NAFLD: Population in need, clinical trial duration and endpoints

The Children's Memorial Health Institute
Warszawa/ POLAND

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Position statements/ practical guidelines

Diagnosis of Nonalcoholic Fatty Liver Disease in Children and Adolescents: Position Paper of the ESPGHAN Hepatology Committee

JPGN 2012

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NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

JPGN 2017

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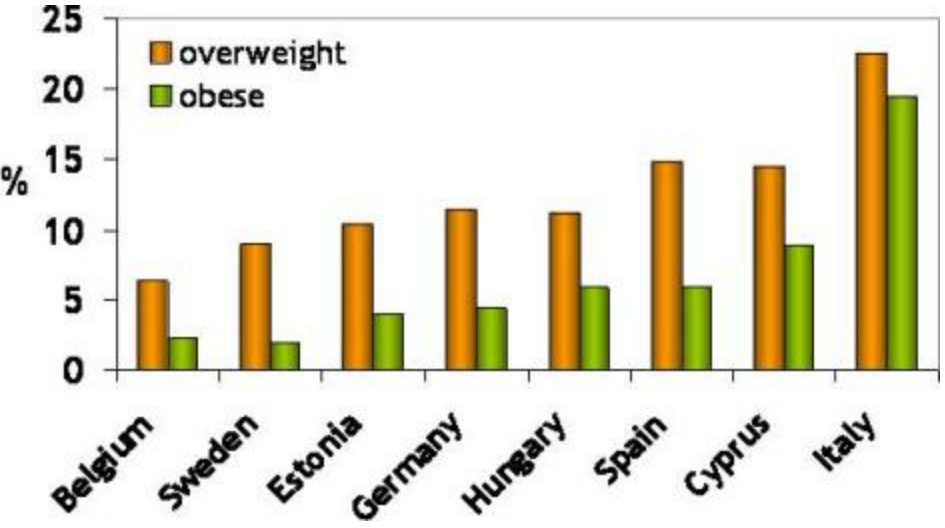
NAFLD and obesity

