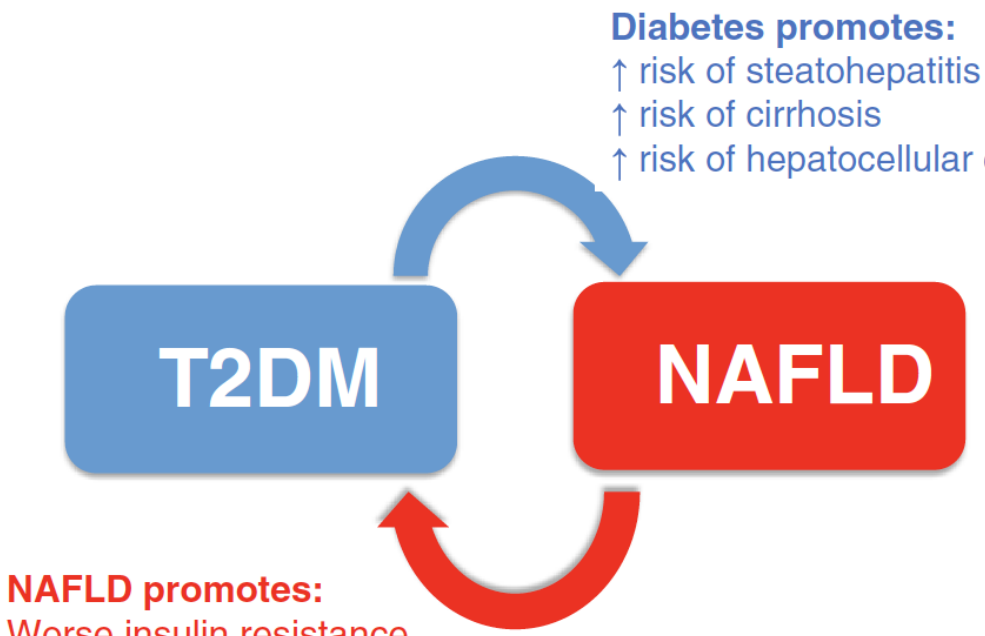
# Global Prevalence of NAFLD* in T2DM: 55.5% (95% Confidence Interval: 47.3-63.7)




**NASH prevalence:**
37.3% (10 studies)

Younossi et al, J Hepatology 2019

# The Liver and Cardiometabolic Risk Reduction in T2DM




American Diabetes Association recommendation for NAFLD:

***Recommendation***

**4.14** Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

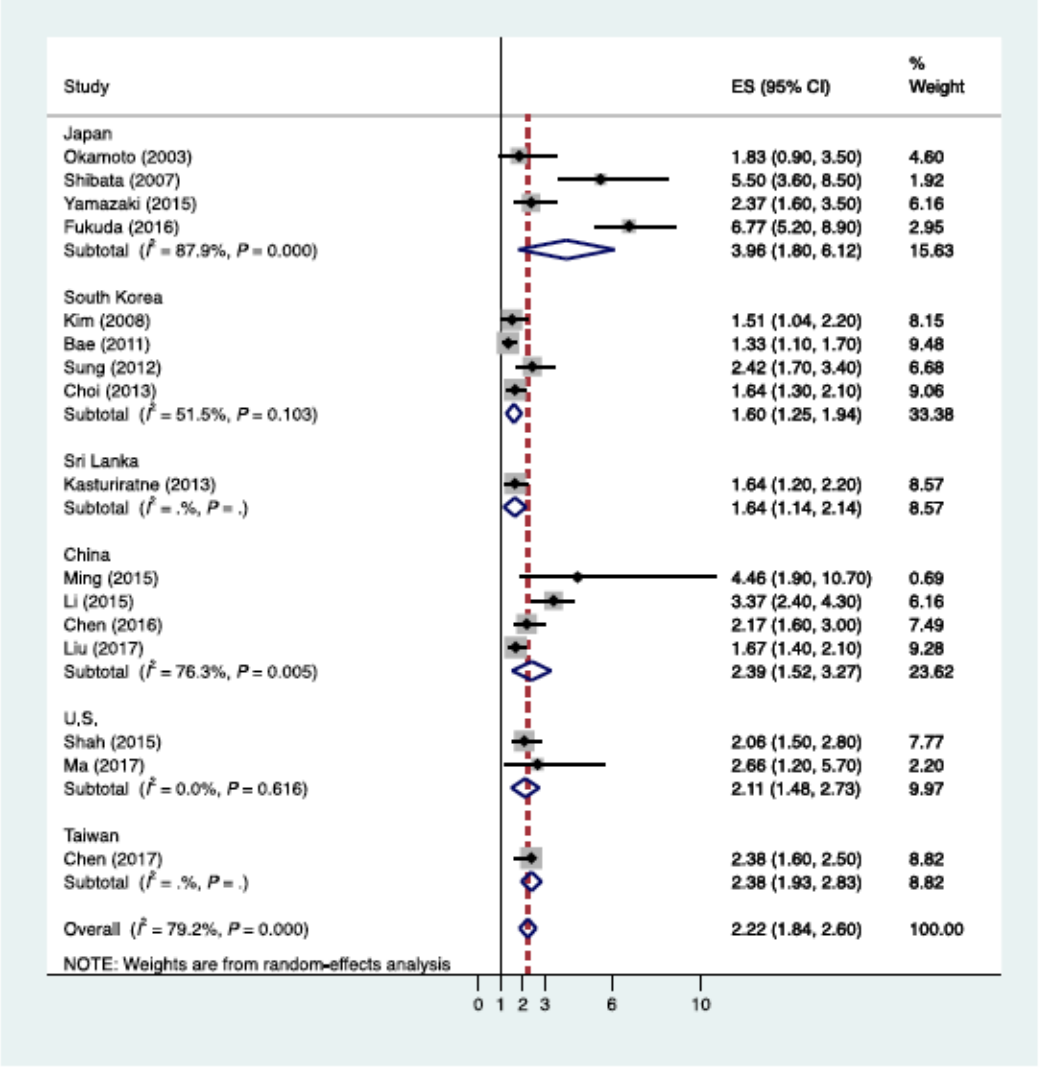
Budd & Cusi K, Current Diabetes Reports 2020; Oct 5;20(11):59.

# Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis

- A total of 19 observational studies with 296,439 individuals (30.1% with NAFLD).
- Nearly 16,000 cases of incident diabetes.
- Follow-up median of 5 years.

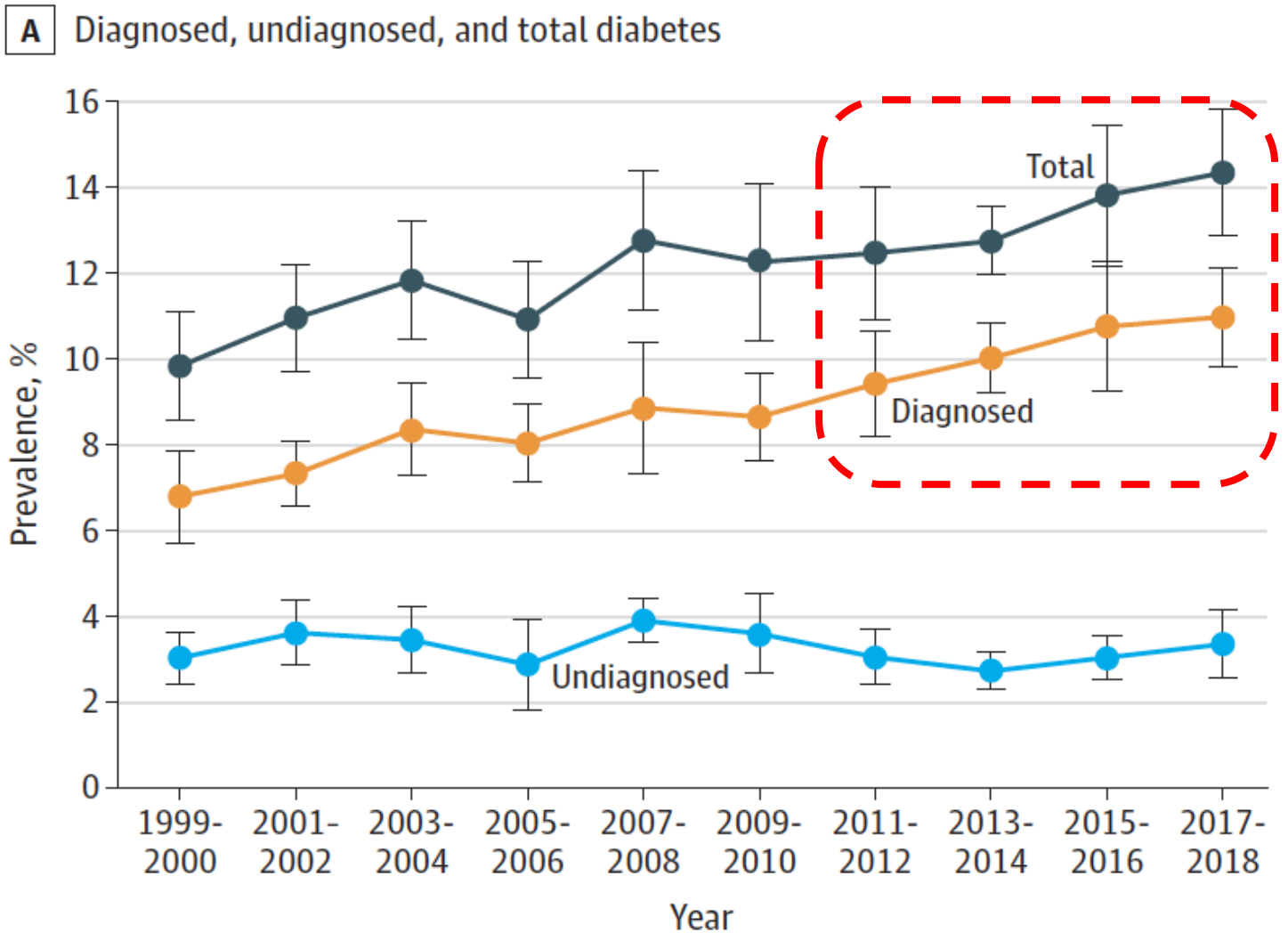
Major findings:

