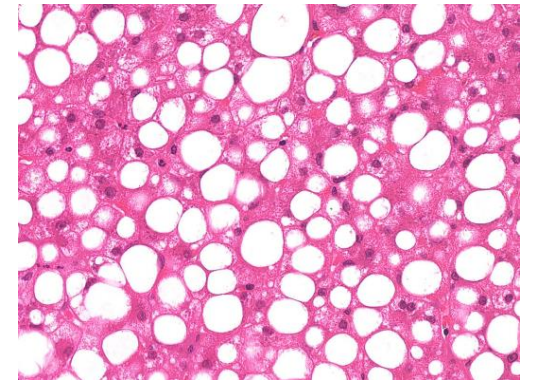


MASLD/MASH, FIB-4 en elastografie



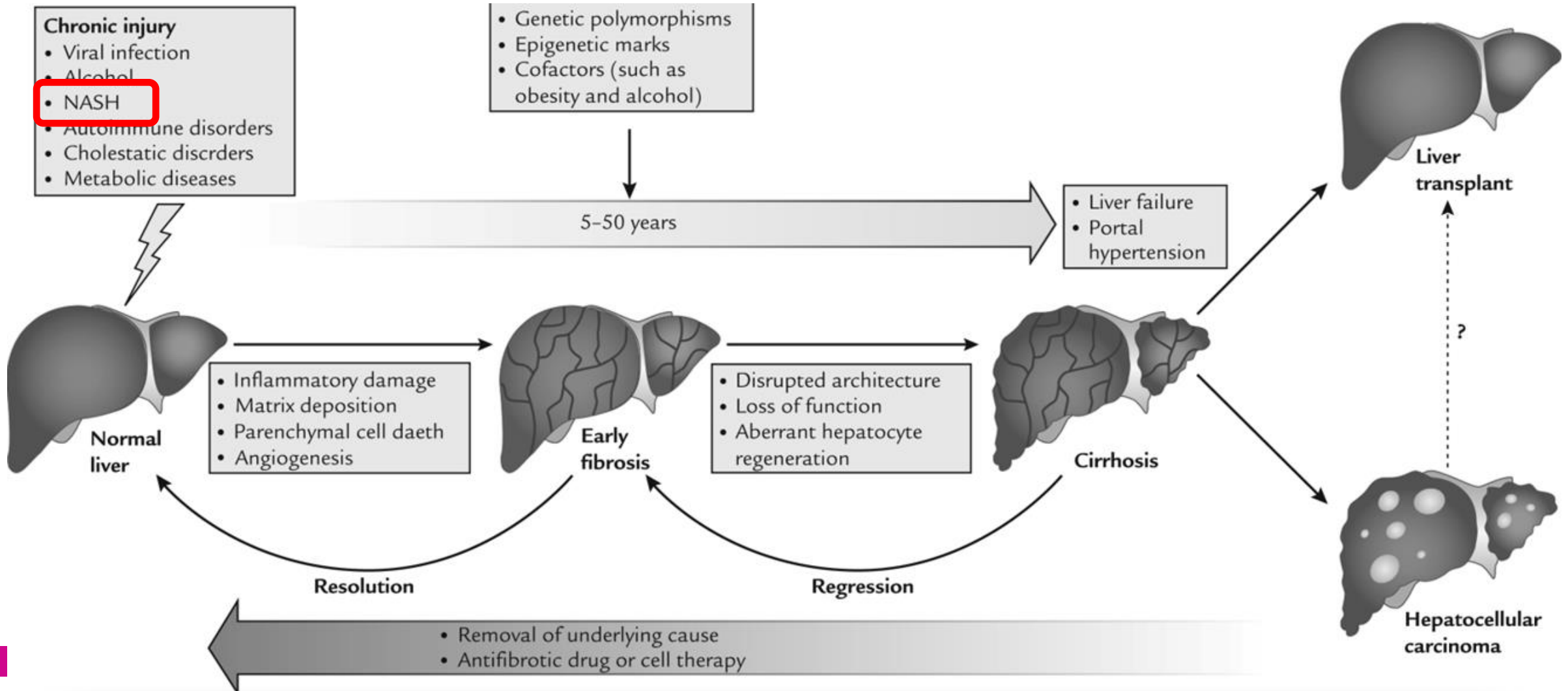
Dr. Brecht Pauwels
Gastro-enteroloog
De Gastrogroep - VITAZ



Planning

- Evolutie chronische leverlijden
- NAFLD to MASLD: nieuwe nomenclatuur
- Prevalentie en natuurlijk beloop
- Screening: waarom, wie en hoe
- Praktische aanbeveling

Evolutie chronisch leverlijden

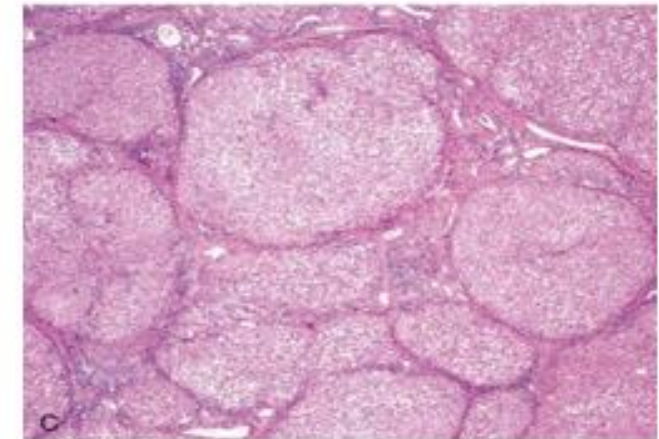
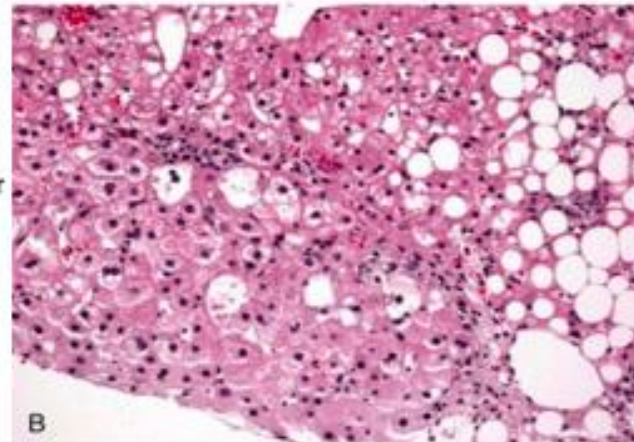


Verzameln naam voor spectrum van histologische afwijkingen



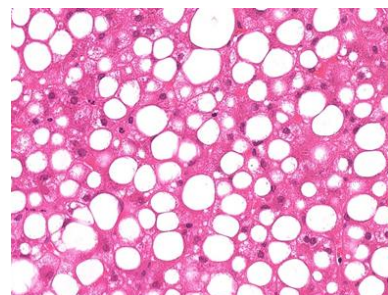
NASH gerelateerde CIRROSE

NASH
(non-alcoholic steatohepatitis) =
Steatose
Inflammation
Ballooning

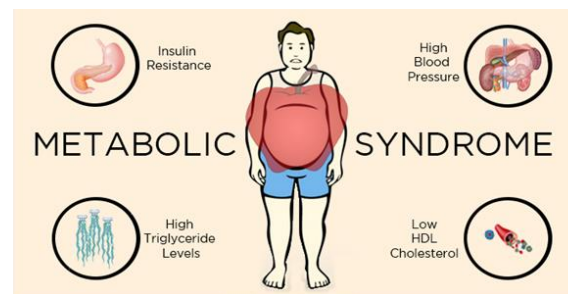


MASLD

=



+



+

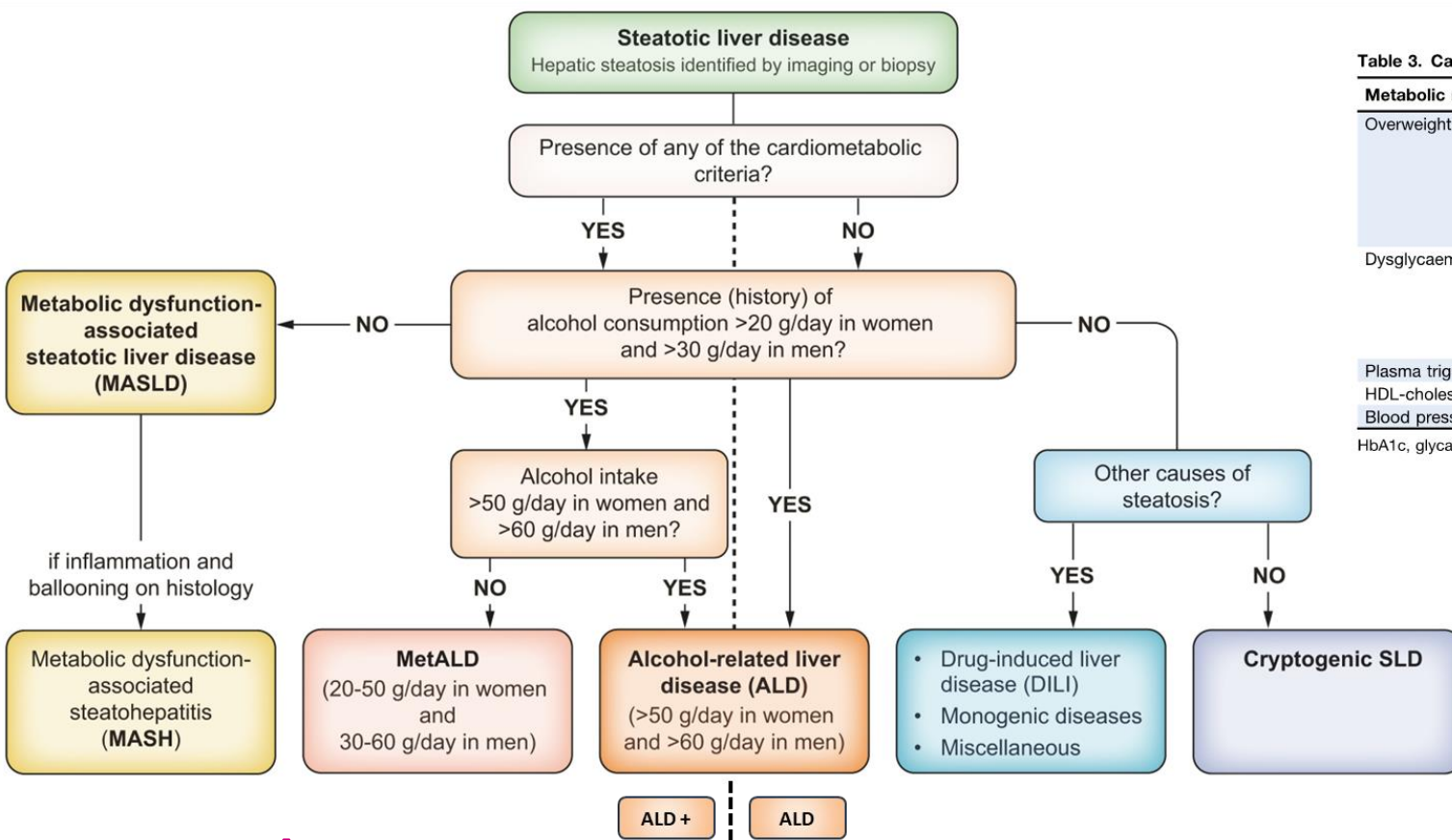


Table 3. Cardiometabolic risk factors in the definition of MASLD.²

Metabolic risk factor	Adult criteria
Overweight or Obesity	Body mass index ≥25 kg/m ² (≥23 kg/m ² in people of Asian ethnicity) Waist circumference • ≥94 cm in men and ≥80 cm in women (Europeans) • ≥90 cm in men and ≥80 cm in women (South Asians and Chinese) • ≥85 cm in men and ≥90 cm in women (Japanese)
Dysglycaemia or type 2 diabetes	<u>Prediabetes</u> : HbA _{1c} 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or glucose during OGTT 7.8-11 mmol/L (140-199 mg/dl) or <u>Type 2 diabetes</u> : HbA _{1c} ≥48 mmol/mol (≥6.5%) or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl) or during OGTT ≥11.1 mmol/L (≥200 mg/dl) or <u>Treatment for type 2 diabetes</u>
Plasma triglycerides	≥1.7 mmol/L (≥150 mg/dl) or lipid-lowering treatment
HDL-cholesterol	≤1.0 mmol/L (≤39 mg/dl) in men and ≤1.3 mmol/L (≤50 mg/dl) in women or lipid-lowering treatment
Blood pressure	≥130/85 mmHg or treatment for hypertension

HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.

NAFLD

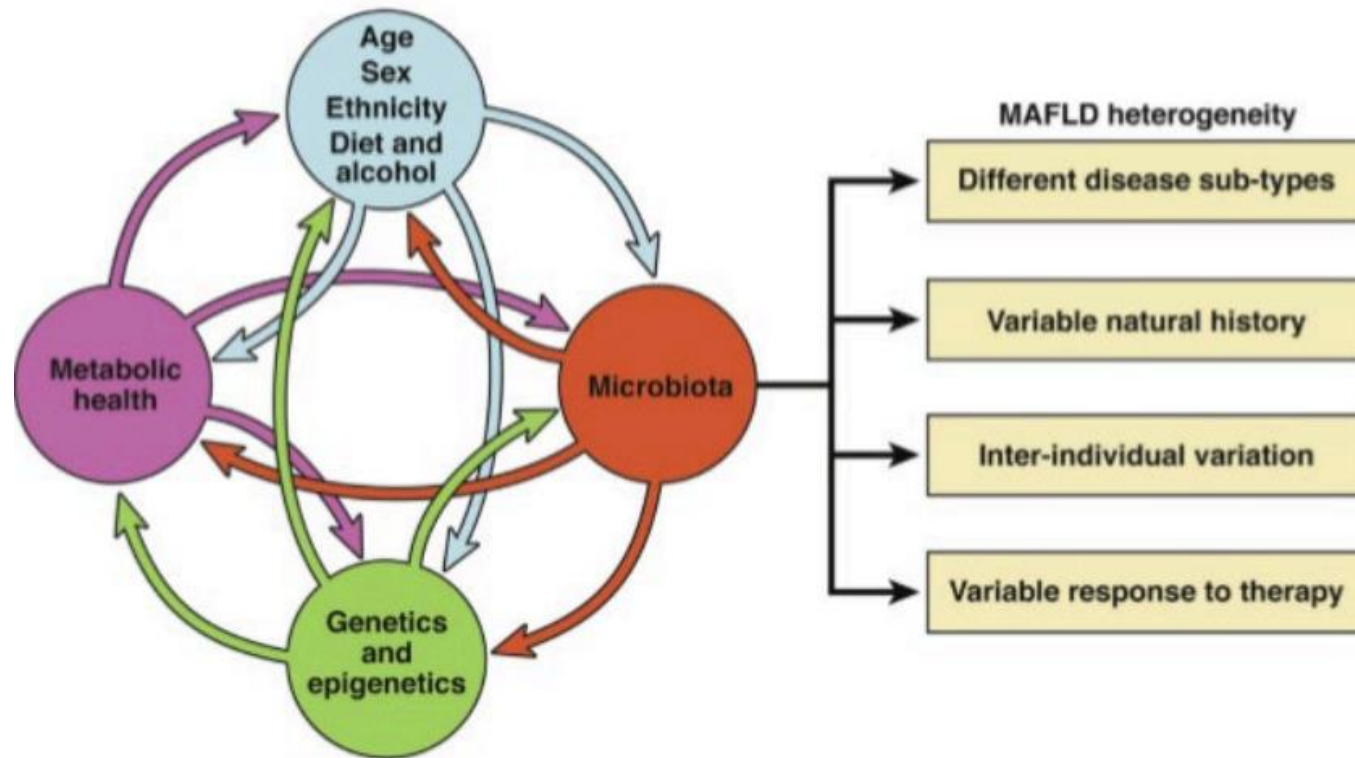
Non-alcoholic fatty liver disease

... MAFLD ...