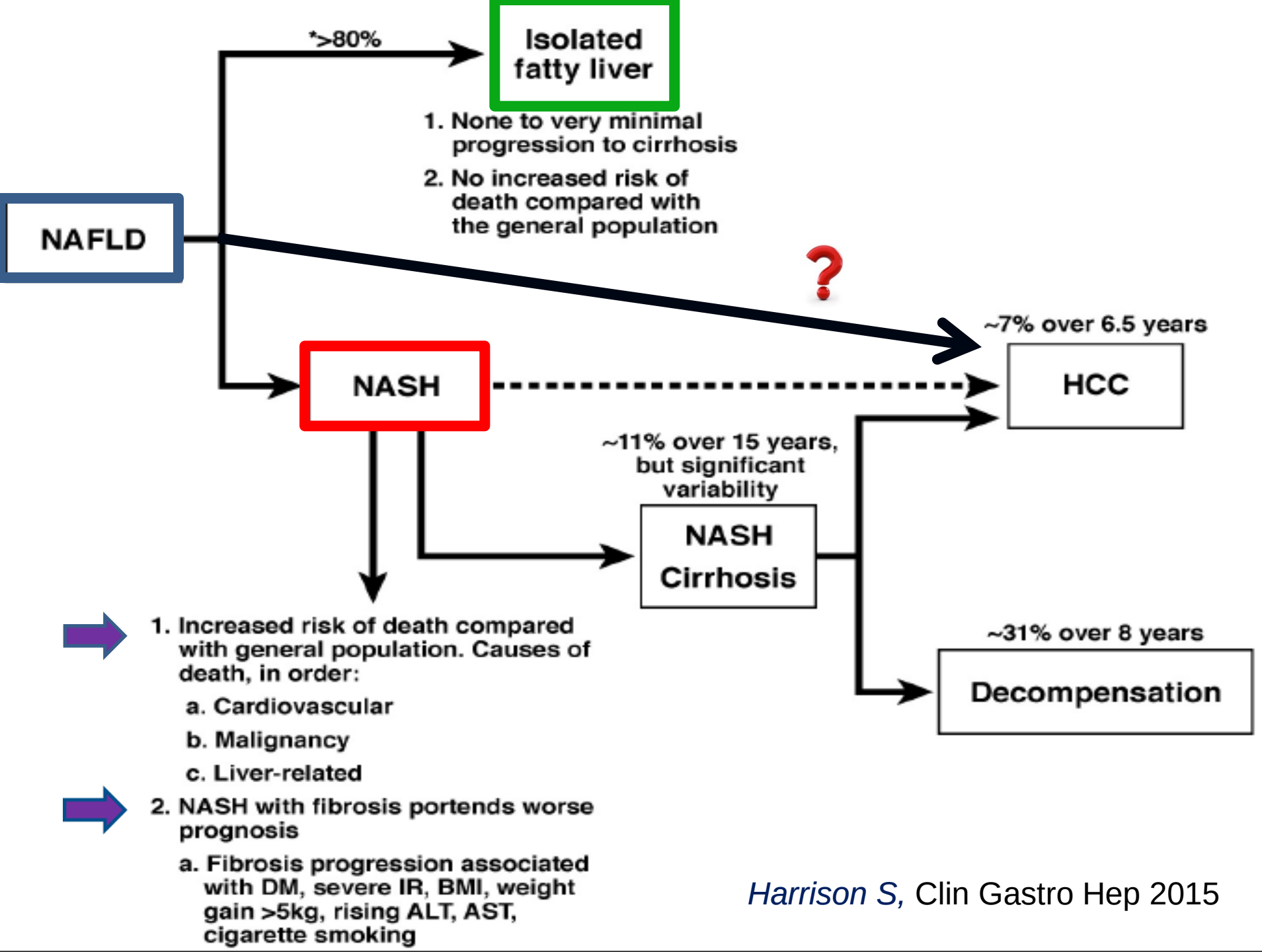


IDEFICS study-childhood obesity

- **NAFLD prevelance in children ≈10%**
  - **autopsy studies in Canada**
  - **more common in older children**
- **NAFLD in obese children≈40%**