- 2-fold greater risk of incident diabetes in patients with vs. without NAFLD ([HR] **2.22**, 95%CI 1.84–2.60).
- Patients with more "severe" NAFLD > incident diabetes (n = only 3 studies). (steatosis assessed only by US).
- In one study the risk greater in NAFLD pts with > NAFLD fibrosis score ([HR] 4.74, 95%CI 3.54–5.94).



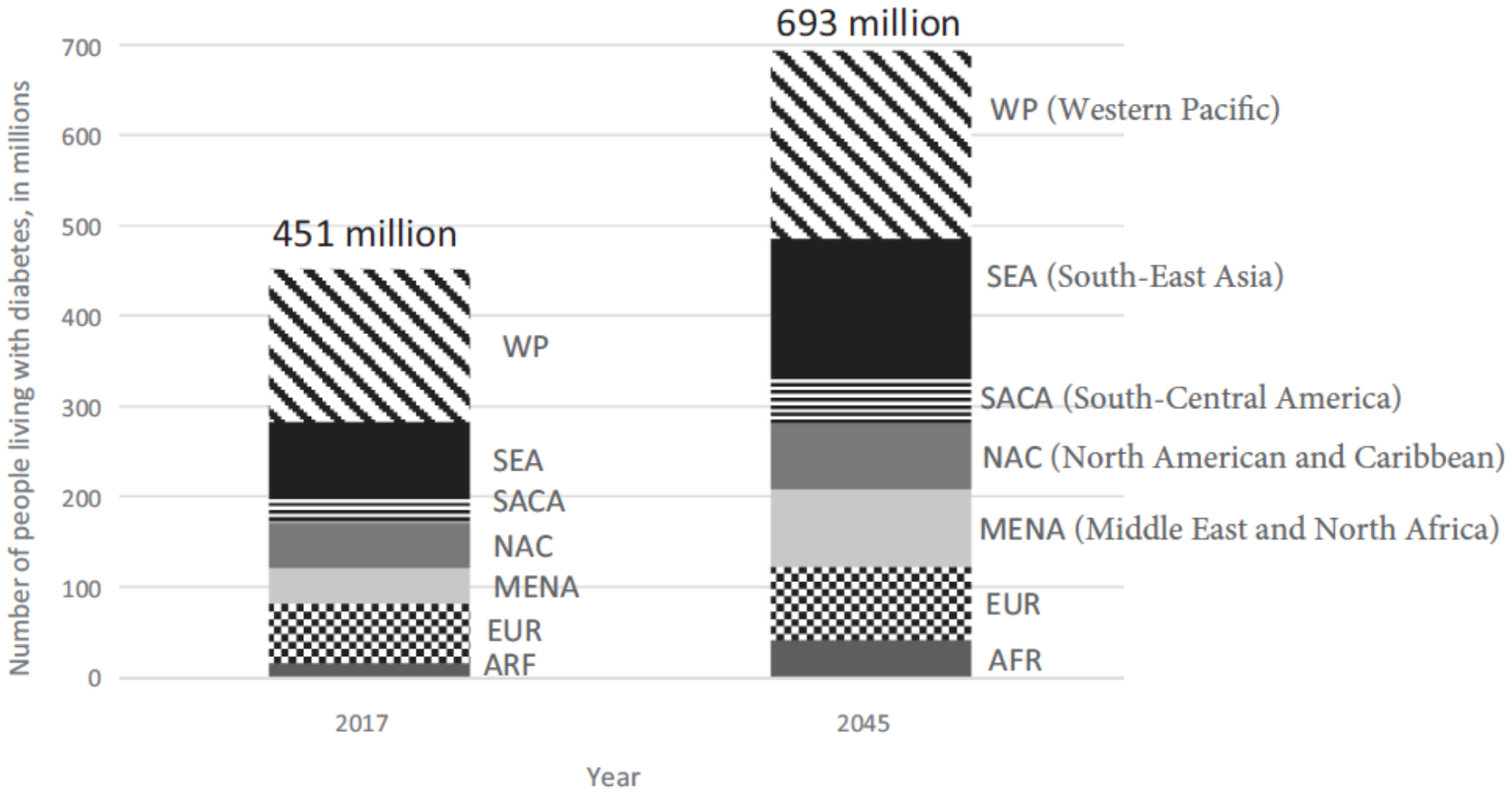

Mantovani et al, Diabetes Care 2018;41:372–382

# Trends in Prevalence of Diabetes in U.S. Adults, 1999–2018




Wang et al, JAMA 2021;326(8):704-716.

# Global estimates of diabetes prevalence for 2017 and projections for 2045




Cho et al, Diabetes Research & Clinical Practice 2018;138:271-281.

# 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2022*

*Diabetes Care 2022;45(Suppl. 1):S46–S59 | https://doi.org/10.2337/dc22-S004*

***Recommendation***

**4.10** Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

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# Diagnosis of Steatosis and Fibrosis in NAFLD/ NASH