MASLD

Metabolic dysfunction associated steatotic liver disease

Grote heterogeniteit van ziektebeeld met grote inter-individuele verschillen



NAFLD

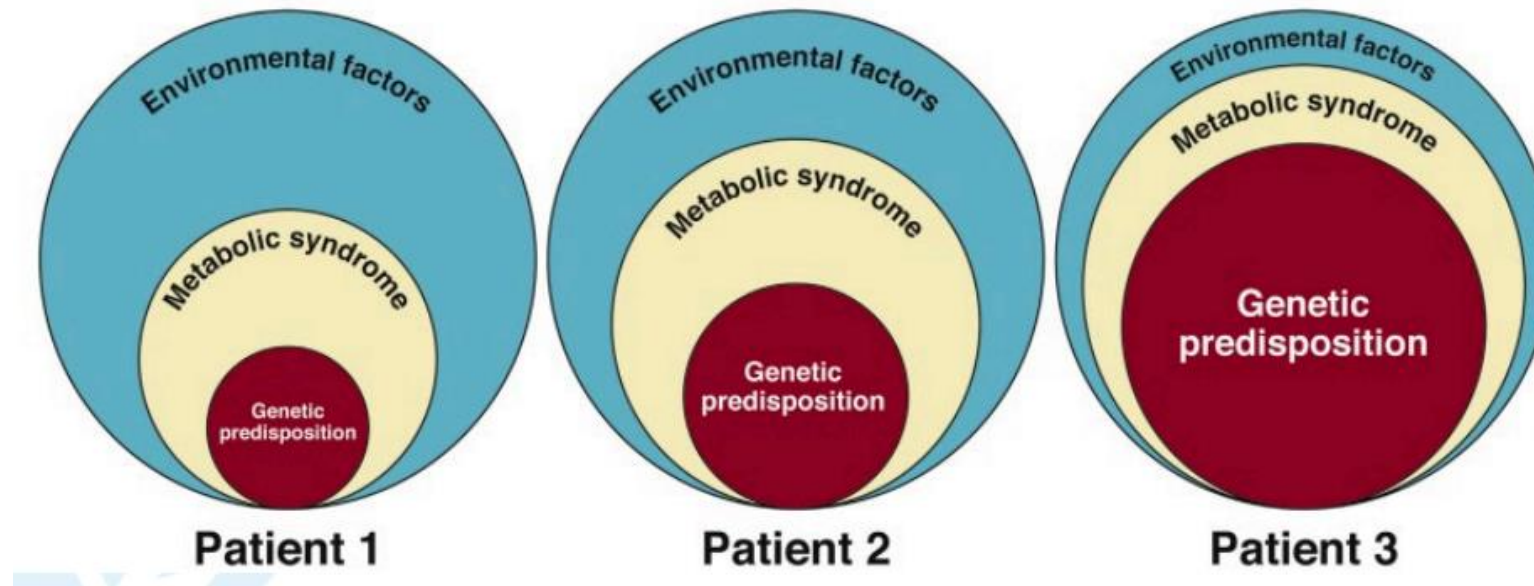
Non-alcoholic fatty liver disease

... MAFLD ...

MASLD

Metabolic dysfunction associated steatotic liver disease

Grote heterogeniteit van ziektebeeld met grote inter-individuele verschillen



NAFLD

Non-alcoholic fatty liver disease

... MAFLD ...

MASLD

Metabolic dysfunction associated steatotic liver disease

Grote heterogeniteit van ziektebeeld met grote inter-individuele verschillen

Steatosis >5%

Exclusion of Alcohol

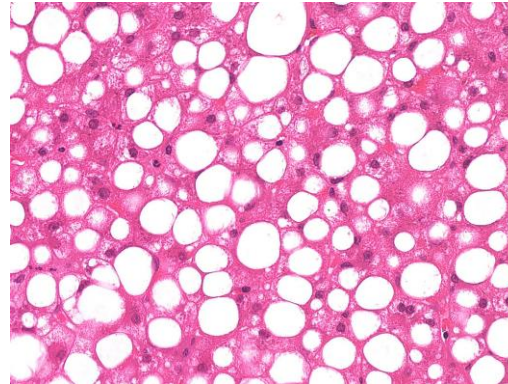
Exclusion of other causes

e.g. HCV or Medication

"Negative"

Stigmatiserend

(Liver biopsy)



Steatosis (>5%)

Exclusion of Alcohol

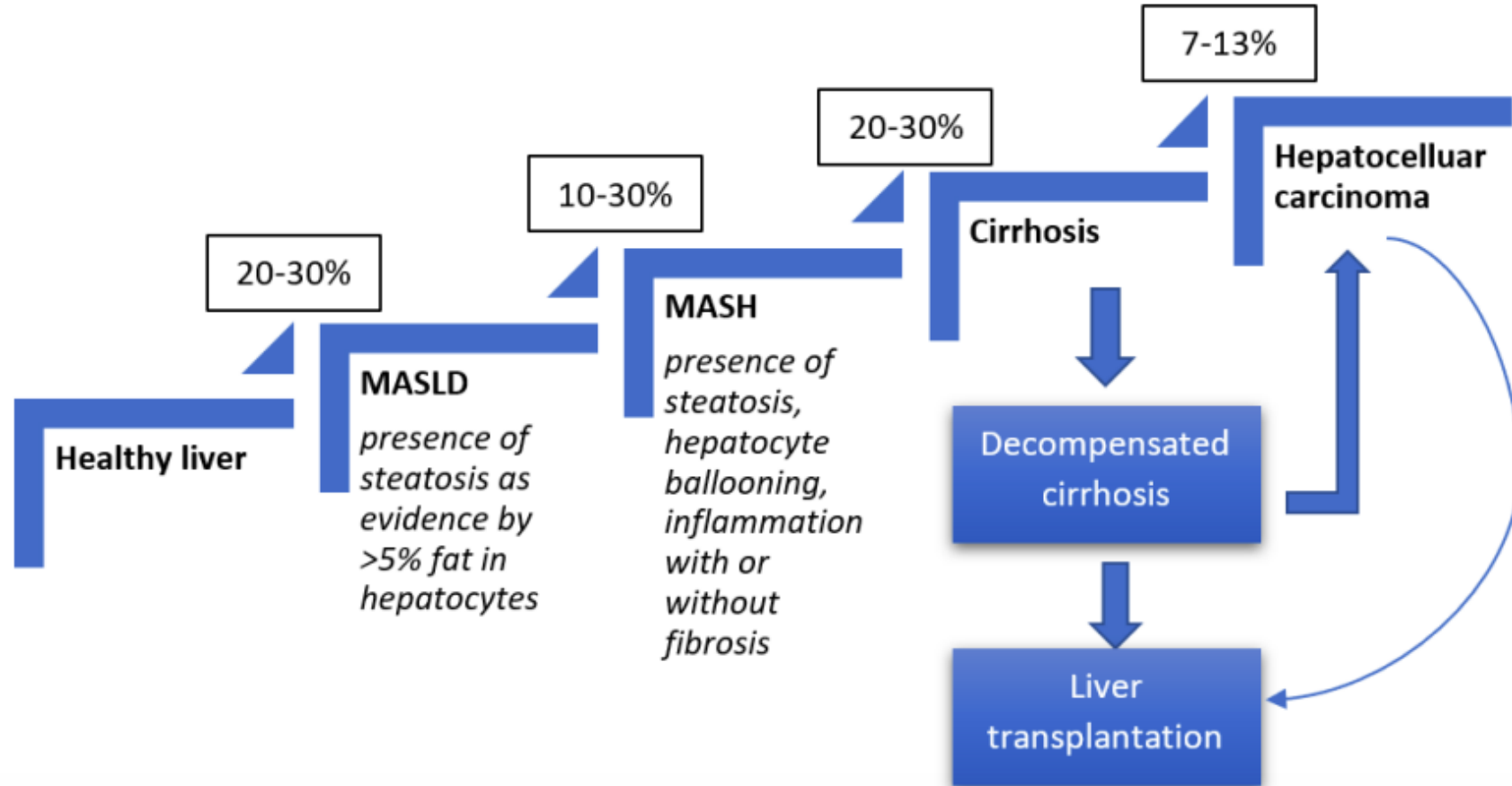
> **Introduction of MetALD**

Combinations possible

"Positive"

(Non-invasive)