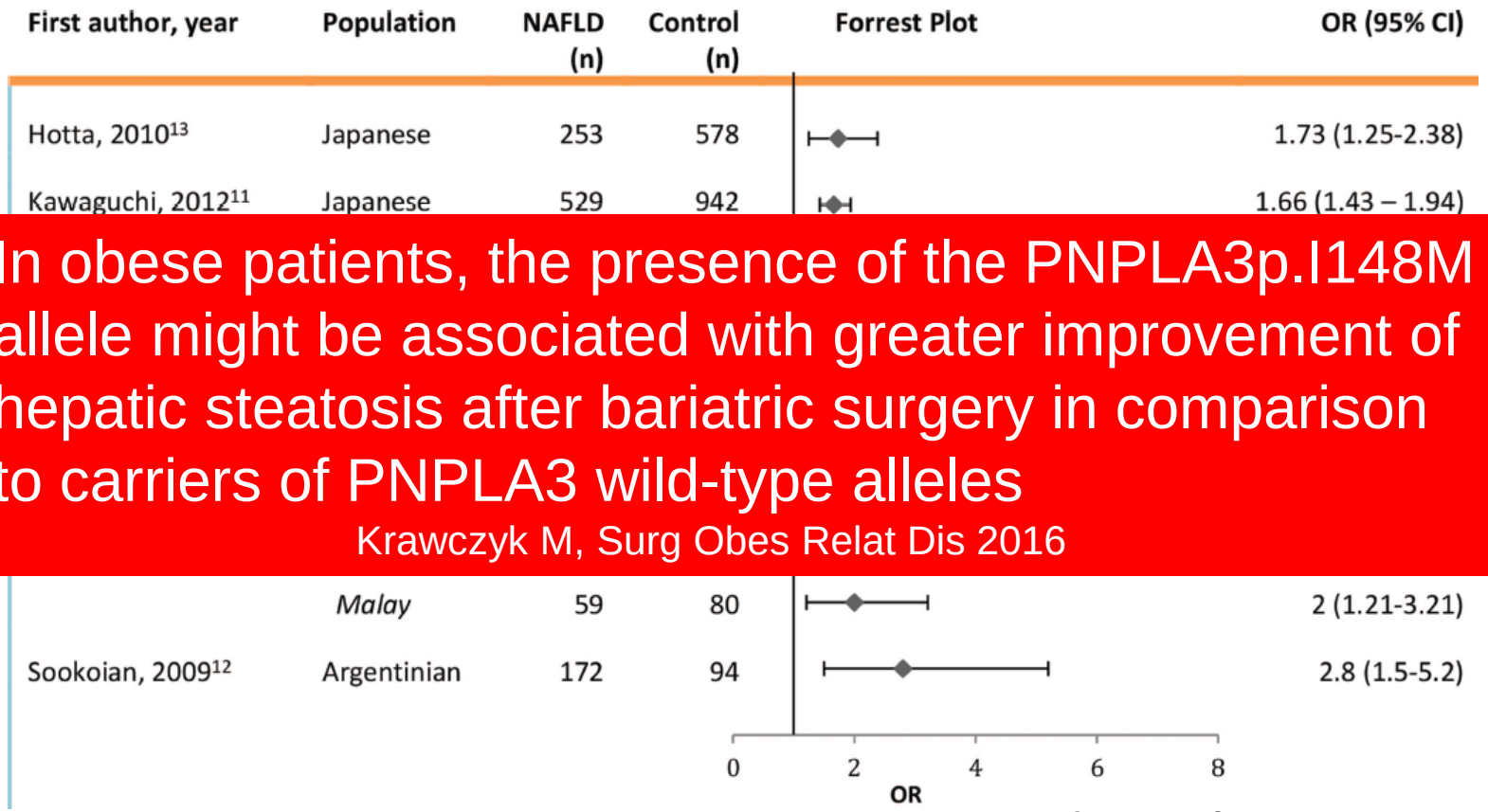
OBESITY

frequency vs severity



Harrison S, Clin Gastro Hep 2015

Population at risk-genetic factors?