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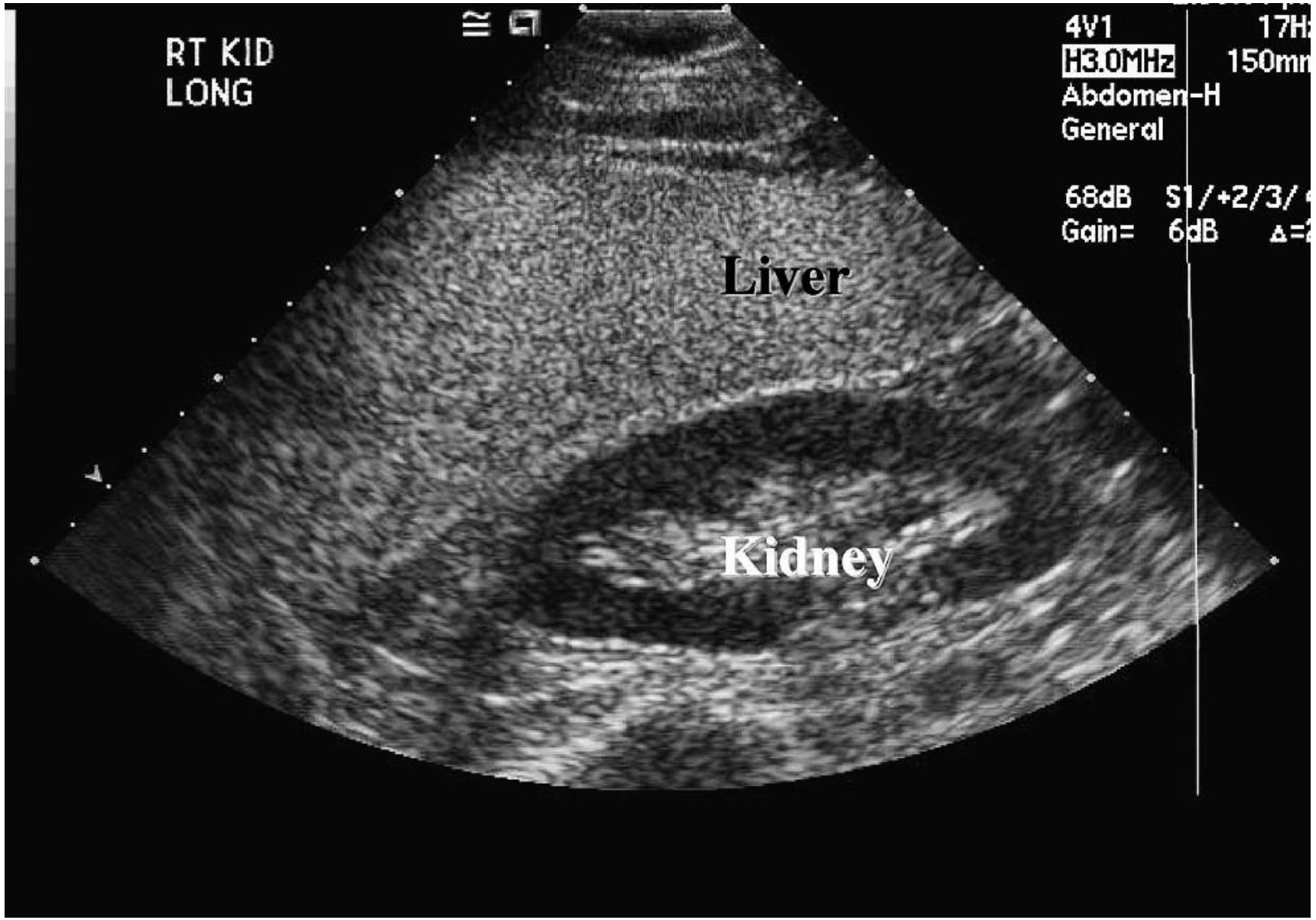
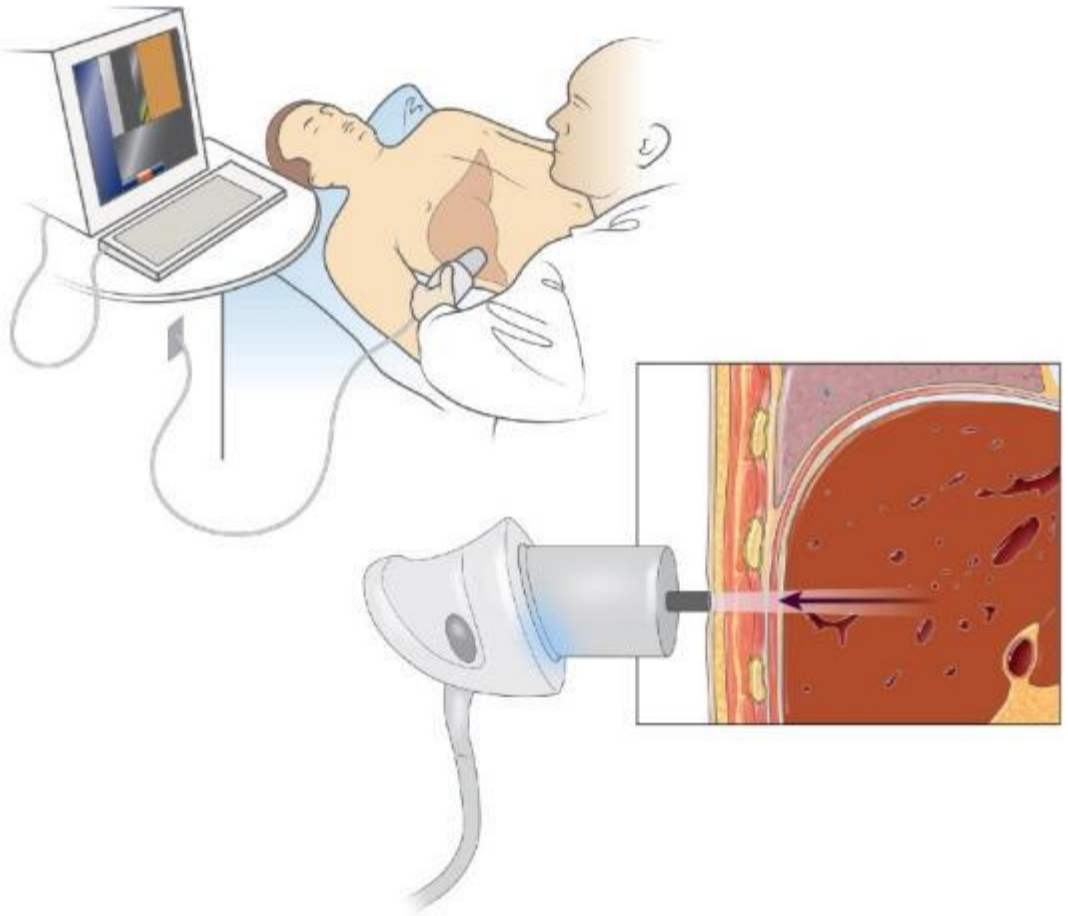
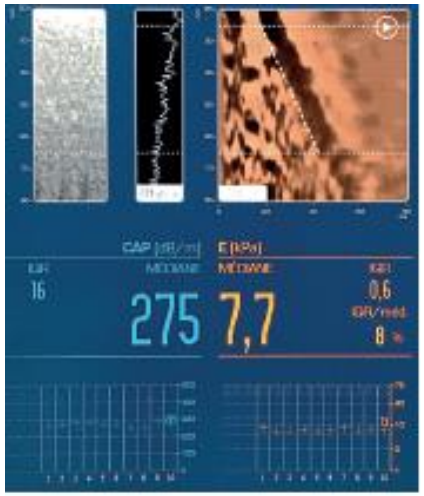
# NAFLD Liver Ultrasound



# Diagnosis of Fibrosis in NASH with Elastography*






* Vibration controlled transient elastography (VCTE by Fibroscan® - Echosens)

# Diagnosis of Liver Fibrosis by Transient Elastography

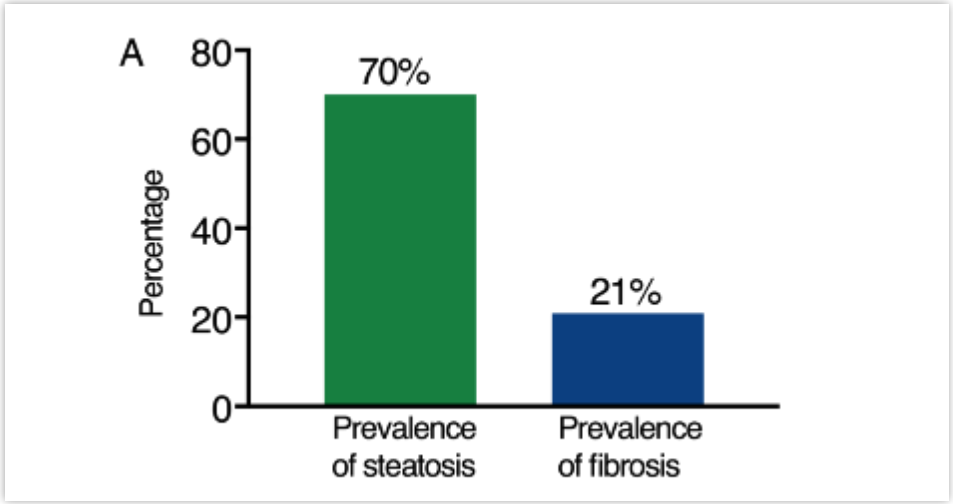
# Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening

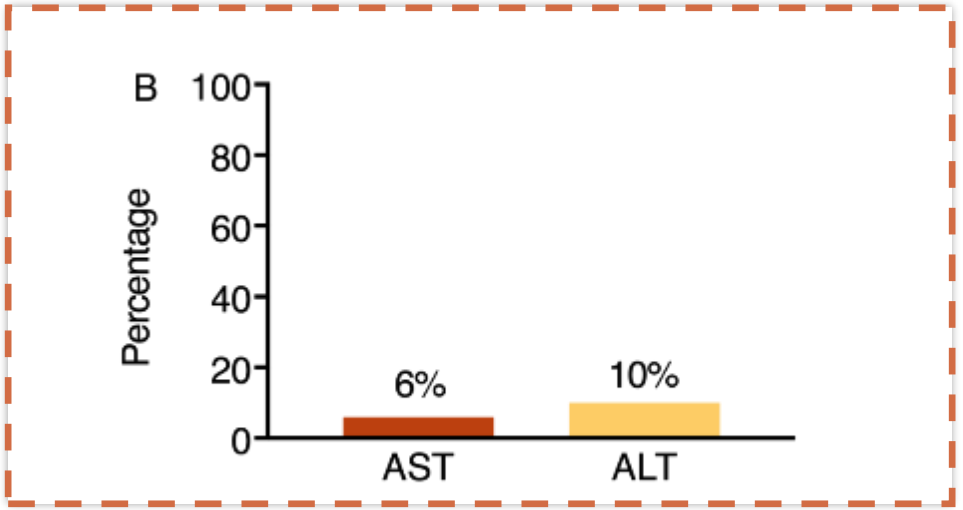
Romina Lomonaco,[1] Eddison Godinez Leiva,[1] Fernando Bril,[1] Sulav Shrestha,[1] Lydia Mansour,[1] Jeff Budd,[2] Jessica Portillo Romero,[2] Siegfried Schmidt,[3] Ku-Lang Chang,[3] George Samraj,[3] John Malaty,[3] Katherine Huber,[2] Pierre Bedossa,[4] Srilaxmi Kalavalapalli,[1] Jonathan Marte,[1] Diana Barb,[1] Danielle Poulton,[1] Nada Fanous,[1] and Kenneth Cusi[1,5]