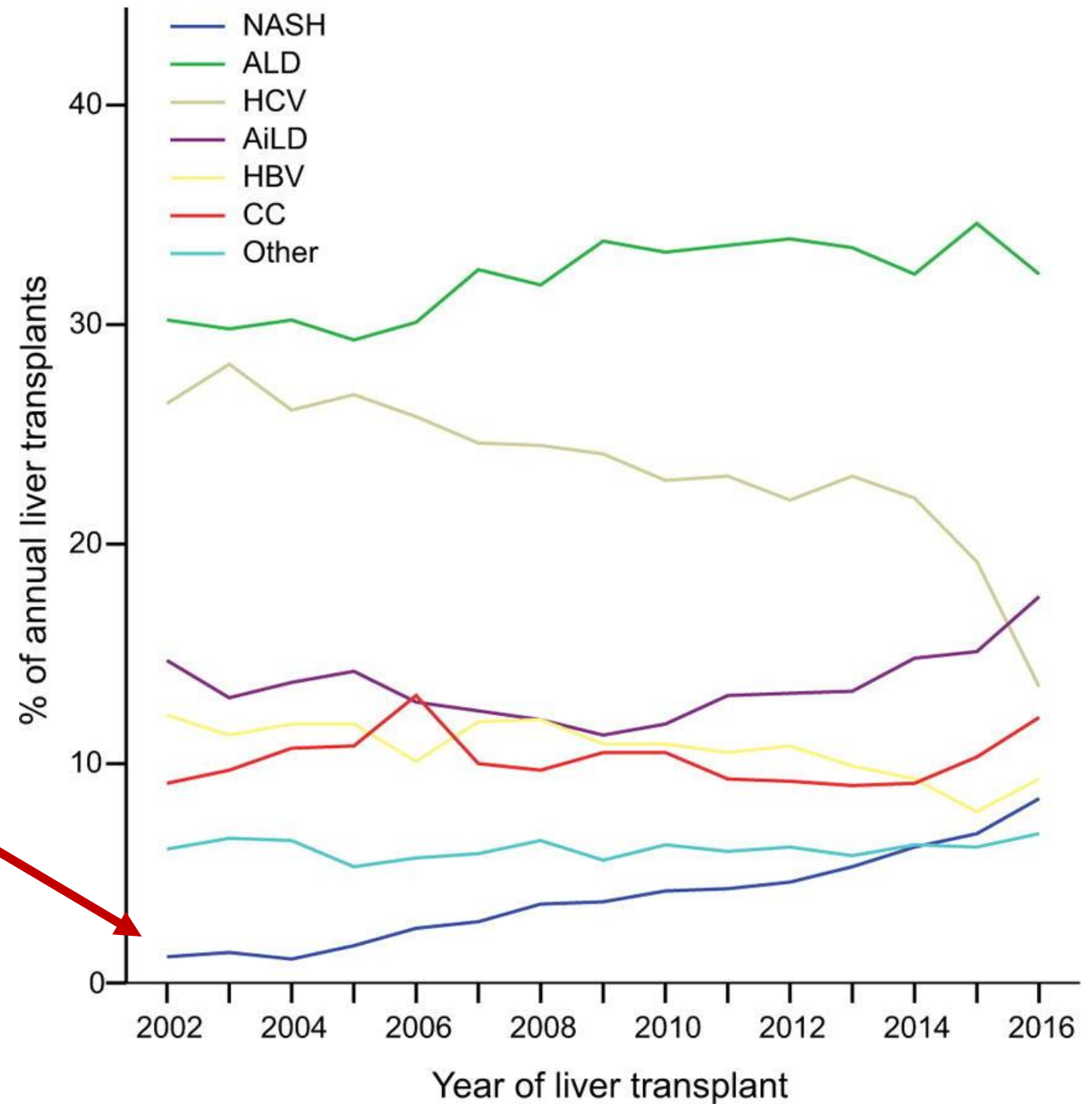
Spectrum van MASLD



Indications LTX

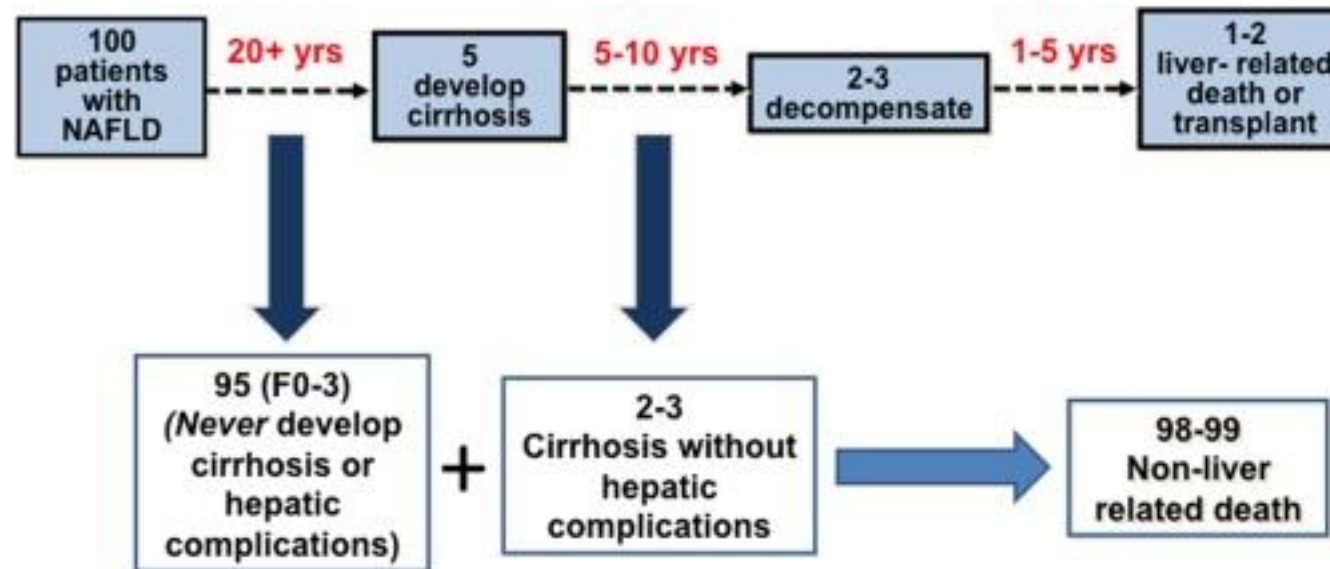
European Liver

Transplant Registry



Haldar, Debashis et al. Journal of Hepatology

Natuurlijk verloop van MASLD

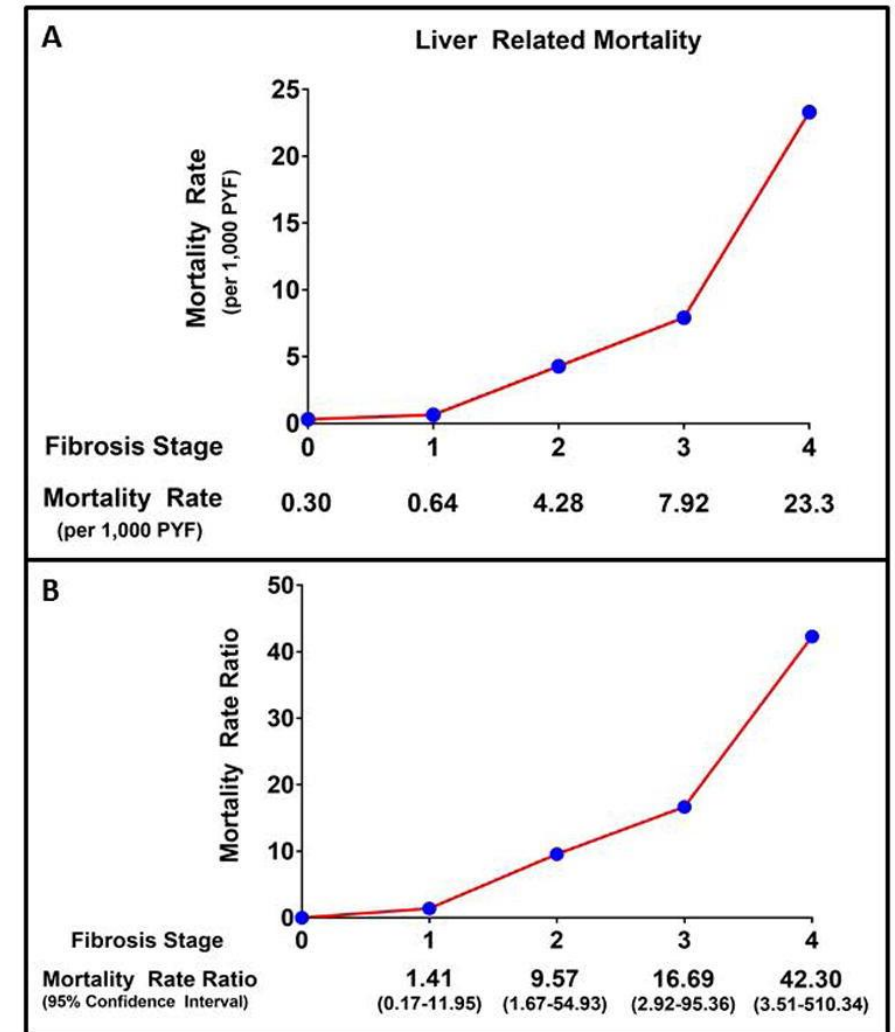


BUT 1 billion adults with NAFLD coupled with a lifetime risk of ~2% for liver-related mortality will eventually translate into ~20,000,000 liver-related deaths among patients currently alive with NAFLD.

Screening naar fibrose: waarom?

- Exponentiële stijging van lever- en overall mortaliteit bij toename van fibrose stadium

Dulai *et al* Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017

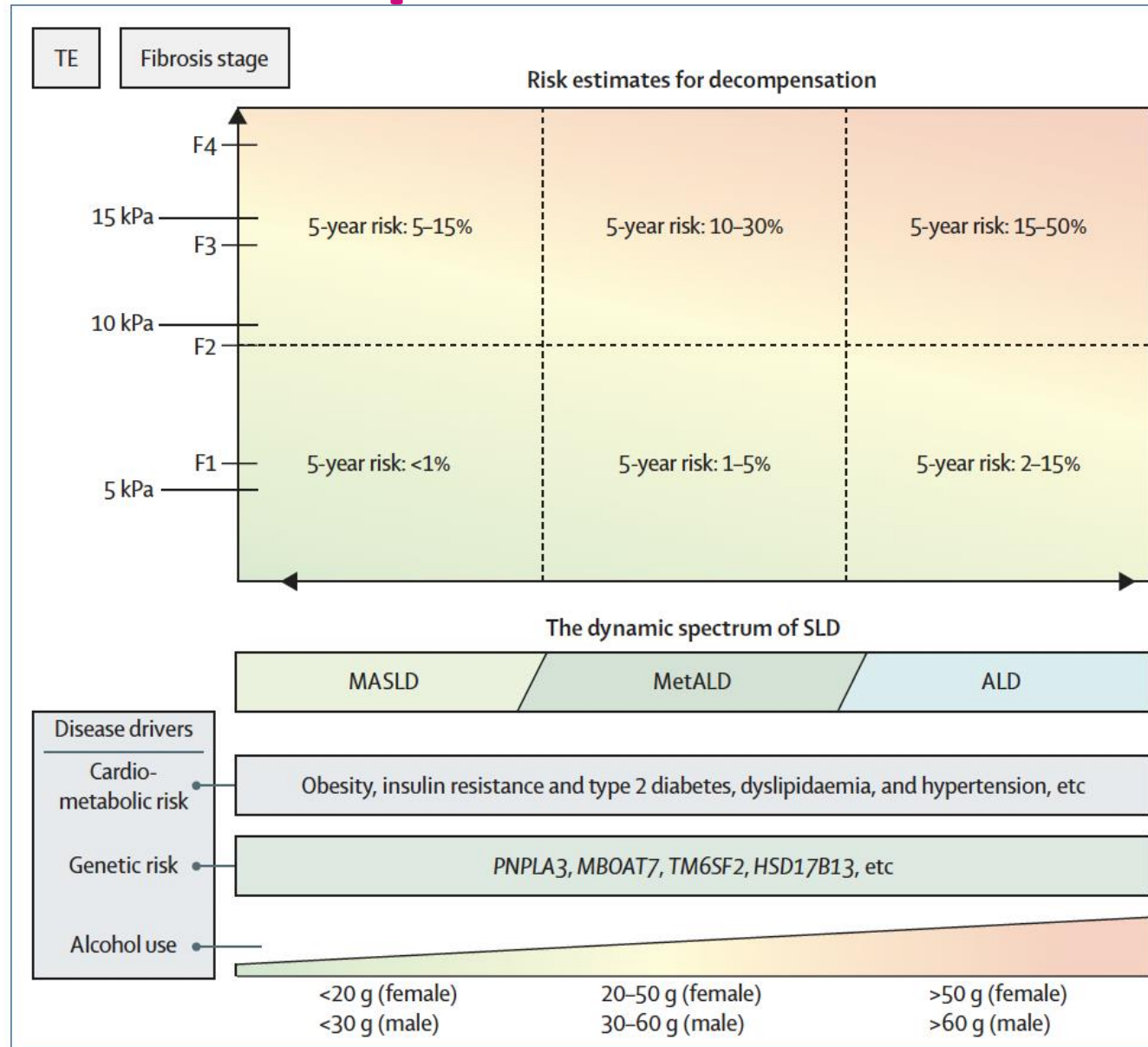


Clinical stages

Normal Liver		Precirrhotic Chronic Liver Disease			Compensated Cirrhosis	Decompensated Cirrhosis
F0	F1	F2	F3	F4		

Histology
(METAVIR)

Dynamisch spectrum MASLD-MetALD-ALD



Alcoholgebruik
interageert met
metabole RF en impact
op risico op
decompensatie

Israelsen et al. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet GI Hep 2023

Screening: wie?

Patiënten met verhoogd risico op leverlijden

- Context van metabool syndroom: hypertensie, T2DM, hyperlipedemie, ...
- Risicofactoren voor chronische HBV/HCV
- High-risk alcoholgebruik (>14 E/week vrouw, >21 E/wk mannen)
- Familiale belasting voor fibrose obv MASLD (2-3x risico)
- Combinatie van bovenstaande factoren
- Wie niet: indien levensverwachting wordt bepaald door extra-hepatische factoren (vb. oudere leeftijd, maligniteit, cardiovasculaire morbiditeiten,...)

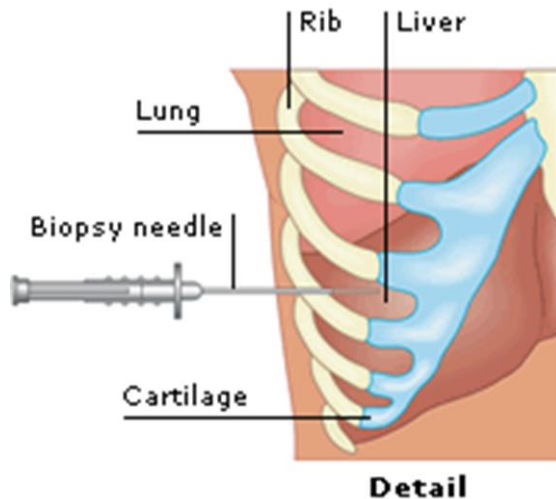
Screening op fibrose: hoe?

- Niet-invasieve testen

Echo +

Vs

- Invasieve test



Serum biomarkers

- AST/ALT ratio
- APRI
- FIB-4
- NAFLD fibrosis score (NFS)

Non Patented

- FibroTest®
- ELF™
- FibroMètre®
- Hepascore

Patented

Elastography techniques



TE



ARFI / 2D SWE



MRE

Availability

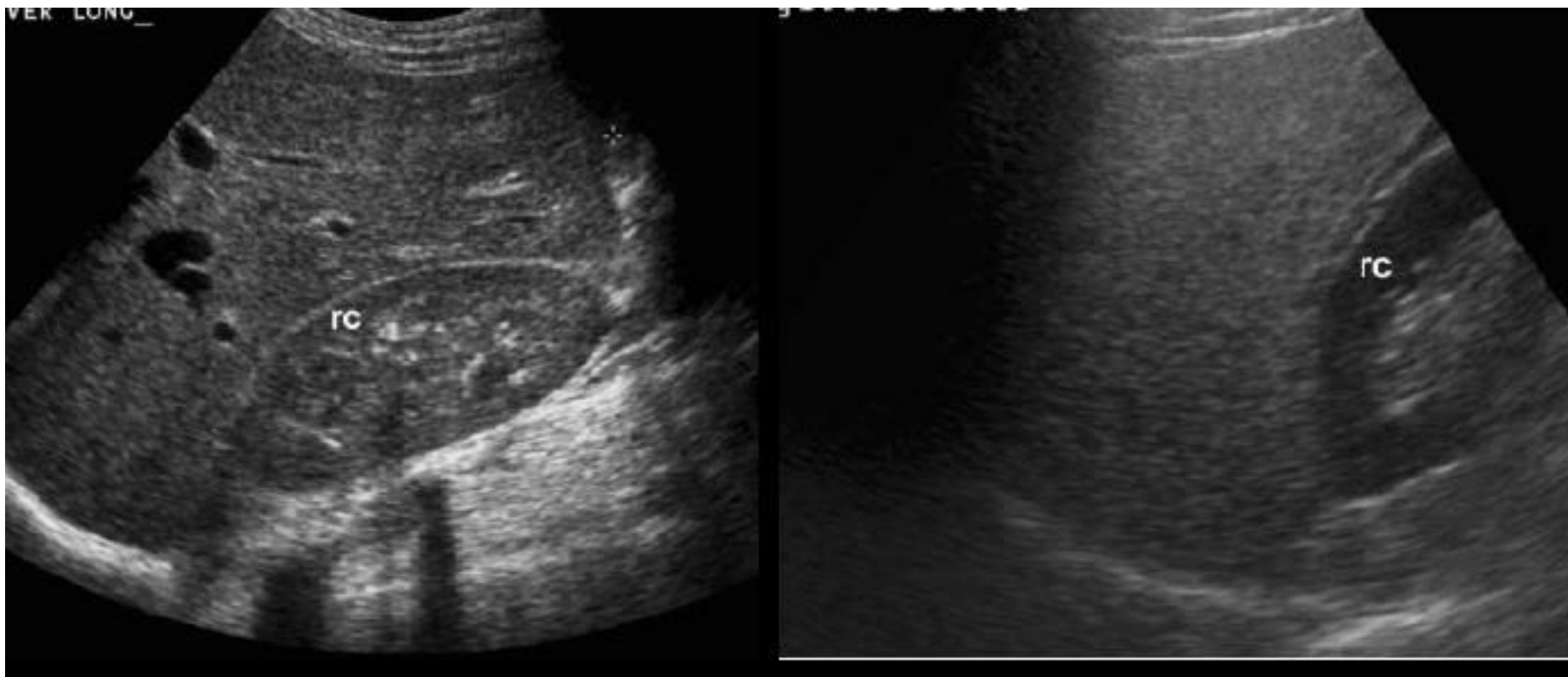
Cost

Primary care

Liver clinics

Niet-invasieve test: beeldvorming

Echo



Niet invasieve test: biochemie

MASLD MEEST VOORKOMENDE OORZAAK VAN AFWIJKENDE LEVERTESTEN BIJ GP'S

Cause	Percentage (n)	GGT [U/L]	ALT [U/L]	AST [U/L]	ALP [U/L]	Bili [μ mol/L]	Alb [g/L]
NAFLD	26.4 (295)	59 (41-88)	38 (27-54)	30 (23-40)	206 (167-266)	9 (6-12)	45 (43-47)
At-risk alcohol intake							
Non-Fatty liver	14.0 (156)	69 (46-115)	30 (22-44)	28 (22-35)	190 (159-238)	10 (7-13)	46 (44-48)
Fatty liver	11.3 (126)	81 (52-148)	46 (33-65)	36 (28-49)	178 (150-218)	9 (8-13)	47 (45-49)
PBC	0.81 (9)	99 (45-186)	15 (20-31)	27 (25-36)	396 (337-463)	7 (6-13)	43 (42-45)
HBV	0.72 (8)	53 (32-418)	92 (49-156)	62 (26-97)	184 (147-242)	8 (5-15)	46 (43-52)
Haemochromatosis							
Homozygote [C282Y or H63D]	0.54 (6)	73 (31-166)	59 (43-79)	39 (32-56)	202 (158-382)	8 (5-23)	46 (45-48)
Comp. heterozygote [C282Y + H63D]	0.36 (4)	56 (25-458)	51 (54-149)	25 (42-238)	121 (75-135)	12 (5-21)	51 (45-53)
Other (inc. cancer, drug, abscess)	0.36 (4)	85 (27-179)	29 (17-58)	31 (18-44)	273 (191-368)	12 (7-18)	44 (39-48)
HCV*	0.17 (2)	x (34, 452)	x (151, -)	x (101, 70)	x (514, 214)	x (8, 8)	x (48, 47)
PSC*	0.17 (2)	x (-, 600)	x (51, 212)	x (33, 124)	x (176, 990)	x (12, 10)	x (47, 46)
A1AD*	0.17 (2)	x (59, 62)	x (41, 50)	x (24, 25)	x (161, 138)	x (11, 12)	x (48, 50)
Unexplained group	45.1 (504)	56 (33-91)	26 (19-38)	26 (22-33)	202 (162-274)	9 (6-13)	45 (43-47)