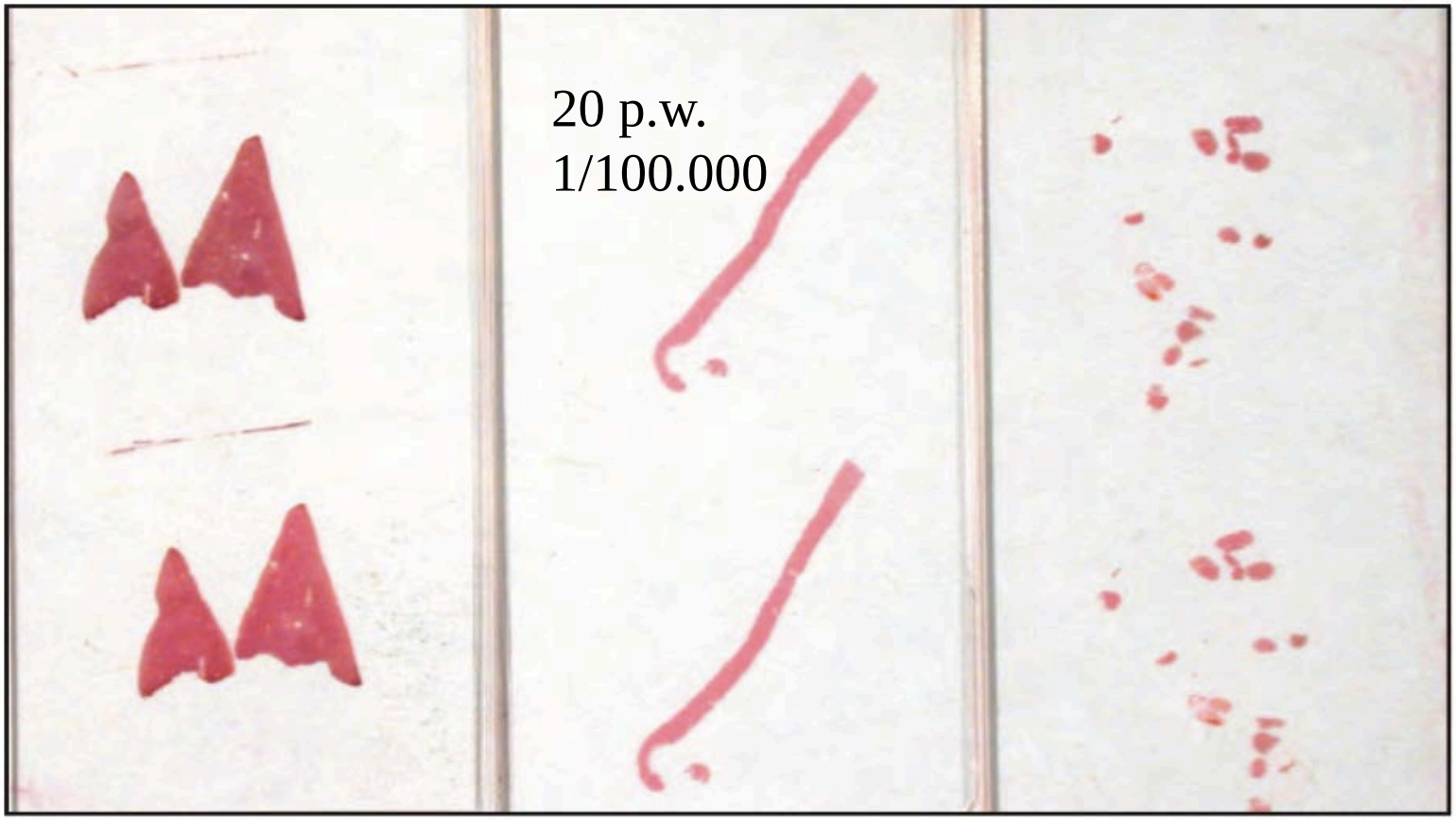
In obese patients, the presence of the PNPLA3p.I148M allele might be associated with greater improvement of hepatic steatosis after bariatric surgery in comparison to carriers of PNPLA3 wild-type alleles

Krawczyk M, Surg Obes Relat Dis 2016

- PNPLA3 p.I148M variant associated with NAFLD
  - No clear association with histology and disease severity

Wood KL, BMJ Open Gastroenterology 2015

Is liver biopsy representative for the organ damage?



Management of an obese child with NAFLD

NAFLD suspected or diagnosed

Response to weight reduction therapy

No response to weight reduction therapy

<u>Defining risk of NASH/fibrosis</u>

Family history, highly increased ALT etc.

Consider liver biopsy

Consider medication:

Metformin- when insulin resistance

DHA, selected probiotics- when advanced steatosis on US and high fibrosis risk

Vitamin E- high fibrosis risk

Valerio Nobili & Piotr Socha; JPGN 2018

Population in need for pharmacotherapy

- **Advancing liver disease**
  - NASH, advanced and/or mild fibrosis?
  - Significant steatosis?
- **Defining the advancing liver disease**
  - Liver biopsy?
  - Surrogate markers
    - US combined with ALT?
    - More specific markers

End points

Histology

- Limited clinical indications
- Sampling error

Non-invasive

- Moderate specificity and sensitivity
- Many to choose
- Some promising markers still under investigation

- Still… the only justified for ethical reasons?

Examples of end points for treatment of NAFLD

DHA trial

•Primary: improvement of US steatosis

• Secondary: insulin resistence, ALT, TG, weight

- Nobili V, Arch Dis Child 2011

DHA/EPA trial

- Primary: decrease of ALT
- Secondary: US steatosis, GGTP, leptin, adiponectin, insulin resistance
  - Janczyk W, J Pediatr 2015