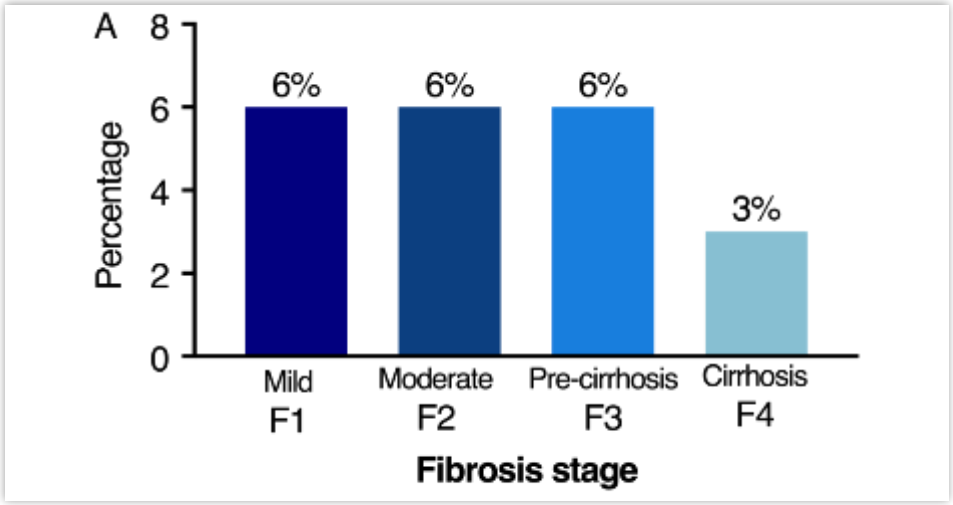
*Diabetes Care 2021;44:399–406 | https://doi.org/10.2337/dc20-1997*

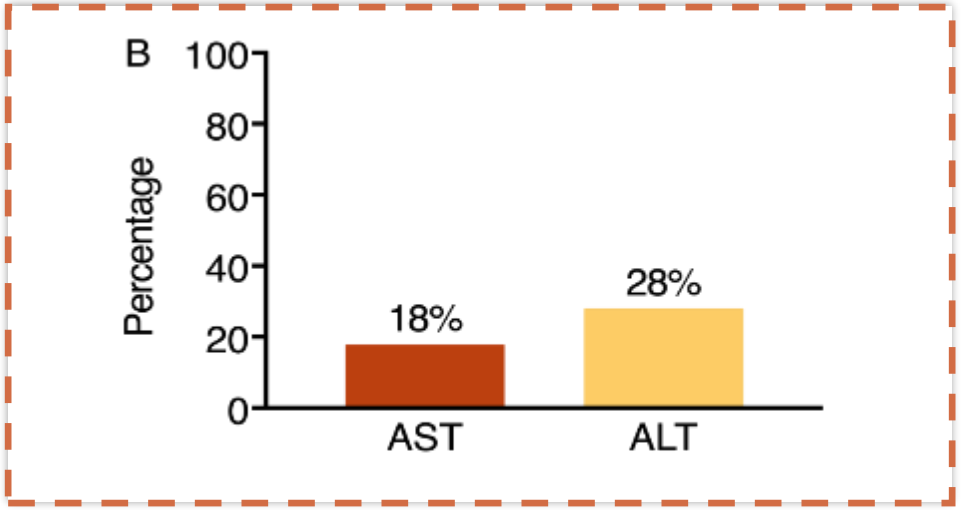
# Prevalence of Elevated Plasma AST or ALT in Steatosis or Fibrosis in Patients with T2DM Unaware of Having NAFLD

**N = 561 patients with type 2 diabetes**




Lomonaco/Cusi et al, Diabetes Care, 2021; 44:399-406.

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# Diagnosis and Management of NAFLD/ NASH: A 2022 Update

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Gainesville, United States

# Management of NAFLD in 2022

## Preparing for the NASH Epidemic: A Call to Action

Fasiha Kanwal,[1] Jay H. Shubrook,[2] Zobair Younossi,[3] Yamini Natarajan,[4] Elisabetta Bugianesi,[5] Mary E. Rinella,[6] Stephen A. Harrison,[7] Christos Mantzoros,[8] Kim Pfotenhauer,[9] Samuel Klein,[10] Robert H. Eckel,[11] Davida Kruger,[12] Hashem El-Serag,[13] and Kenneth Cusi[14]

| History and medical review | Investigations |
|---|---|
| Obesity | Liver biochemistries (ALT, AST) |
| T2D | Exclude/identify other liver diseases[a] |
| Metabolic syndrome | HBV and HCV serology (and viral load) |
| Alcohol intake<br><14 drinks/wk for women<br><21 drinks/wk for men | Auto antibodies (ANA, AMA, ASMA)<br>Serum ferritin, A1AT<br>Liver ultrasound: increased echogenicity |
| No known pre-existing liver disease | — |

A1AT, $\alpha$1 antitrypsin; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.

**Gastroenterology, Obesity, Diabetes Care, and Metabolism - Available online 26 July 2021**

# Diagnosis of NAFLD: Guideline Summary

**Table 4.** Summary of Published Nonalcoholic Fatty Liver Disease Guidelines

| Organization | Year | First-line diagnosis test | When to refer to hepatologist | Noninvasive tests |
|---|---|---|---|---|
| American Association for the Study of Liver Diseases (AASLD) | 2018 | Not clear in the guideline<br>Routine screening for NAFLD in high-risk groups is not recommended | Not clear in the guideline | Diagnosis for NASH: liver biopsy<br>Assessment for fibrosis: NFS or FIB-4 |
| American Gastroenterological Association (AGA) | 2012 | Routine screening for NAFLD is not recommended | Not clear in the guideline | Metabolic syndrome can be used to target patients for liver biopsy |
| European Association for the Study of the Liver (EASL) | 2016 | Ultrasound + liver enzymes for patients with risk factors | Refer patients with abnormal liver enzymes or medium-/high-risk fibrosis markers to specialist | Diagnosis for NASH: liver biopsy<br>Assessment for fibrosis: NFS or FIB-4 |
| World Gastroenterology Organization (WGO) | 2012 | Ultrasound + liver enzymes for patients with risk factors | Not clear in the guideline | Diagnosis for NASH: liver biopsy |
| National Institute for Health Care and Excellence (NICE) | 2016 | Ultrasound + liver enzymes for patients with risk factors<br>But routine liver function blood tests are not sensitive, and ultrasound is not cost-effective | Refer adults with advanced liver fibrosis to a hepatologist<br>Refer children with suspected NAFLD to a pediatric specialist in hepatology | Assessment for advanced fibrosis: enhanced liver fibrosis (every 2–3 y) |

FIB-4, Fibrosis-4 Index; NFS, NAFLD fibrosis score.

Gastroenterology, Obesity, Diabetes Care, and Metabolism - Available online 26 July 2021

# Management of NAFLD in 2022

## Preparing for the NASH Epidemic: A Call to Action

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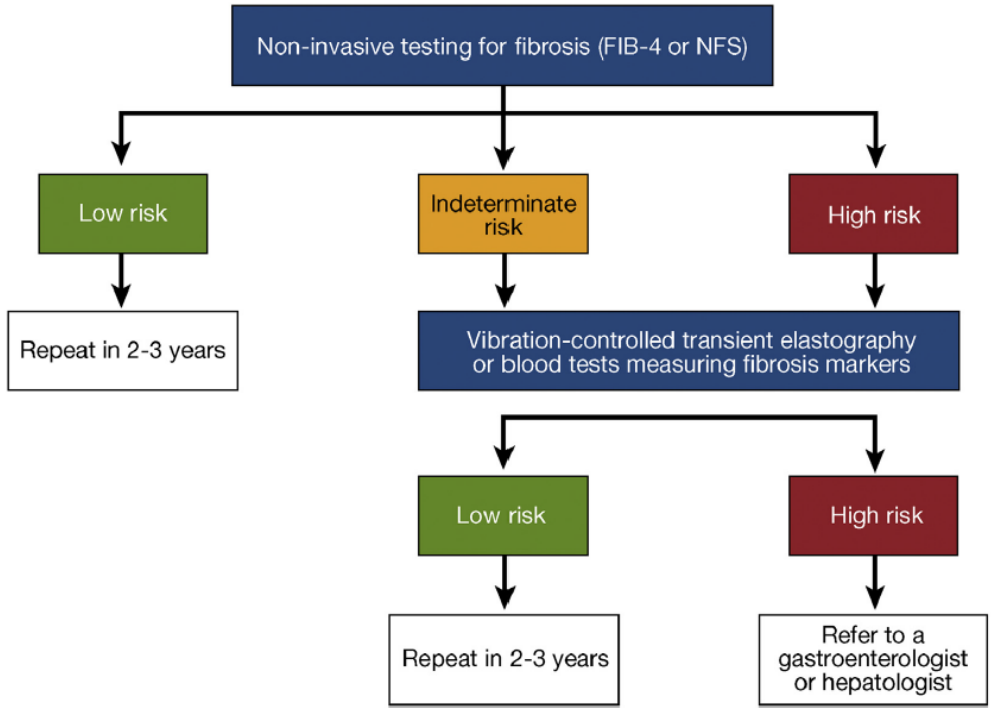