Niet-invasieve test: biochemie

FIB-4

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

a FIB-4 score <1.45: negative predictive value of 90% for advanced fibrosis

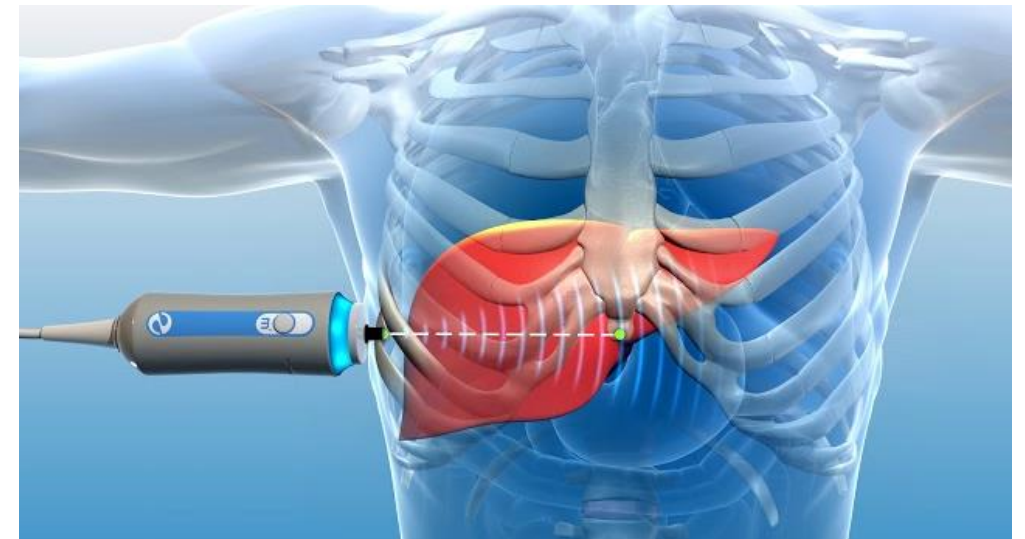
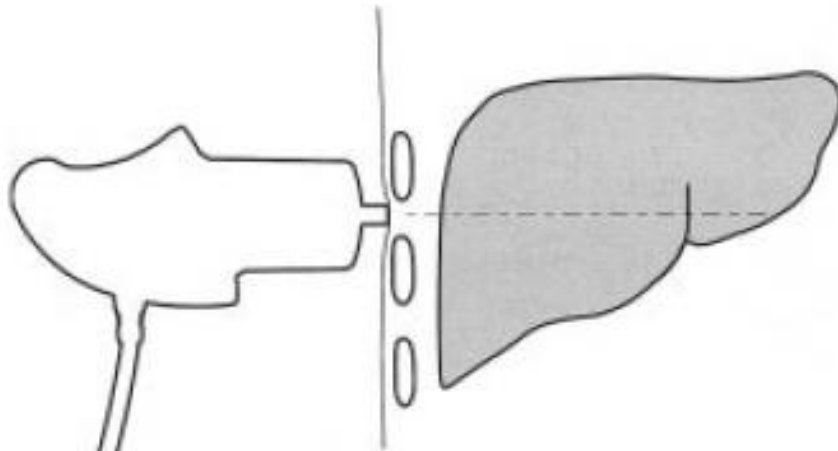
a FIB-4 >3.25: a 97% specificity and a positive predictive value of 65% for advanced fibrosis

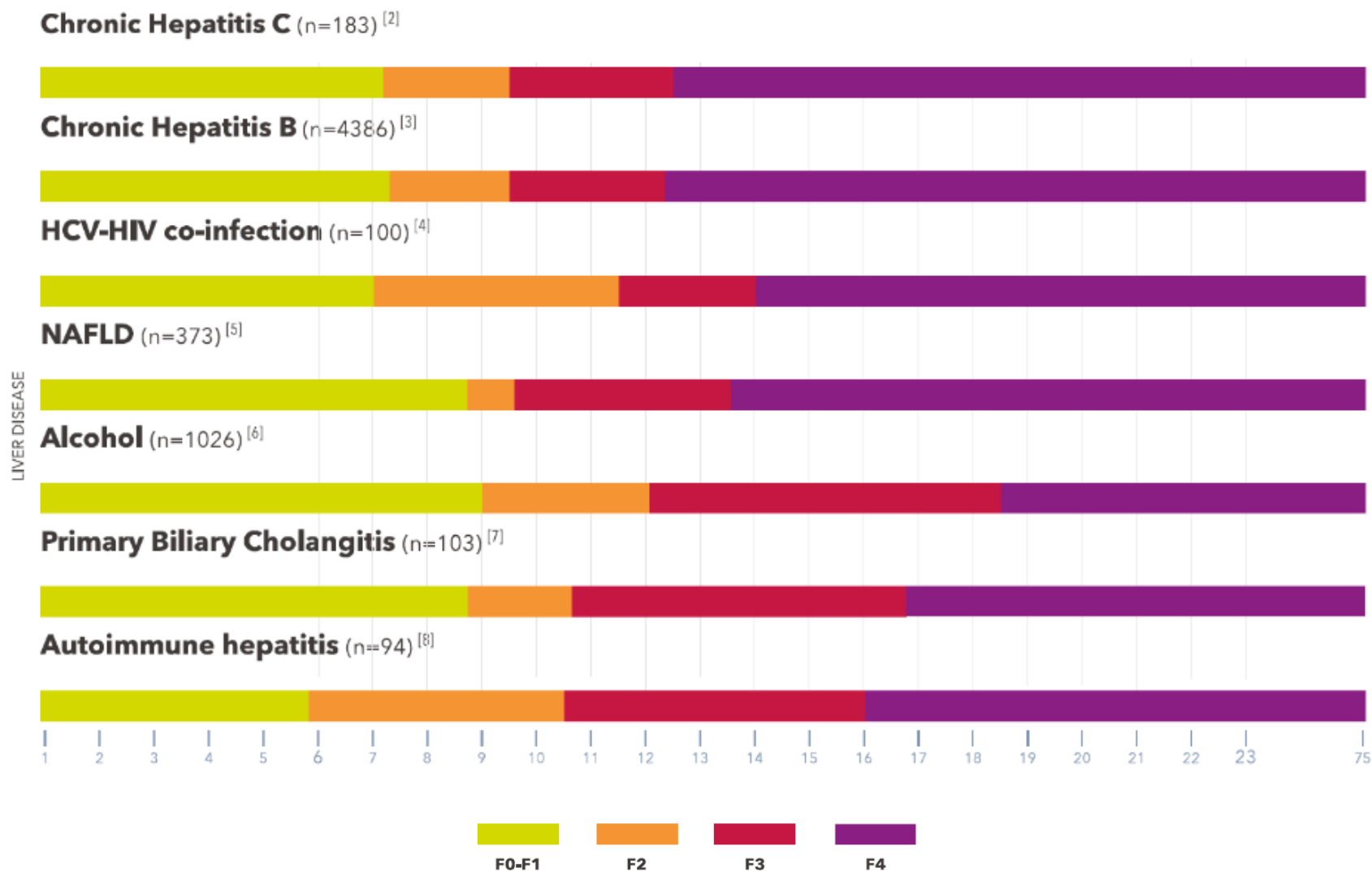
Less reliable scores in patients < 35 years old or > 65 years old

Niet-invasieve testing: elastografie

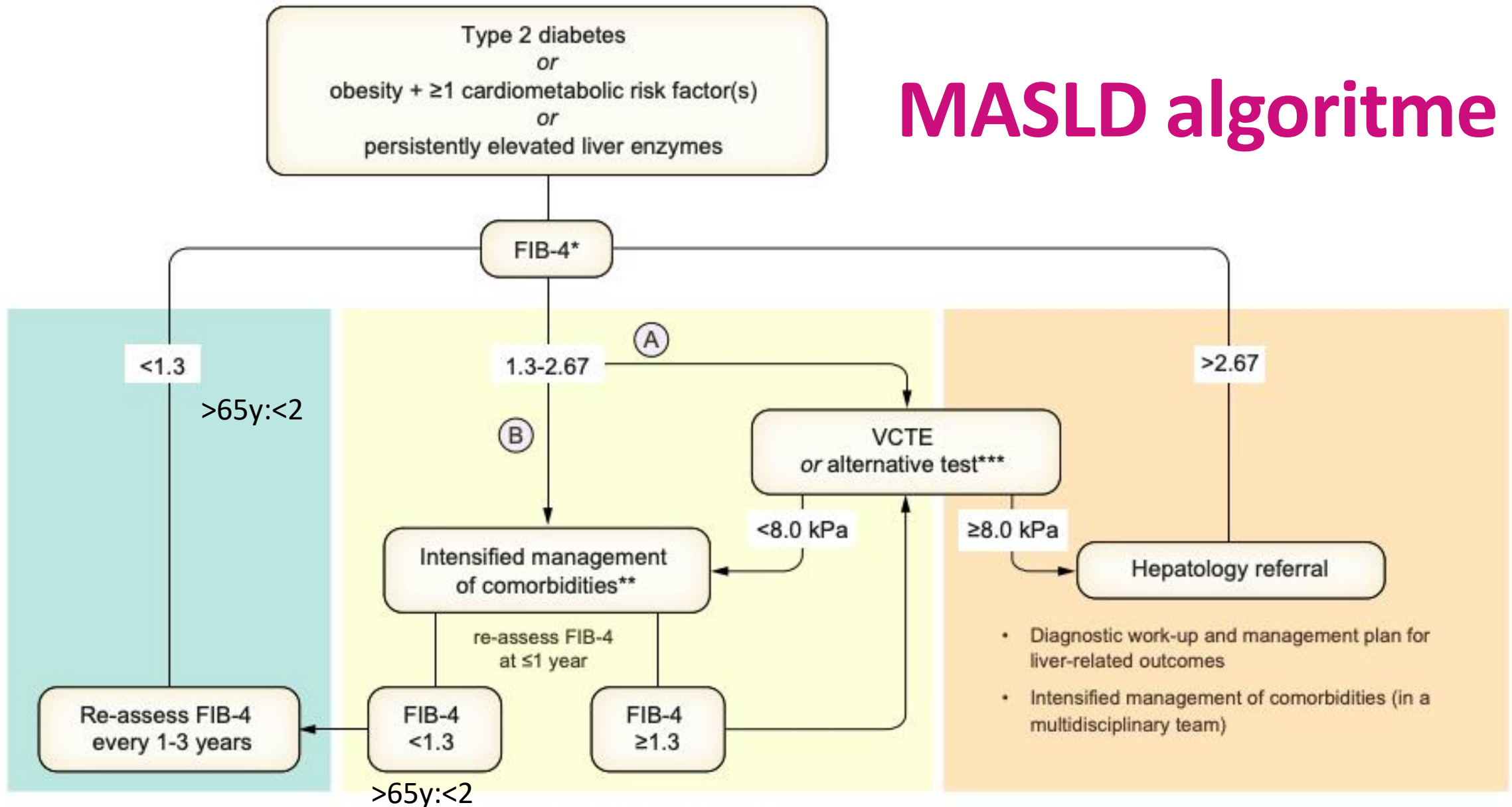
Fibroscan

- Meet de stijfheid van de lever = maat voor fibrose
- Creatie van een 'vibration wave'
- Snelheid van de golf wordt op bepaald eindpunt gemeten
- Fibrose = snellere passage
- Uitgedrukt in kPa
- Met name hoge negatieve predictieve waarde





MASLD algoritme



* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)

** e.g. lifestyle intervention, treatment of comorbidities (e.g. GLP1RA), bariatric procedures

*** e.g. MRE, SWE, ELF, with adapted thresholds

Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

Table 3. Protocol for a comprehensive evaluation of suspected NAFLD patients.

Level	Variable
Initial	1. Alcohol intake: <20 g/day (women), <30 g/day (men)
	2. Personal and family history of diabetes, hypertension and CVD
	3. BMI, waist circumference, change in body weight
	4. <u>Hepatitis B/Hepatitis C virus infection</u>
	5. History of steatosis-associated drugs
	6. Liver enzymes (aspartate and alanine transaminases (γ-glutamyl-trans-peptidase))
	7. Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR])
	8. Complete blood count
	9. Serum total and HDL-cholesterol, triacylglycerol, uric acid
	10. Ultrasonography (if suspected for raised liver enzymes)
Extended *	1. <u>Ferritin and transferrin saturation</u>
	2. <u>Tests for coeliac and thyroid diseases</u> , polycystic ovary syndrome
	3. Tests for rare liver diseases (Wilson, autoimmune disease, α1-antitrypsin deficiency)

*According to a priori probability or clinical evaluation.