TONIC trial

- Primary- decrease of ALT,
- Secondary- **histology**
  - Lavine JE, JAMA 2011

Vitamin D+DHA trial

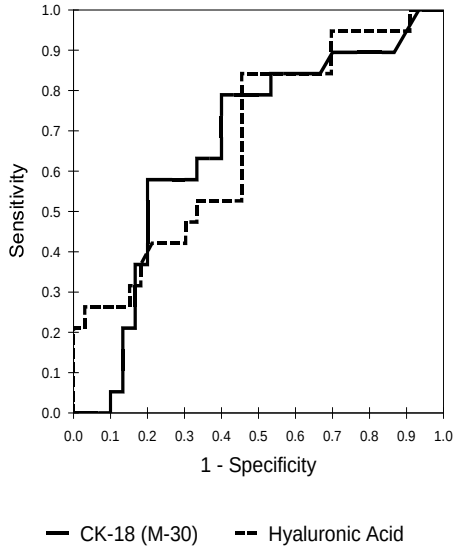
- Primary: **histology** (NAFLD score)
- Secondary: insulin-resistance, lipid profile, ALT
  - Corte CD, PlosOne 2017

Assessment of fibrosis: Metaanalysis- elastography+CK18

- Transient elastography
  - good in diagnosing F ≥ 3
    - (85% sensitivity, 82% specificity)
  - excellent inF4
  - moderate accuracy for F ≥ 2
    - (79% sensitivity, 75% specificity)
- CK18 (serum)
- moderate accuracy for diagnosing NASH
  - 66% sensitivity, 82% specificity
  - when optimal cut-offs are used, sensitivity improves to 82%, while specificity is 98%.

Kwok R. Aliment Pharmacol Ther 2014

Receiver Operating Characteristic Analysis

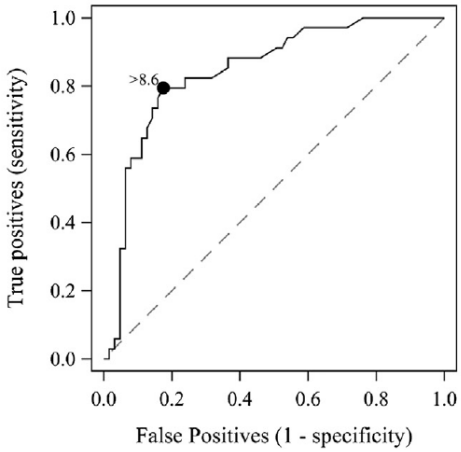


Lebensztejn D, Acta Biochim Pol. 2011

Fibroscan to detect significant fibrosis and steatosis in children

- 128 patients with liver biopsy
- 8.6 kPa optimal cutoff to predict significant fibrosis

Lee CK,
J Pediatr 2013



N*	METAVIR Stage F0 – F2 (N = 63)	F3 – F4 (N = 34)	P
97	6.1 (4.9, 7.6)	14.6 (8.9, 22.6)	<.0001

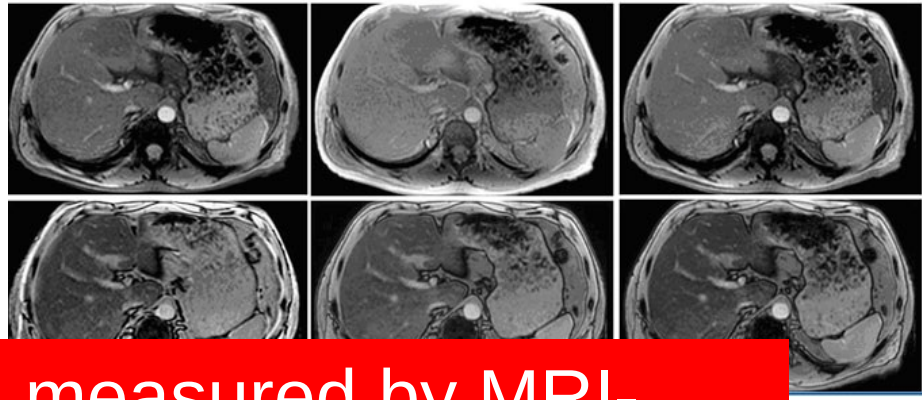
*Group 2 (serum + TE)

TE (kPa)

- CAP to detect steatosis- cut off values discussed:
  - 225 dB/m- compared to histology in 69 ch.
    - Deasai NK, J Pediatr 2016
  - 249 dB/m from >300 children with obesity
    - Ferraioli G, BioMed Central 2017