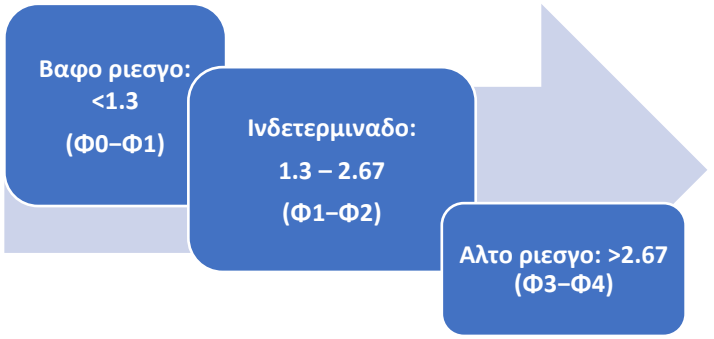

Algorithm for risk stratification in patients with NAFLD/NASH. FIB-4, Fibrosis-4 Index; NFS, NAFLD fib

**Gastroenterology, Obesity, Diabetes Care, and Metabolism - Available online 26 July 2021**

# Interpretation of FIB-4 and NFS for the Diagnosis of Advanced Fibrosis (stages 3-4)

## FIB-4

**Risk of advanced fibrosis (stages 3-4)**




$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} =$$

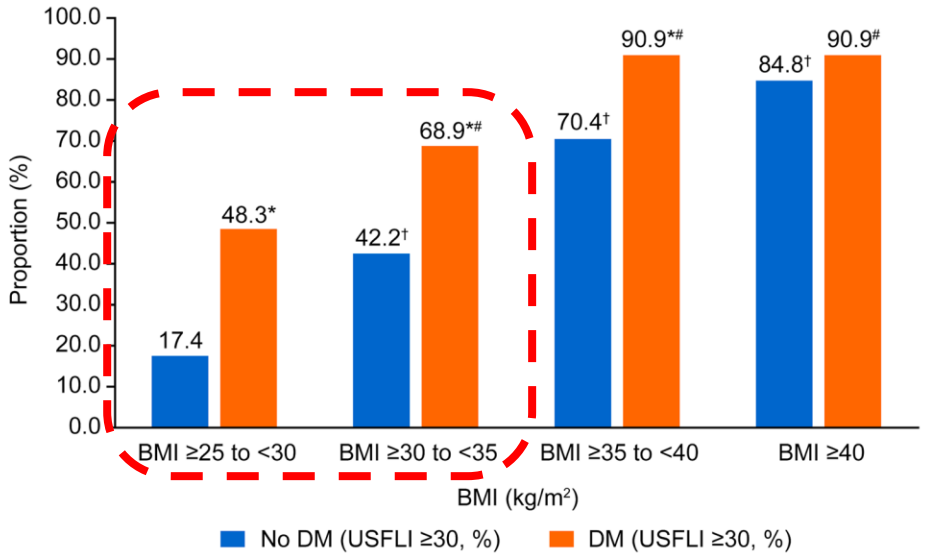
| Parameters |
|---|
| Age |
| AST |
| ALT |
| Platelets |
| BMI |
| Serum Glucose (IGT or DM?) |
| Albumin |

FIB-4: Fibrosis-4 score.

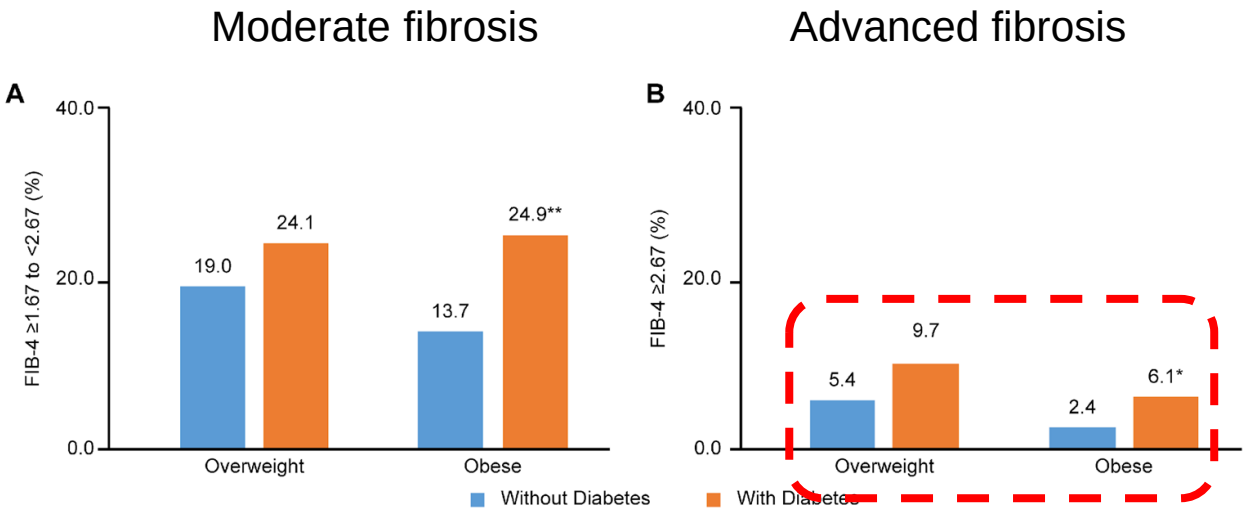
Budd & Cusi, American Journal of Medicine, 2020 ;133:536-543.