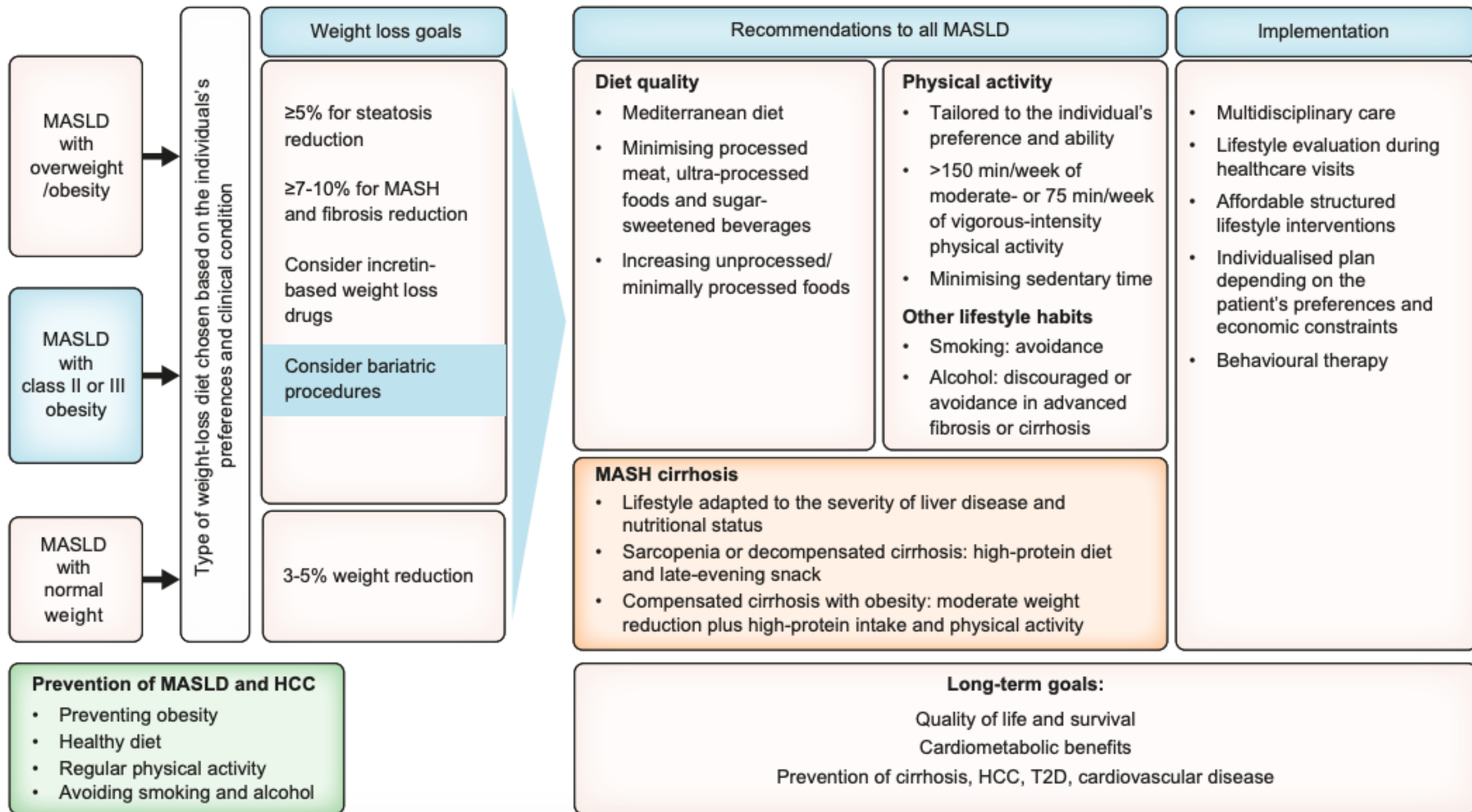
Conclusie

- NAFLD > MASLD
 - Belangrijkste verschil in klinische praktijk: verminderen stigmatiseren en toevoeging (combinatie) alcoholgebruik
- **Fibrose** is de belangrijkste voorspeller voor levergerelateerde mortaliteit
- Screening bij patiënten met een metabool syndroom (**obesitas en T2DM**) of familiale belasting
- Voorkeur voor **gebruik van FIB-4** in de eerste lijn met aansluitend Fibroscan

Table 4. SLD due to aetiologies other than MASLD, MetALD or ALD.

Condition	Clinical/lab/histological findings	Diagnostic criteria
Hepatitis C virus-associated steatotic liver (genotype 3)	Low triglycerides, HCV genotype 3	HCV antibody with reflex testing HCV RNA and HCV genotype
Drug-induced liver disease (DILI)	Mostly microvesicular SLD	Investigate for drug intake: • Corticosteroids • Tamoxifen • Amiodarone • Irinotecan • Methotrexate • Lomitapide • Valproate • 5-Fluorouracil Liver biopsy for confirmation
Hypobetalipoproteinaemia	Low triglycerides and cholesterol, fat malabsorption, vitamin A deficiency	ApoB level, genetic testing (<i>APOB</i> , <i>MTTP</i> , <i>PCSK-9</i> , targeted panel sequencing)
Lipodystrophy	Accumulation of fat in the visceral area and in the muscle (generically inherited or induced by HAART therapy)	CT scan or MRI, targeted panel sequencing for congenital lipodystrophies, MRI
LAL deficiency (Wolman disease, cholesteryl ester storage disease-CESD)	Elevated LDL-C and triglycerides, low HDL-C, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis	Enzyme assay, genetic testing (LIPA)
Pregnancy associated	HELLP syndrome Acute onset	Elevated liver enzymes and low platelets, haemolysis, SLD at abdominal ultrasound
Wilson disease	Younger age, neuropsychiatric symptoms, low ceruloplasmin	24-h urine copper excretion; quantitative copper on liver biopsy, genetic testing (<i>ATP7B</i>)
Nutrient deficiency/malnutrition	Parenteral nutrition, bypass surgeries, bariatric surgery, anorexia	Nutrient levels
Celiac disease	Diarrhoea, iron deficiency, vitamins deficiency	Tissue transglutaminase IgA, duodenal biopsy
Endocrine diseases	Hypothyroidism, PCOS, growth hormone (GH) deficiency, panhypopituitarism (primary or secondary)	TSH, fT4, fT3, endocrine testing
Other inherited metabolic conditions	Early age and severe onset, absence of triggering factors, systemic involvement, positive history of advanced disease in first degree relatives	Targeted panel sequencing, whole exome sequencing (WES)

ALD, alcohol-related liver disease; ApoB, apolipoprotein B; fT3, free triiodothyronine; fT4, free thyroxine; HCV, hepatitis C virus; HAART, highly active antiretroviral therapy; HELLP, haemolysis, elevated liver enzymes and low platelets; LAL, lysosomal acid lipase; MASLD, metabolic dysfunction-associated steatotic liver disease; PCOS, polycystic ovary syndrome; SLD, steatotic liver disease; TSH, thyroid-stimulating hormone.



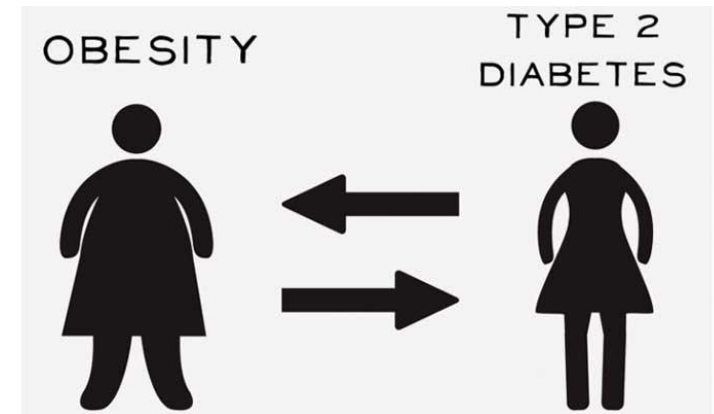
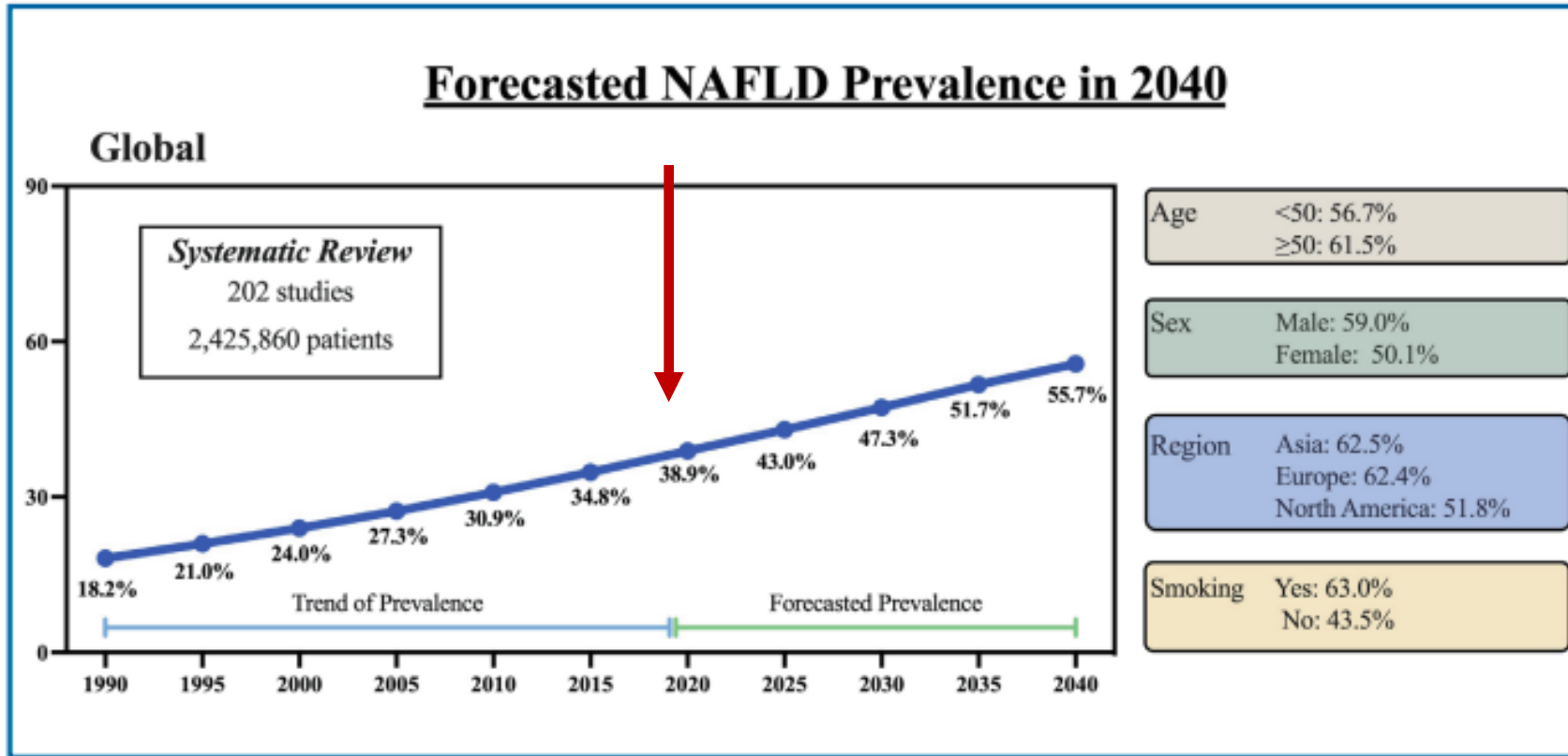
	Components	Cutoff	Sensitivity	Specificity	NPV
NFS	Age, BMI, type 2 diabetes, AST, ALT, PLT, albumin	-1.455, 0.676	0.80	0.66	0.98
Fibrosis-4	AST, ALT, age, PLT	1.30, 2.67	0.84	0.74	0.98
ELF	Hyaluronic acid, PIIINP, TIMP-1	10.3	0.80	0.90	0.99
FibroTest	α -2-macroglobulin, haptoglobin, apo-A1, bilirubin, GGT, γ -globulin	0.3, 0.7	0.88	0.73	0.99
FibroScan	Imaging modality	8.7–9.8 KPa	0.82	0.82	0.99
ARFI	Imaging modality	1.2–1.3 m/s	0.81	0.78	0.99

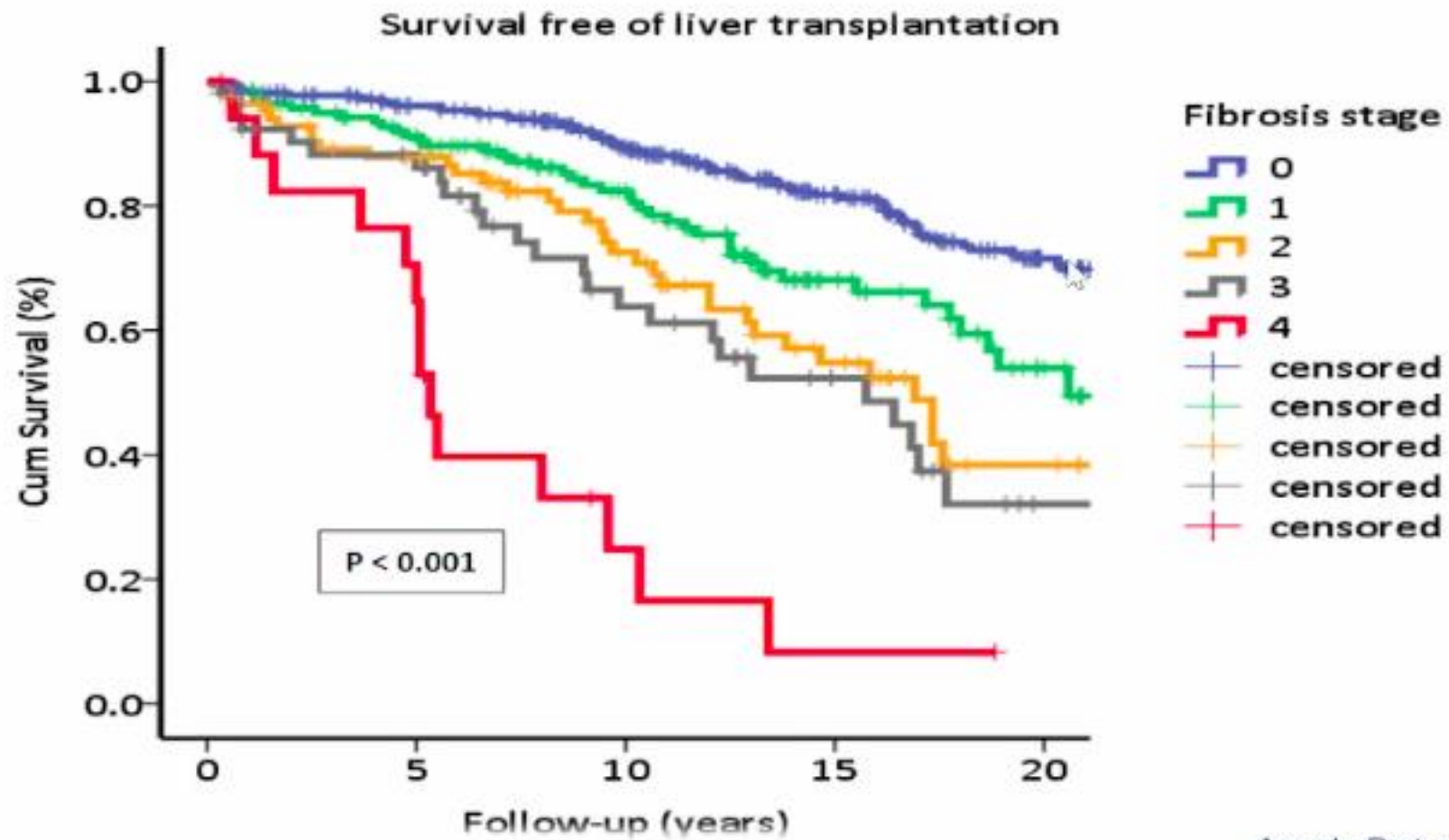
Advanced fibrosis categorised as stage 3 in the non-alcoholic steatohepatitis Clinical Research Network classification. The negative predictive value (NPV) is based on a prevalence of advanced fibrosis of 5%. The diagnostic accuracy data are derived from Crossan and colleagues.³⁷ NFS=NAFLD Fibrosis Score. BMI=body-mass index. AST=aspartate aminotransferase. ALT=alanine aminotransferase. PLT=platelet count. ELF=Enhanced Liver Fibrosis test. PIIINP=amino-terminal propeptide of type III collagen. TIMP-1=metalloproteinase inhibitor 1. apo-A1=apolipoprotein A1. GGT=glutathione hydrolase 5 proenzyme. ARFI=acoustic radiation force impulse.