MRI: steatosis and fibrosis

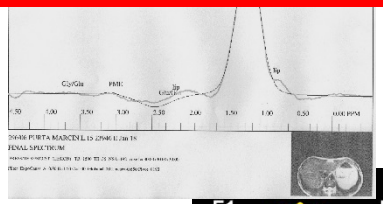
- MRI-imaging
  - **Fat** fraction assesment
    - very high sensitivity and specificity
    - steatosis> 5% detected



- MRI
  - 05
  - Comparable to CAP

Higher liver fat content, measured by MRI-PDFF, is associated with fibrosis progression.

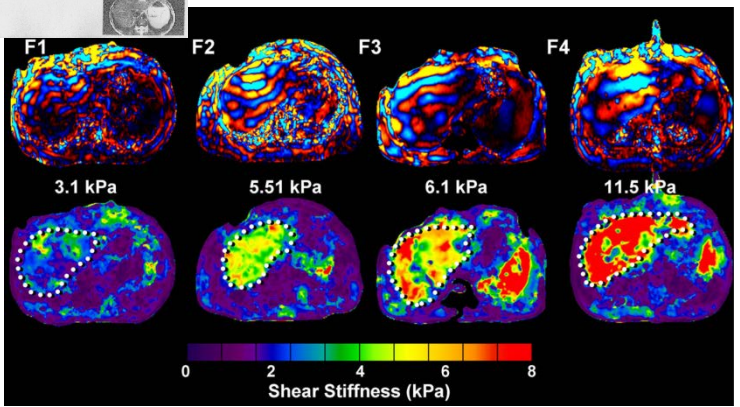
- Ajmera V, Gastroenterology 2018



Karlas T. PLOS One 2014

- MR elastography
  - AUROC for staging **fibrosis** F1-F4: 0.94, 0.97, 0.96, and 0.97

Guo Y, Metaanalysis.Abdom Imaging 2014

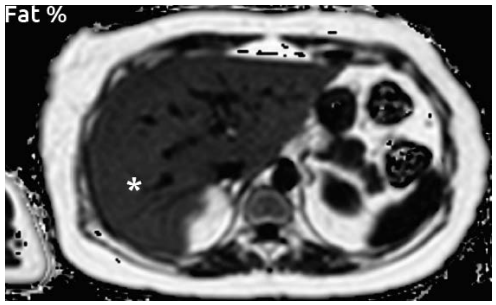


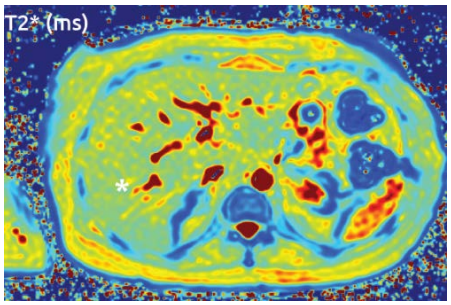
MRI elastography

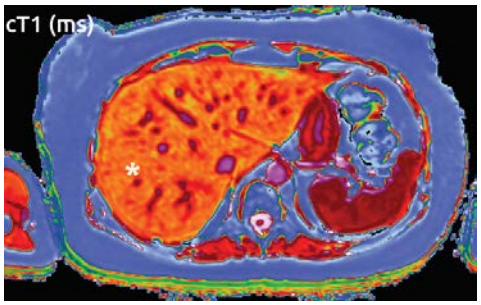
- Under investigation in children
- Sedation needed in young children
- Expensive
- It requires specific hardware and software
- Experience in children
  - 90 children with NAFLD
    - *Schwimmer JB, Hepatology 2017*
  - 86 pts with liver biopsy, good performance, steatosis as a confounding factor
    - *Trout TE, Radiology 2018*