# Steatosis and Fibrosis in Individuals with Overweight or Obesity, with or without Diabetes

Prevalence of Steatosis:
Role of obesity vs. diabetes

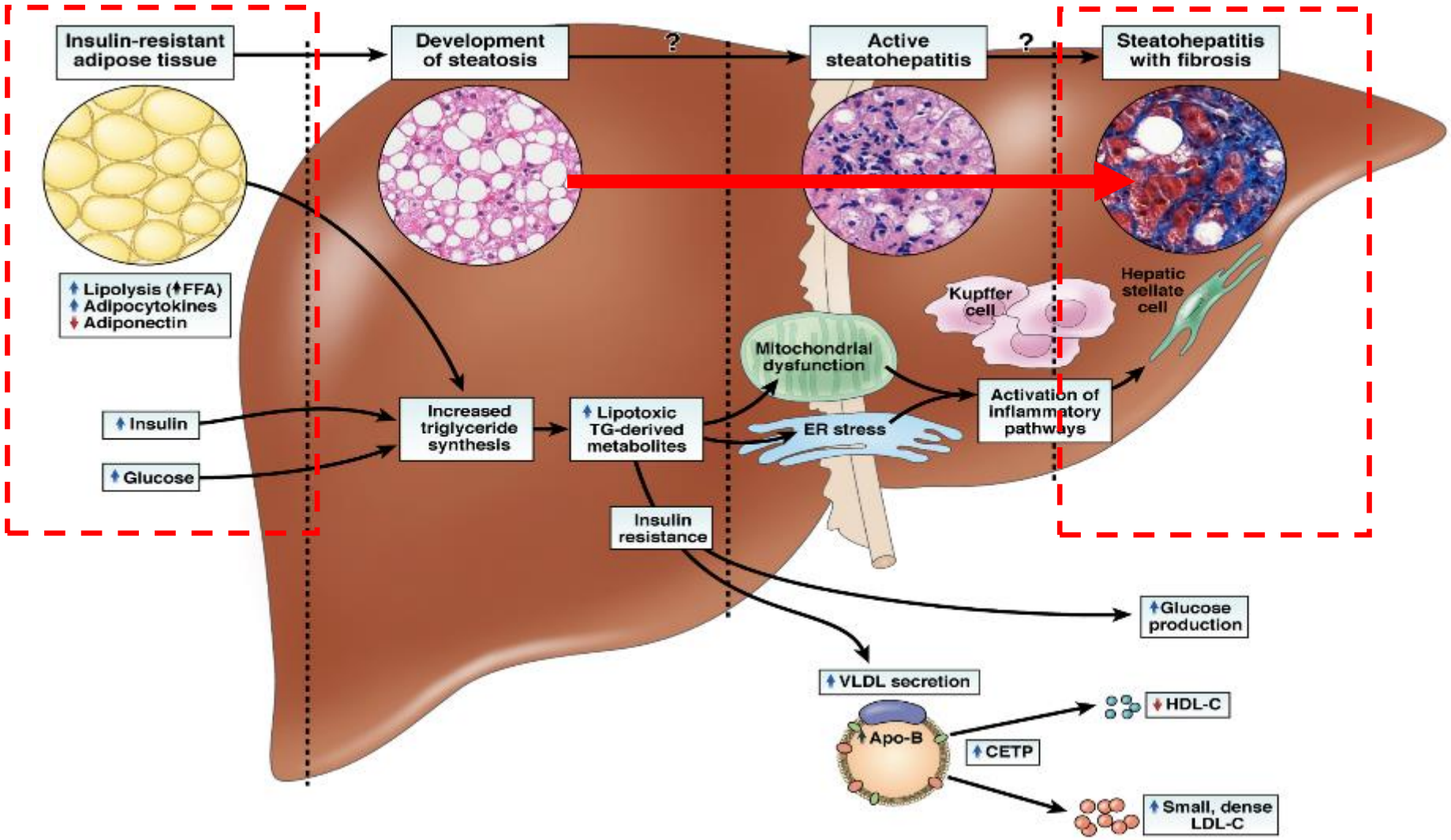



Prevalence of Fibrosis:
Role of obesity vs. diabetes




Barb et al, Obesity 2021 (in press; DOI: 10.1002/oby.23263)

# The Natural History of NAFLD: from Steatosis to Hepatocyte Lipotoxicity (NASH) to Cirrhosis




Cusi K, Gastroenterology, April 2012, 142:711-725

# Additional Diagnostic Approaches in NAFLD

| A. Blood Liver Funtion Tests | Parameter Measured | Pros | Cons | AUROC |
|---|---|---|---|---|
| ELF panel [39] | Hyaluronic acid (HA), Tissue inhibitor metalloproteinase 1 (TIMP1), and Aminoterminal peptide of procollagen 3 (PIIINP). | Feasible in large number of subjects Good outcome correlation | Commercial test not routinely available | 0.93 in adults 0.99 in pediatric patients |
| Pro-C3 [42] | Pro collagen III | Able to discriminate simple fatty liver from NASH and different stages of fibrosis | Commercial test | 0.86 |
| NASH NIS4 [44] | MicroRNA 34a-5p; alpha2 macrogobulin (A2M), Haemooglobin A1c (HbA1c), and Chitinase-3-like protein 1 (CHI3L1 also known as YKL40) | This tool can enrich the selection of patients—candidate to experimental trials—with active NASH and significant fibrosis | Commercial test; performances might vary according to the baseline characteristics of the studied population | 0.82 |
| Lipidomic serum test § (OWLiver) [45] | Two subsequent analyses of 11 and 20 triglycerides panel to be used in adults with BMI > 25 | Able to discriminate normal liver form NAFLD and NAFLD from NASH | Commercial test performed in a centralized laboratory | 0.79 or 0.81 (according to inclusion or exclusion of patients with glucose >136 mg/dl) |
| **B.US-Based Physical Tests** | **Parameter Measured** | **Pros** | **Cons** | **AUROC** |
| TE [47,48] | Liver stiffness | Short processing time and outpatient clinic setting | Measurement failures reported in up to 20% and XL probe required in obese patients | 0.95 for F4 0.93 for F3 0.84 for F2 fibrosis |
| Point shear wave elastgraphy (ARFI) [49] | Liver stiffness | Short processing and outclinic setting | Quality criteria not well defined, lack of large-scale studies | 0.78–0.89 for F4 0.74–0.97 for F3 0.70–0.83 for F2 fibrosis |
| **3. Not US-Based physical tests** | **Parameter Measured** | **Pros** | **Cons** | **AUROC** |
| MRE [50,51] | Liver stiffness | Not influenced by BMI and inflammation | Long processing, expensive, and not largely available | 0.88–0.97 for F4 0.89–0.96 for F3 0.86–0.89 for F2 |
| LiverMultiScan (multiparametric resonance) [52] | Fibrosis and inflammation mapping | Quick and no contrast agent required | Further validation studies required | 0.85 for F4 |

§ compared to histology.

Piazzolla & Mangia, Cells 2020; 9, 1005; doi:10.3390/cells9041005

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# Emerging Biomarkers and Diagnostic Tools

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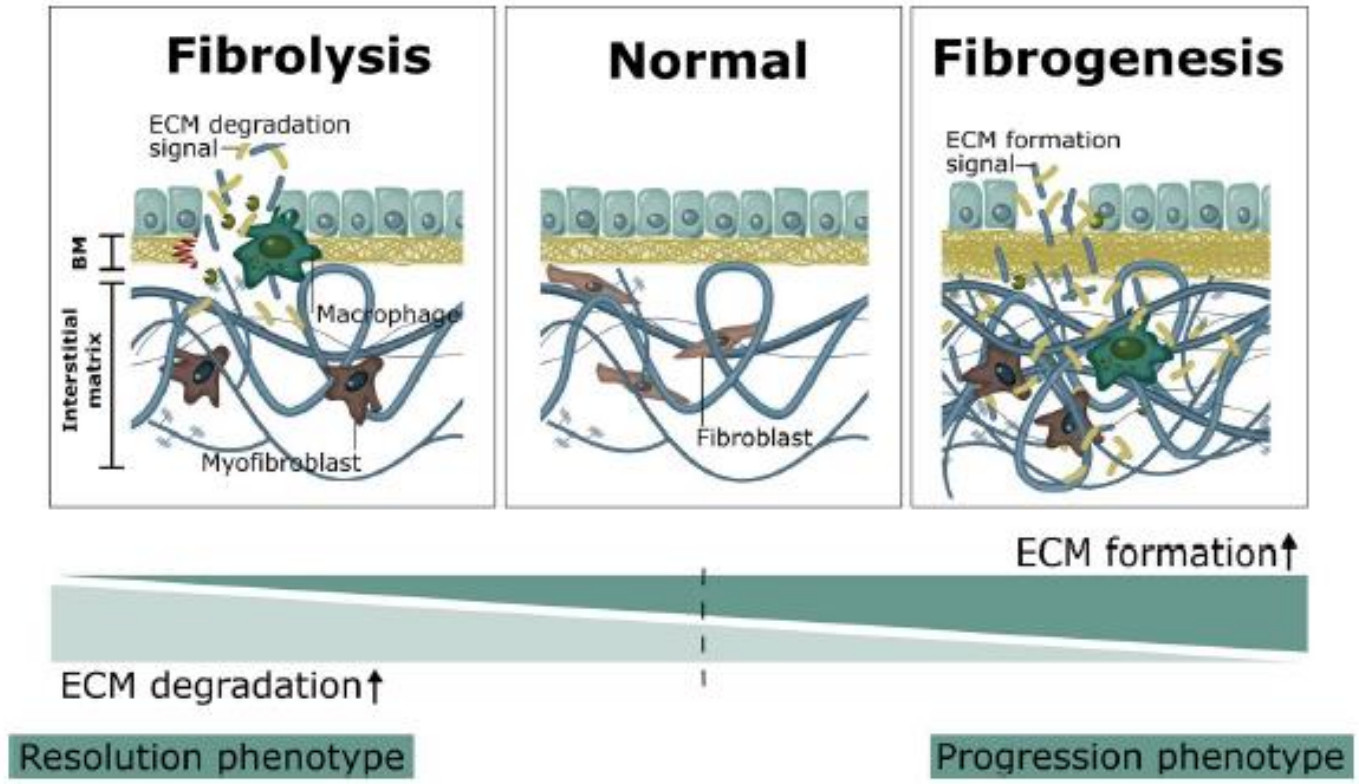
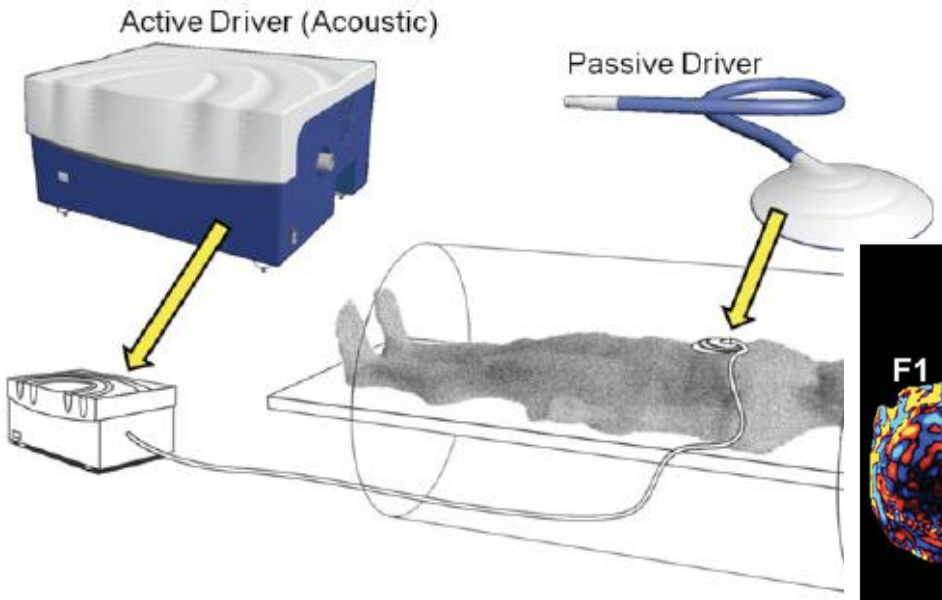
# Future Biomarker Development/Approaches will Depend on a Better Understanding of the Biology of Liver Fibrosis