Table 1: Most widely available non-invasive fibrosis tests for advanced fibrosis in patients with non-alcoholic fatty liver disease (NAFLD)

Tsochatzis E. Lancet Gastroenterol Hepatol.2018

Prevalentie

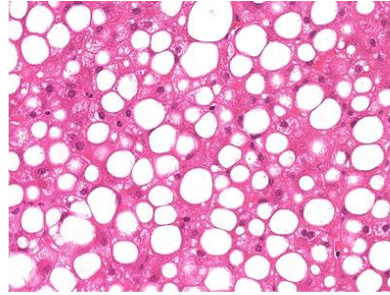




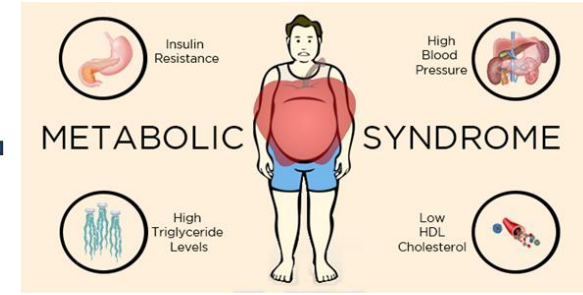
Angulo P et al., C

MASLD

=



+



+



NAFLD = +/- MASLD = 'Metabolic dysfunction associated steatotic liver disease'

Gedefinieerd door:

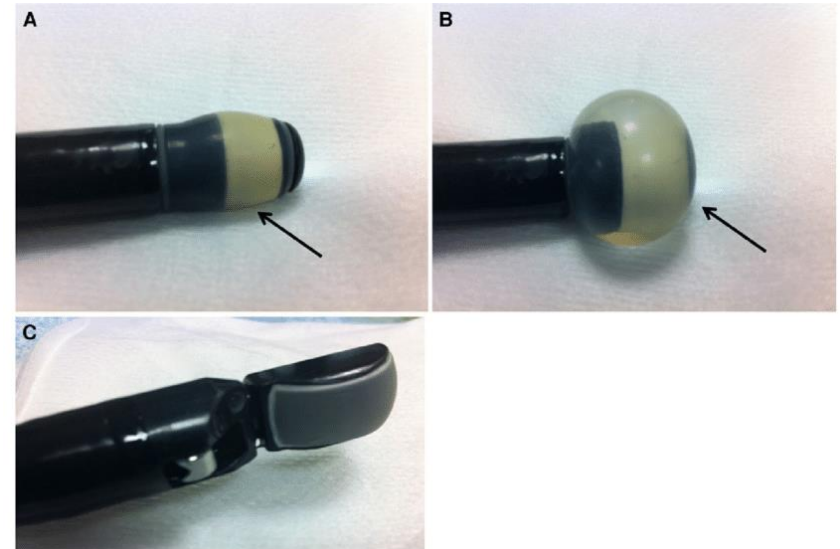
- Aanwezigheid van steatosis of accumulatie van vet (>5%) in hepatocytent
- Afwezigheid van significant alcohol consumptie of andere etiologie van leverlijden

Nieuwe zaken binnen de echo-endoscopie

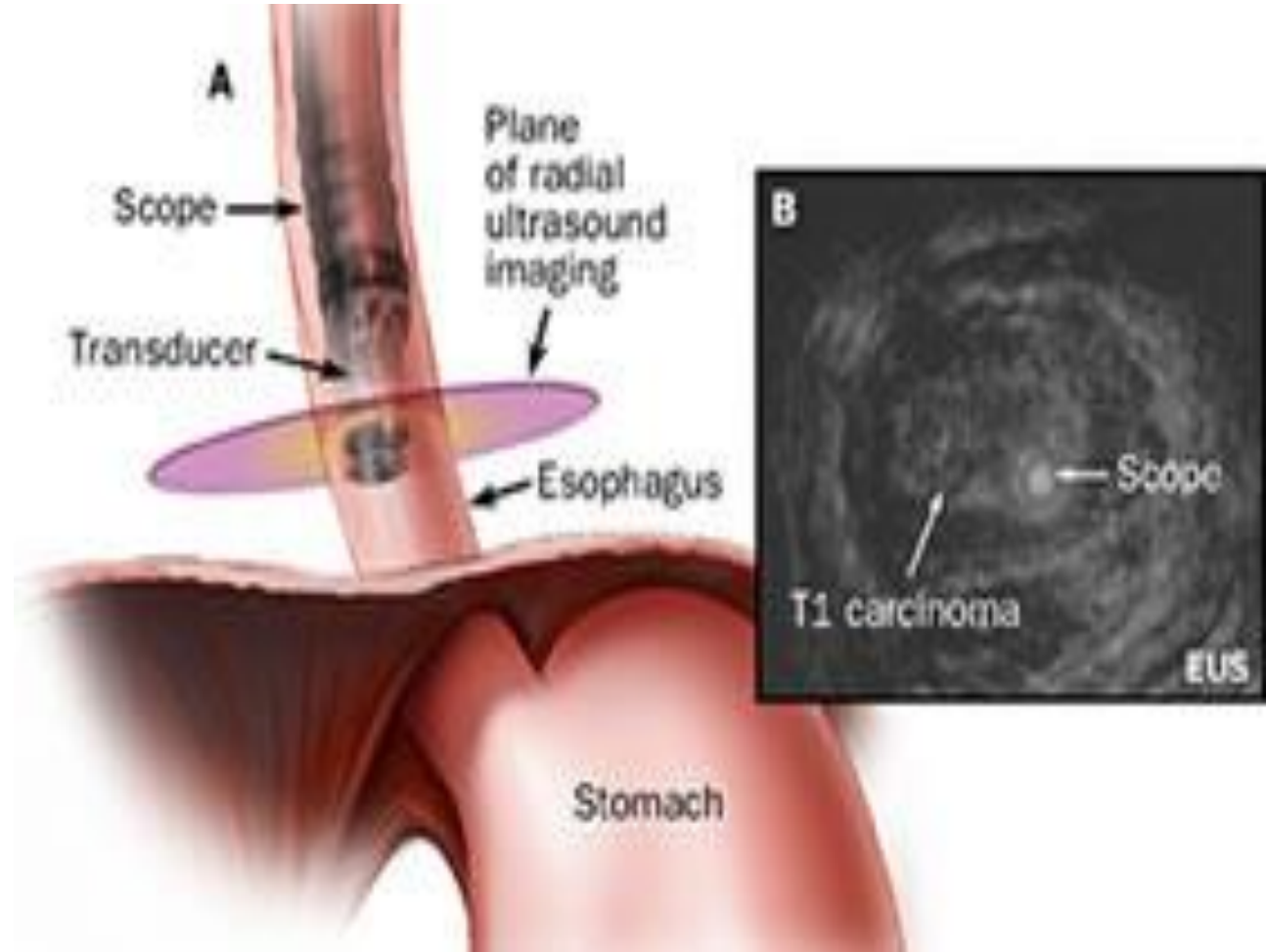
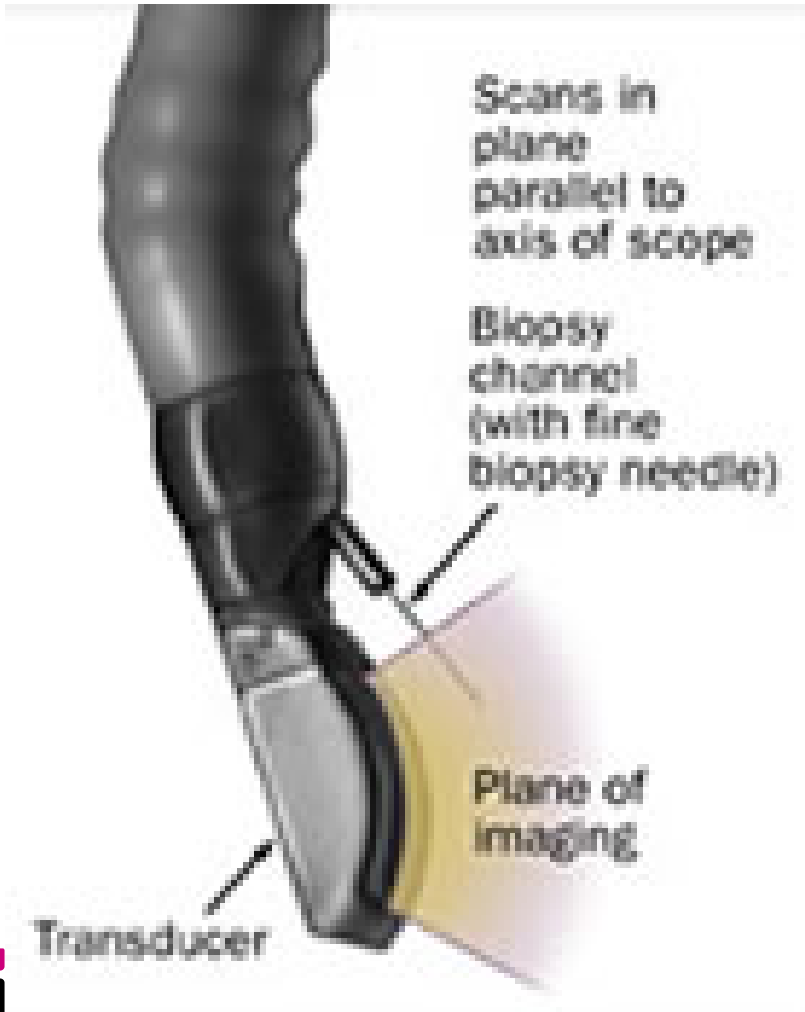
Florence Anné
Brecht Pauwels
VITAZ