A virtual biopsy using Liver*MultiScan*

Kids4Life project



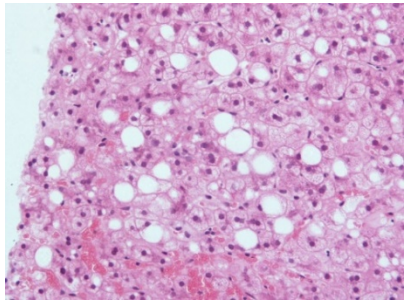


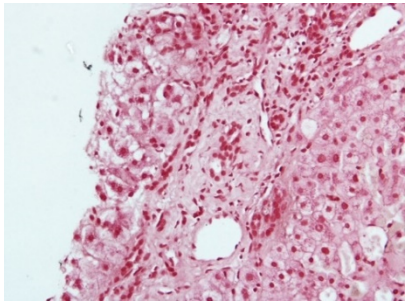


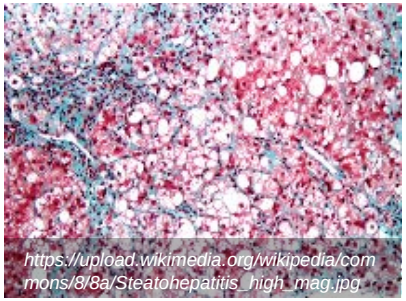
MRI-PDFF

T2* map

Corrected T1 / LIF Score







cT1/LIF score is associated with clinical outcomes (unlike fat and iron)
LIF <2 (cT1 875ms) has 100% NPV – can be used to stratify patients at risk

- **Pavlides M, J Hepatol 2016**

Children's Memorial Health Institute

LiverMultiScan Discover

JOURNAL OF HEPATOLOGY
The Home of Liver Research

MRI – a crystal ball for your liver's future?

In a prospective study at the University of Oxford, 112 patients with chronic liver disease (n = 112) were subjected to MR imaging and standardised multiparametric analysis. MRI findings (Liver Inflammation and Fibrosis score, iron, fat) were predictive for future liver-related clinical events such as ascites, cancer or death.

Fibrotic markers

Biomarker	formula
Fibrotest	α-2-makroglobulin, γGT, apolipoprotein A1, haptoglobin, bilirubin, age, sex
Forns Index	7.811 - 3.131 x ln(PLT) + 0.781 x ln(GGT) + 3.467 x ln(age) - 0.014 x (cholesterol)
APRI	AST (/ULN)/PLT (109/L) x 100
FibroSpect	α-2-makroglobulin, hialuronic acid and TIMP-1
Enhanced Liver Fibrosis score (ELF)	Hialuronic acid, MMP-3 and TIMP-1
Fibroindex	1.738 - 0.064 x (PLT [104/mm3]) + 0.005 x (AST [IU/L]) + 0.463 x (gammaglobulin [g/dl])
Fibrometer	PLT, INR, AST, α-2-makroglobulin, hialuronic acid, urea and age
FIB-4	age x AST [U/L]/(PLT [109/L] x (ALT [U/L]
NAFLD Fibrosis Score	(-1.675 + 0.037 x age + 0.094 x BMI (kg/m2) + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT - 0.013 x PLT (x109/L) - 0.66 x albumin [g/dl])
BARD score	(BMI ≥28 = 1; AST/ALT ≥0.8 = 2; diabetes= 1; score ≥2, advanced fibrosis= 17)

Clinical trial duration

- VSL#3 trial: **4 months**
  - *Alisi A, Aliment Pharmacol Ther. 2014*
- TONIC trial (vitamin E& metformin): **96 weeks**
  - *Lavine JE, JAMA 2011*
- DHA/EPA study: **6 months**
  - *Janczyk W, J Pediatr 2015*
- DHA study: **6 months**
  - *Nobili V, Arch Dis Child 2011*
- Vitamin D+DHA study: **12 months**
  - *Corte DC, PlosOne 2017*

Trial duration and end points

Short duration: better compliance
Longer duration: better end points

3-4 months

6-12 months

>1 year

Suggested solutions

- **Population**
  - Preferentially selected based on liver biopsy
  - Genetic factors and risk/surrogate markers to consider
- **End points**
  - Preferentially surrogate markers
- **Duration**
  - Min. 1 year for fibrosis as outcome parameter
  - Min. 6 months for combined parametres