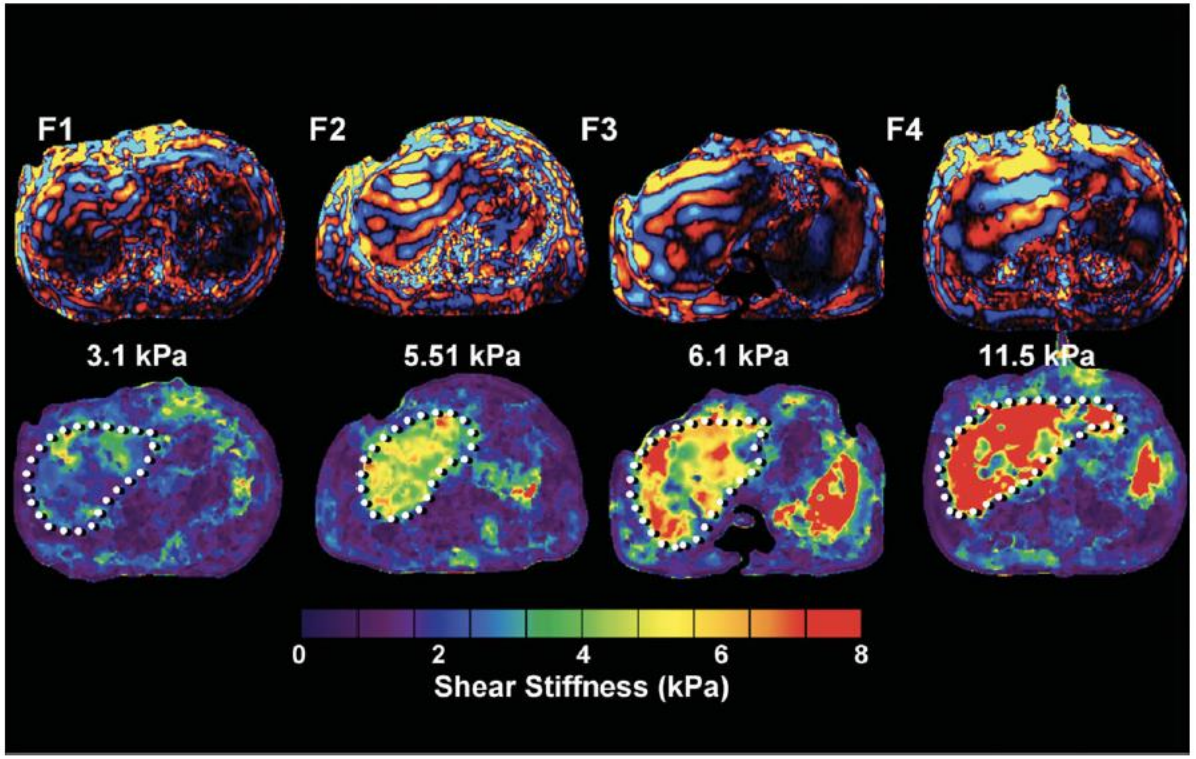



| ECM component | Stage of liver fibrosis | |
|---|---|---|
| | Mild to moderate | Severe and cirrhotic |
| Type I collagen | ↑↑ | ↑↑↑ |
| Type III collagen | ↑↑ | ↑↑↑ |
| Type IV collagen | ↑ | ↑↑ |
| Type V collagen | ↑ | ↑↑↑ |
| Type VI collagen | ↑ | ↑↑ |
| Type X collagen | – | ↑↑↑ |
| Type XVIII collagen | ↑ | ↑↑↑ |
| Elastin | ↑ | ↑↑ |
| Fibulin-5 | ↑ | ↑↑↑ |
| MFAP (microfibril associated protein)-4 | ↑ | ↑↑ |
| Vitronectin | ↑ | ↑↑ |
| Lumican | ↑ | ↑↑ |
| Fibronectin | ↑ | ↑↑ |
| Laminin | (↑) | ↑ |

Karsdal et al, Liver Int 2020; 40(4):736-750.

# Magnetic Resonance Elastography




Venkatesh et al, J of Magnetic Resonance Imaging, 2013;37:544-555.

# Diagnosing Steatohepatitis at the University of Florida

Age: 50 yo female
BMI: 32.8 kg/m$^2$
FPG: 68 mg/dL
A1c: 6.1%
AST: 56 IU/L
ALT: 85 IU/L
Platelets: 356 x10$^9$/L
Fibroscan:
CAP: 355
VCTE: 8.9

LiverMultiScan

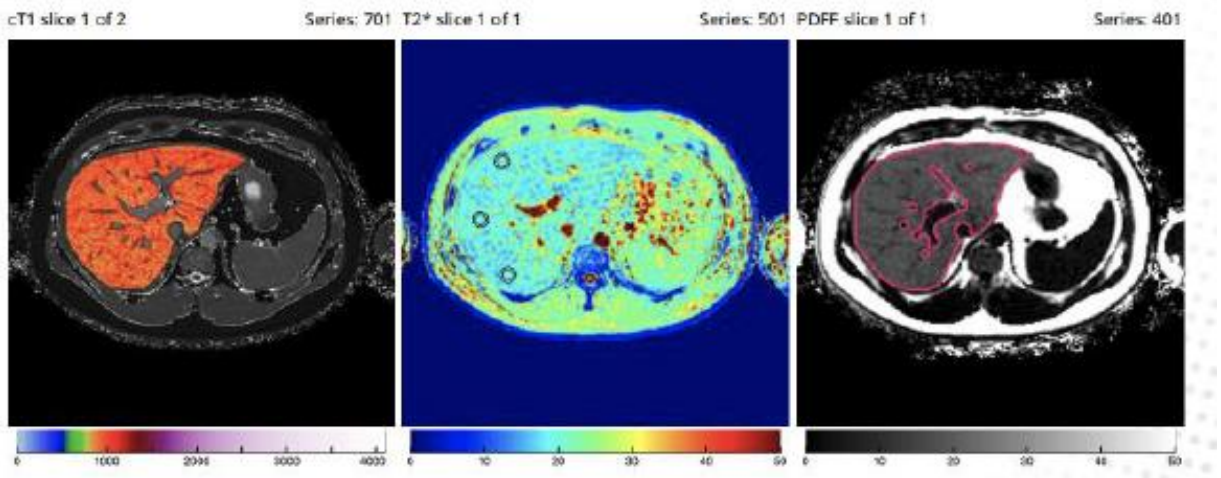
AMRIS/University of Florida
1149 Newell Drive

| | | | |
|---|---|---|---|
| **Patient name:** | 003_BASELINE | | |
| **Patient ID:** | 003_BASELINE | | |
| **Referring physician:** | Not recorded | | |
| **Scan date:** | 2021-Feb-01 | **Scan time:** | 09:47 |

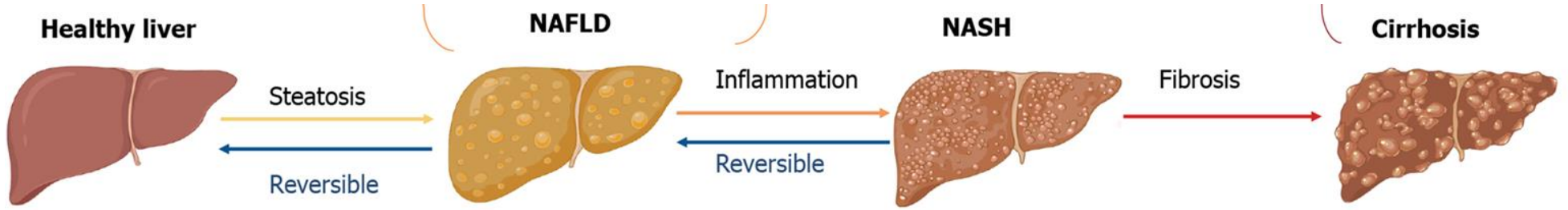
Metrics are displayed as median with interquartile range (IQR) and are calculated from multiple regions of interest over potentially more than one slice. The slices below are examples from the acquisition. Slices are shown on subsequent pages, with more detailed analysis. Please refer to 'A Guide to Interpreting Liver Tissue Characterization for Clinicians' available from the Manufacturer.