Doel

Introductie

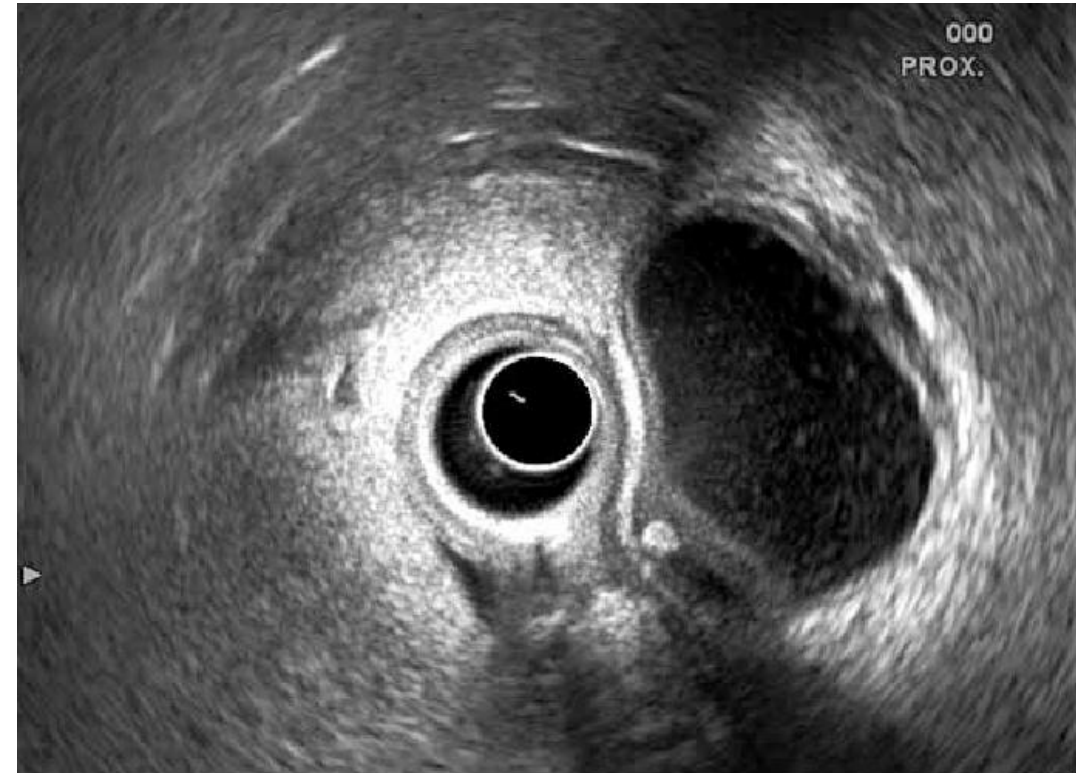


Lineair versus radiaal



Diagnostische EUS

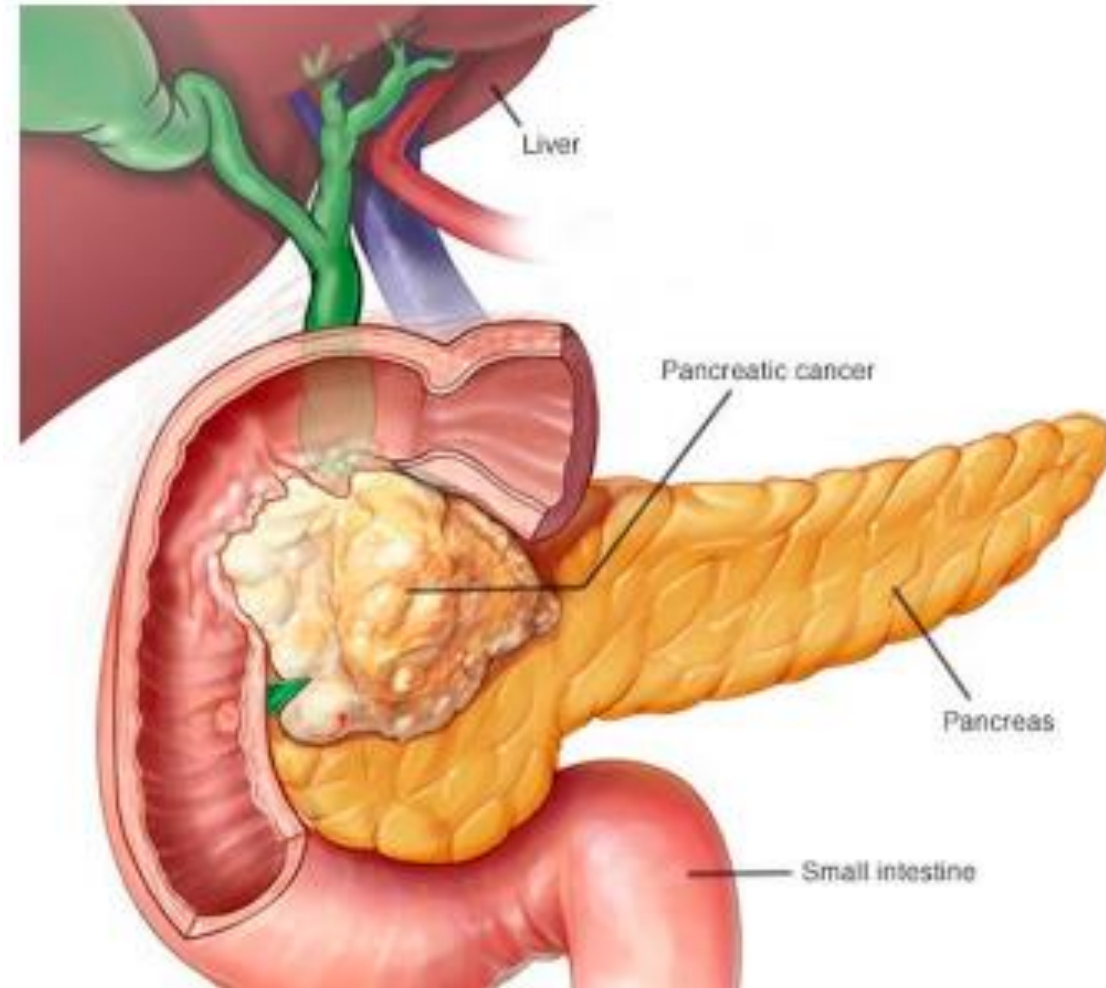
Diagnostische EUS – voorbeeld

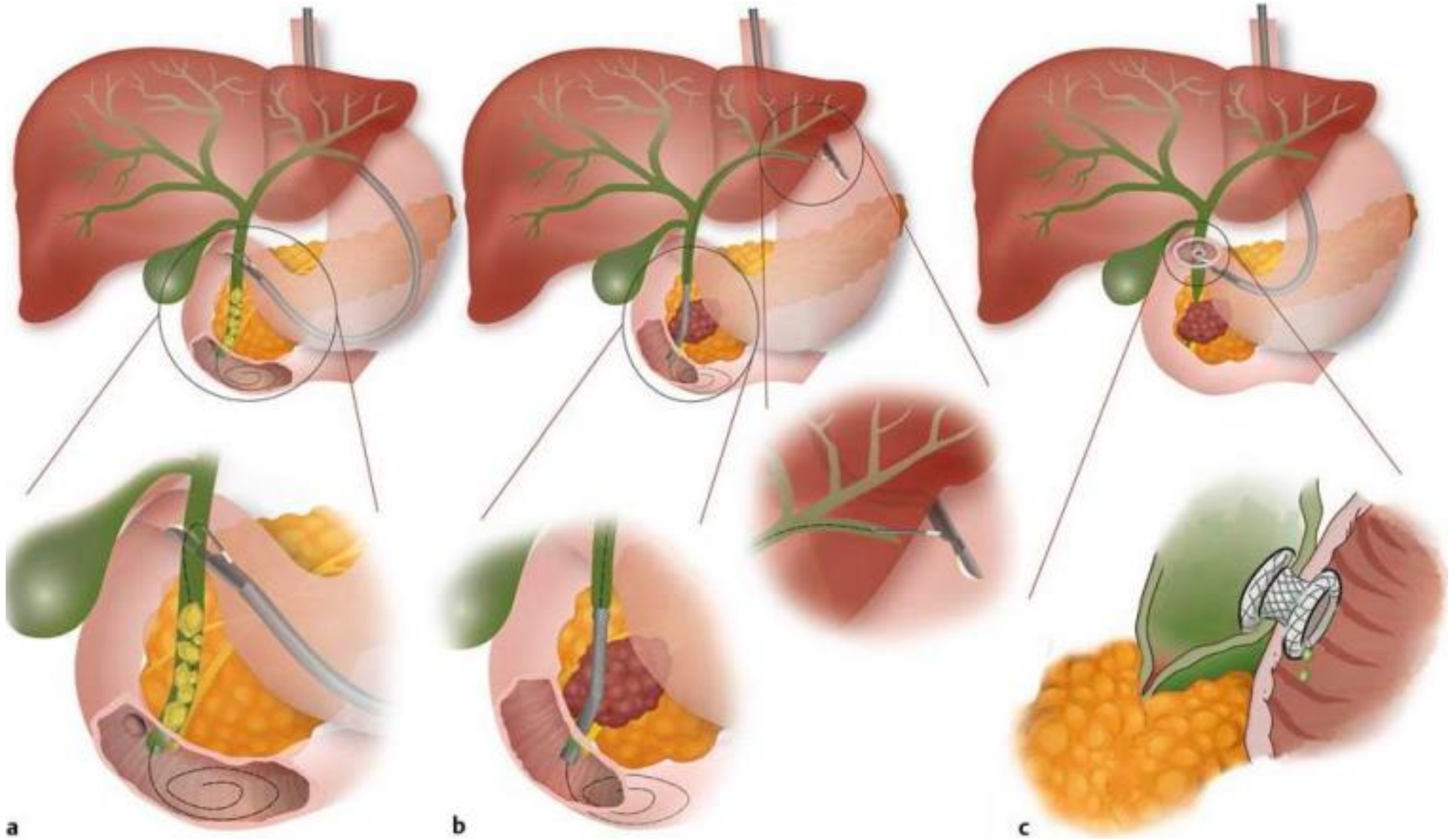


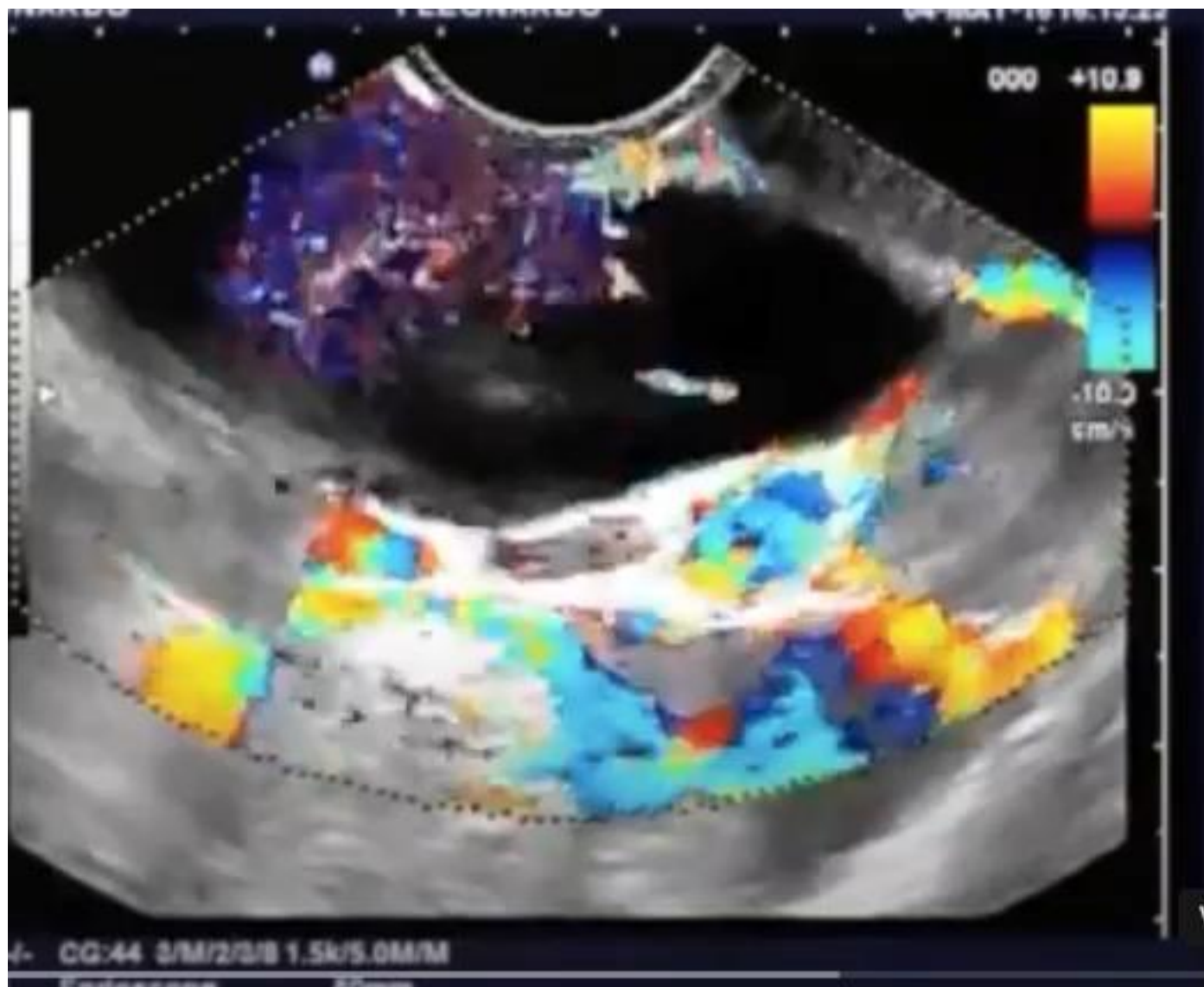
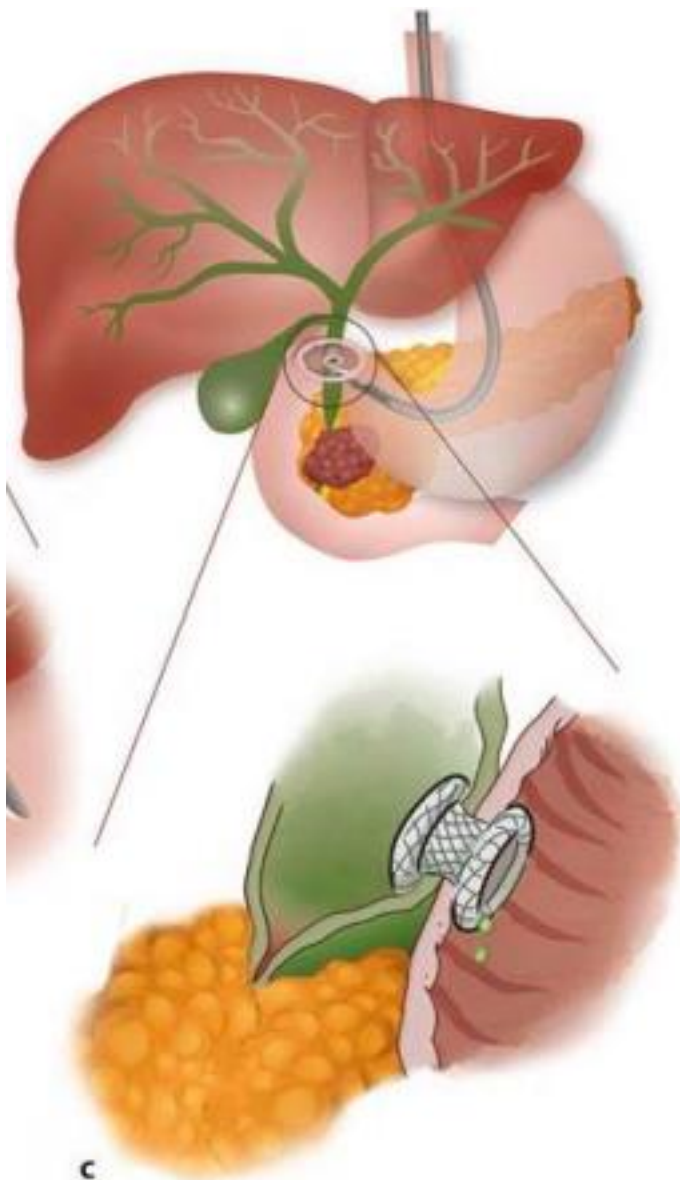
Therapeutische EUS: indicaties

Therapeutische EUS – courante klinische situaties

- ▶ Inoperabele pancreaskoptumor
 - ▶ ERCP met oog op (retrograde) stenting faalt

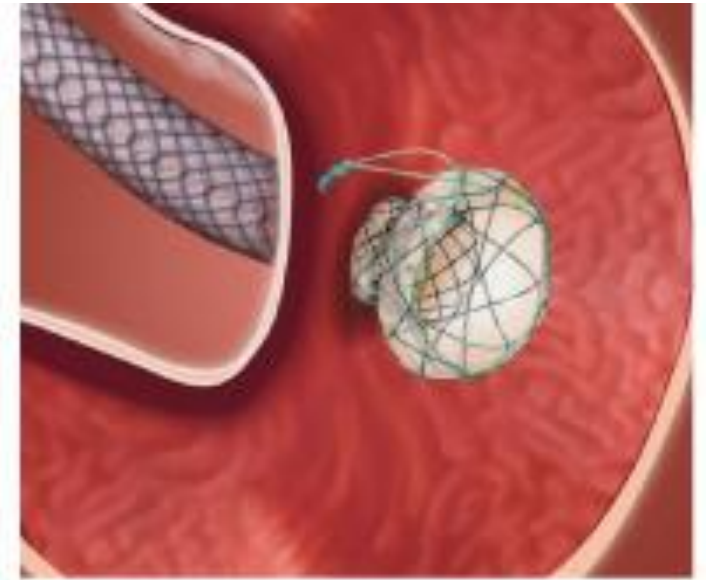








a)



b)