This report was generated with investigational software and is not for clinical use.

| Whole liver cT1 (ms) | Liver ROI T2* (ms) | Whole liver PDFF (%) |
|---|---|---|
| **Median: 950ms** | **Median: 18.9ms** | **Median: 17.1%** |
| IQR: 900 to 1005ms | IQR: 18.0 to 19.7ms | IQR: 15.4 to 18.5% |
| Ref range: 633 to 794ms | Reference: >12.5ms at 3T[4] | Reference: <5.6%[5] |
| cT1 is corrected for iron and field strength[3] | T2* is dependent on field strength | PDFF generated with the IDEAL method |
| | T2* generated with the MOST method | |



# Potential Biomarkers for the Diagnosis or Monitoring of NAFLD



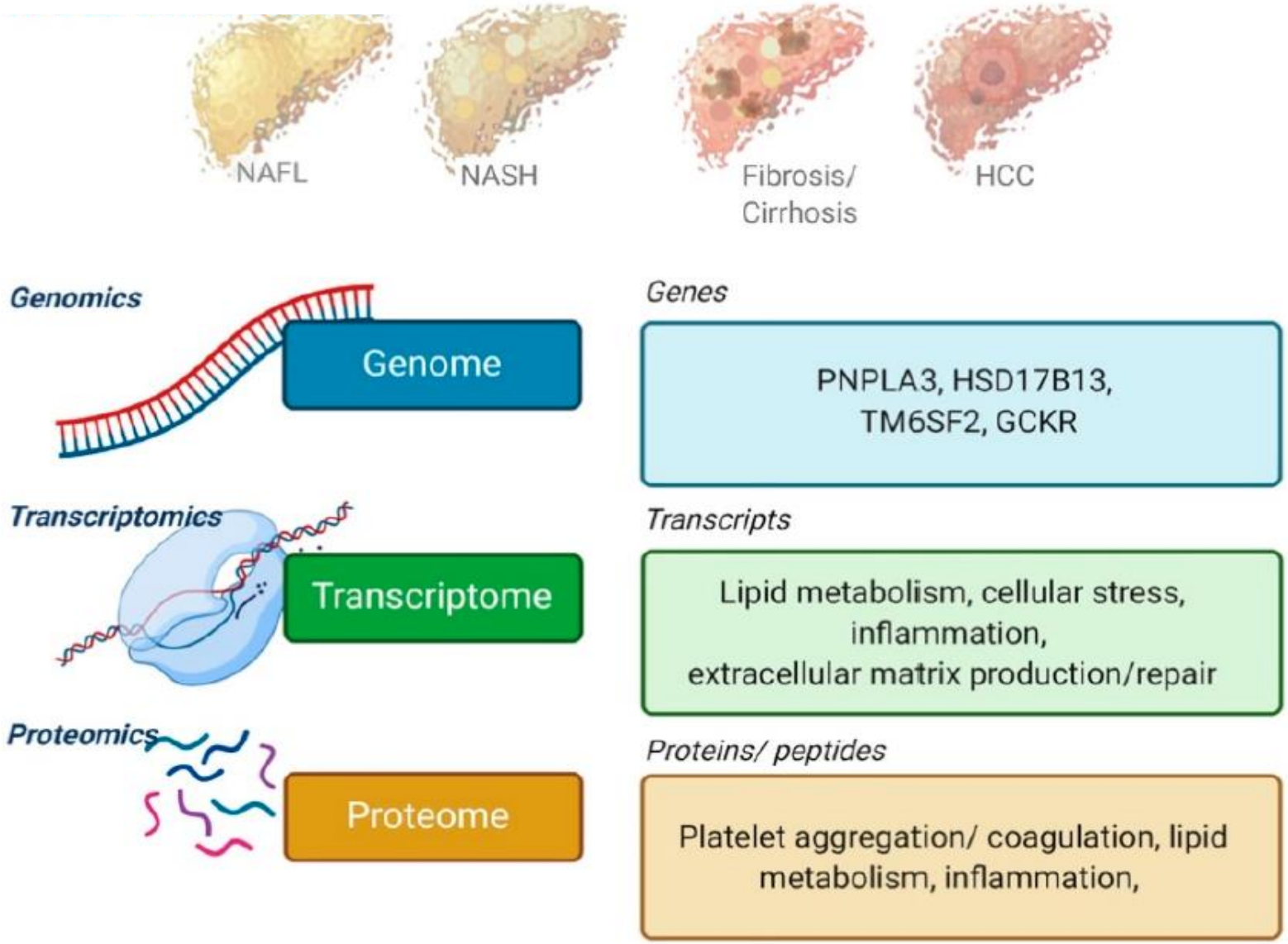

**Promising diagnostic biomarkers**

| NAFLD | | NASH | Cirrhosis |
|---|---|---|---|
| ↑ Hb | ↓ Betaine: Choline | ↑ DR5 | ↑ ASGPR1+ |
| ↑ FGF-21 | ↑ TMAO | ↑ miRNA-122 | ↑ CNN2 |
| ↑ RBP4 | ↑ Ethanol | ↑ miR-192 | ↓ miRNA-214 |
| ↑ CK18Asp396 | ↑ LDL-c | ↑ Homocysteine | ↑ miR-34a |
| ↑ Inosine | ↑ Fecal SCFAs | ↑ Cysteine | ↑ 3-(4-hydroxyphenyl) lactate |
| ↑ Hypoxanthine | ↑ fCh | N/L ratio | Hfib1 |
| ↓ Glutathione | ↑ IL-17 | Th17/T reg imbalance | N/L ratio |
| ↑ Phenylacetic acid | ↑ IL-22 | ↑ IL-1 | ↑ Monocytes |
| ↓ Dietary choline | ↑ PPARα | ↑ IL-6 | ↑ IFNγ |
| ↓ Bile acids | ↓ Lipid β-oxidation | ↑ TNFα | ↑ IL-4 |
| | | | ↑ IL-13 |

Liver biopsy remains as the gold standard

Castillo-Castro et al, World J Hepatol 2021; 13: 1494-1511

# NAFLD omics overview




Wernberg et al, Clin. Med. 2021, 10, 930.

# Clinical Translational Science Institute at the University of Florida

# Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease

Fasiha Kanwal,[1,2] Jay H. Shubrook,[3] Leon A. Adams,[4] Kim Pfotenhauer,[5] Vincent Wai-Sun Wong,[6] Eugene Wright,[7] Manal F. Abdelmalek,[7] Stephen A. Harrison,[8] Rohit Loomba,[9] Christos S. Mantzoros,[10] Elisabetta Bugianesi,[11] Robert H. Eckel,[12] Lee M. Kaplan,[10,13] Hashem B. El-Serag,[1,2] and Kenneth Cusi[14,15]

## NAFLD Treatment

| | LOW RISK<br>FIB-4 < 1.3 or<br>LSM < 8 kPa or<br>liver biopsy F0-F1 | INDETERMINATE RISK<br>FIB-4 1.3 - 2.67 and/or<br>LSM 8 - 12 kPa and<br>liver biopsy not available | HIGH RISK[1]<br>FIB-4 > 2.67 or<br>LSM > 12 kPa or<br>liver biopsy F2-F4 |
|---|---|---|---|
| | Management by PCP, dietician, endocrinologist, cardiologist, others | Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others) | |
| Lifestyle intervention[2] | Yes | Yes | Yes |
| Weight loss recommended if overweight or obese[3] | Yes<br>May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery | Yes<br>Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery | Yes<br>Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery |
| Pharmacotherapy for NASH | Not recommended | Yes[4, 5, 6] | Yes[4, 5, 6, 7] |
| CVD risk reduction[8] | Yes | Yes | Yes |
| Diabetes care | Standard of care | Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA) | Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA) |

Kanwal, Shubrook/Cusi et al, Gastroenterology, September 2021 (online)

# Take Home Messages: Diagnosis of NAFLD

- The diabetes epidemic will worsen in the coming decade and will fuel the epidemic of NASH and liver cirrhosis
- This may be prevented by early diagnosis in primary care and endocrinology clinics
- Still significant clinical inertia

- Diagnostic and management algorithms (i.e., Kanwal et al, Gastroenterology 2021, AACE/AASLD 2022) that combine blood tests and imaging will increase the demand for new treatments
- Treatments that reverse the fundamental defects associated with obesity (excess fat mass) or with diabetes (dysfunctional adipose tissue, insulin resistance) will be increasingly used for NAFLD.

Cusi K, 2021 (unpublished)

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