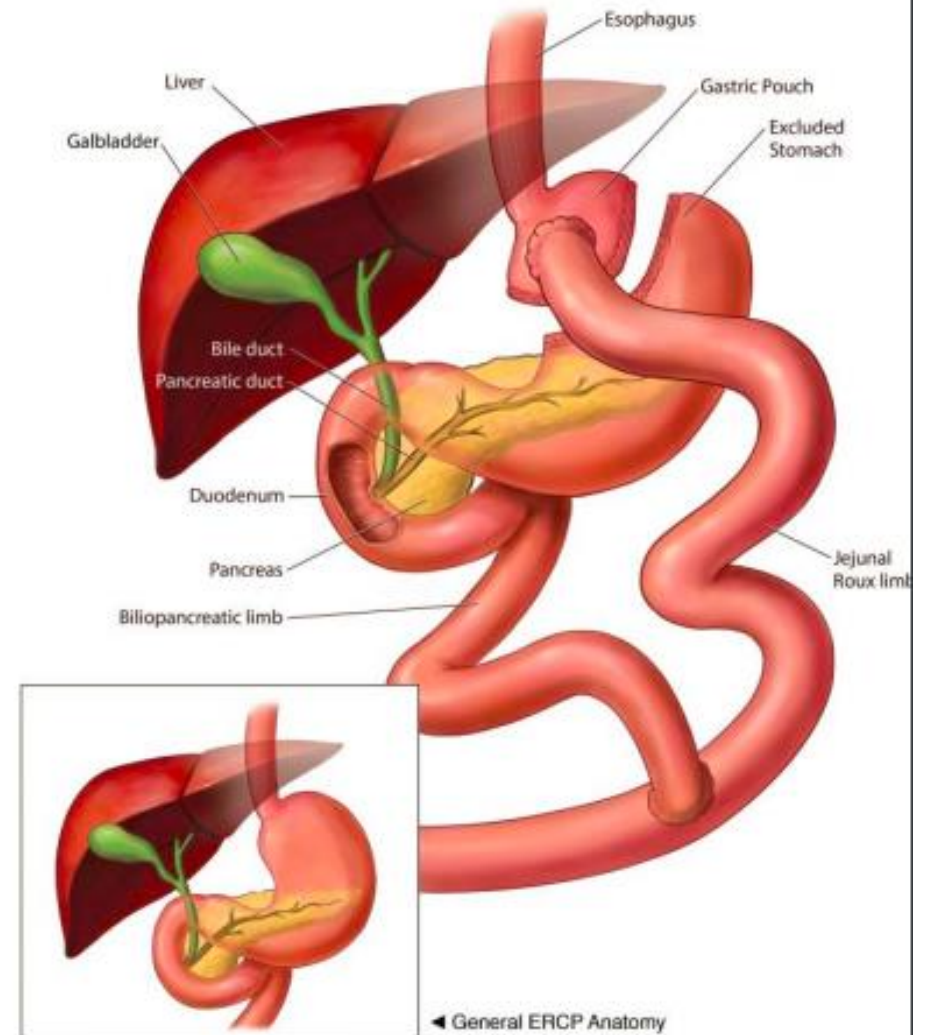
c)

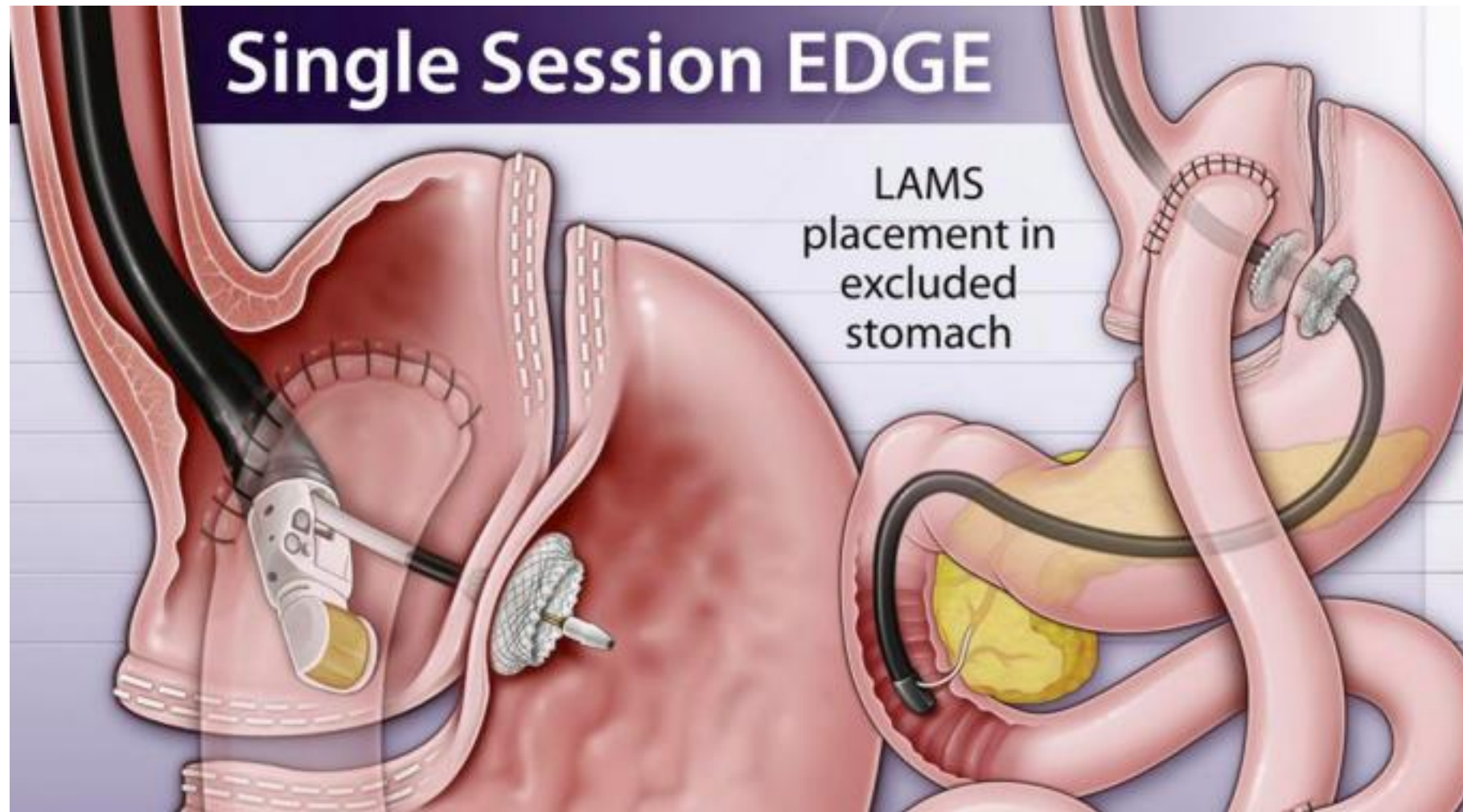
Hepicogastrostomie

Therapeutische EUS – courante klinische situaties

- Gastric bypass
- Verschillende opties:
 - Lap assisted ERCP - Igv CCE
 - Enteroscopic assisted ERCP
 - EDGE
 - (PTC)

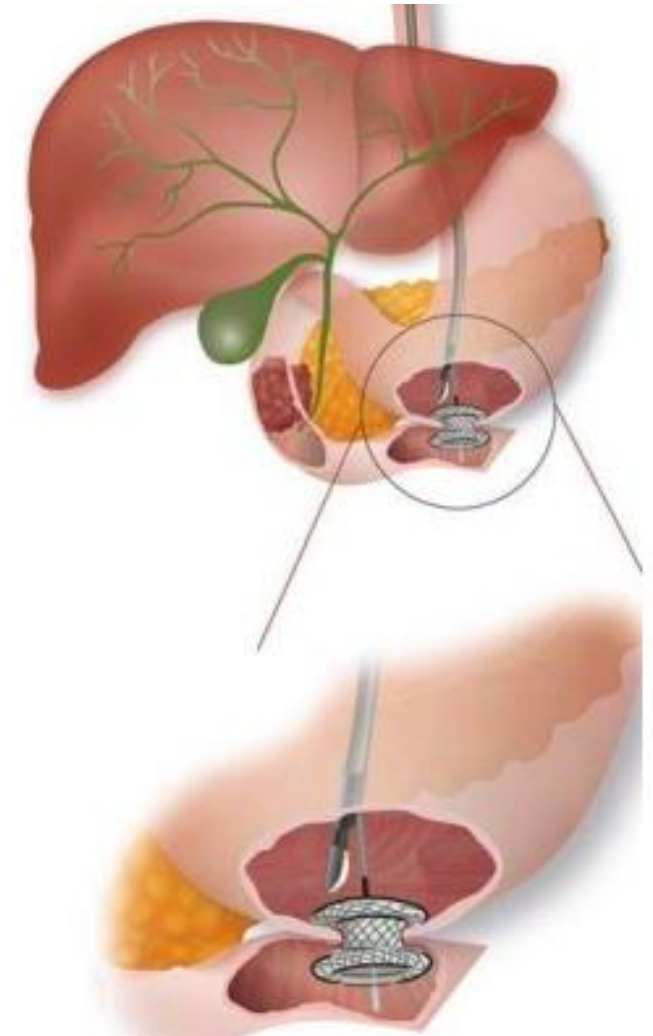
ERCP with Roux-en-y Gastric Bypass Surgery





Therapeutische EUS – courante klinische situaties

- Gastric outlet obstructie
 - Maligne
 - Benigne
- Verschillende behandelopties:
 - Duodenale stent
 - Gastro-enterostomie
 - Chirurgisch
 - EUS-guided
 - (Maagsonde)

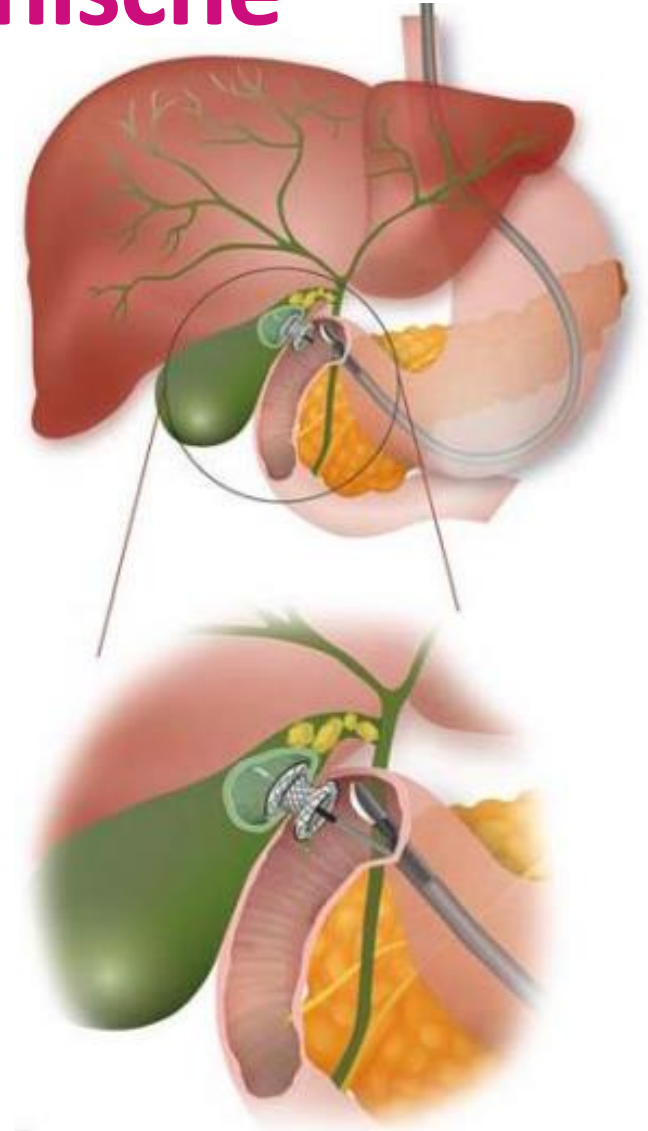


EUS-guided
gastro-
enterostomy

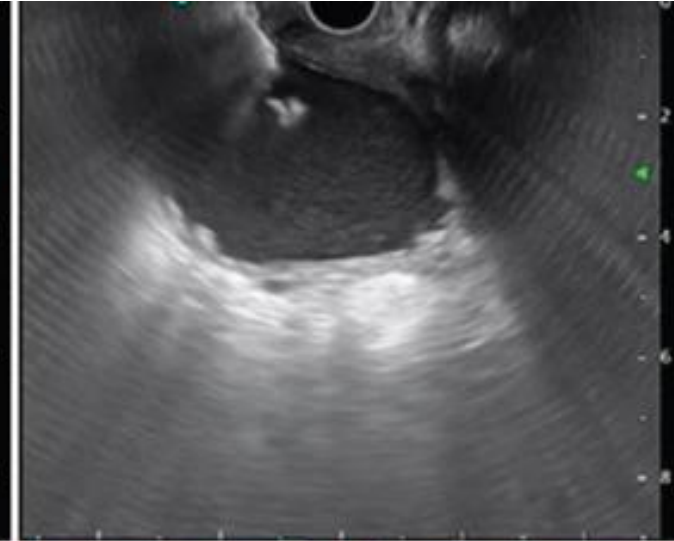
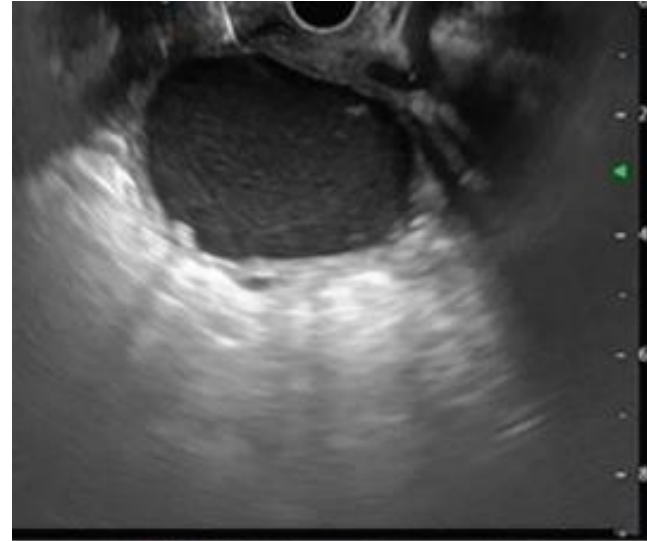


Therapeutische EUS – courante klinische situaties

- Galbaasdrainage
 - Acute cholecystitis
 - Chirurgie niet mogelijk
 - Niet fit
 - Duur van klachten
 - Geriatrische of oncologische patiënt
 - Niet reagerend op medicamenteuze behandeling
 - (galwegdrainage)
- Plaatsing LAMS
 - Verbinding galblaas – maag/duodenum







Historische eerste lijns behandeling

- tekststijl van het model te bewerken



eau
eau
niveau
niveau

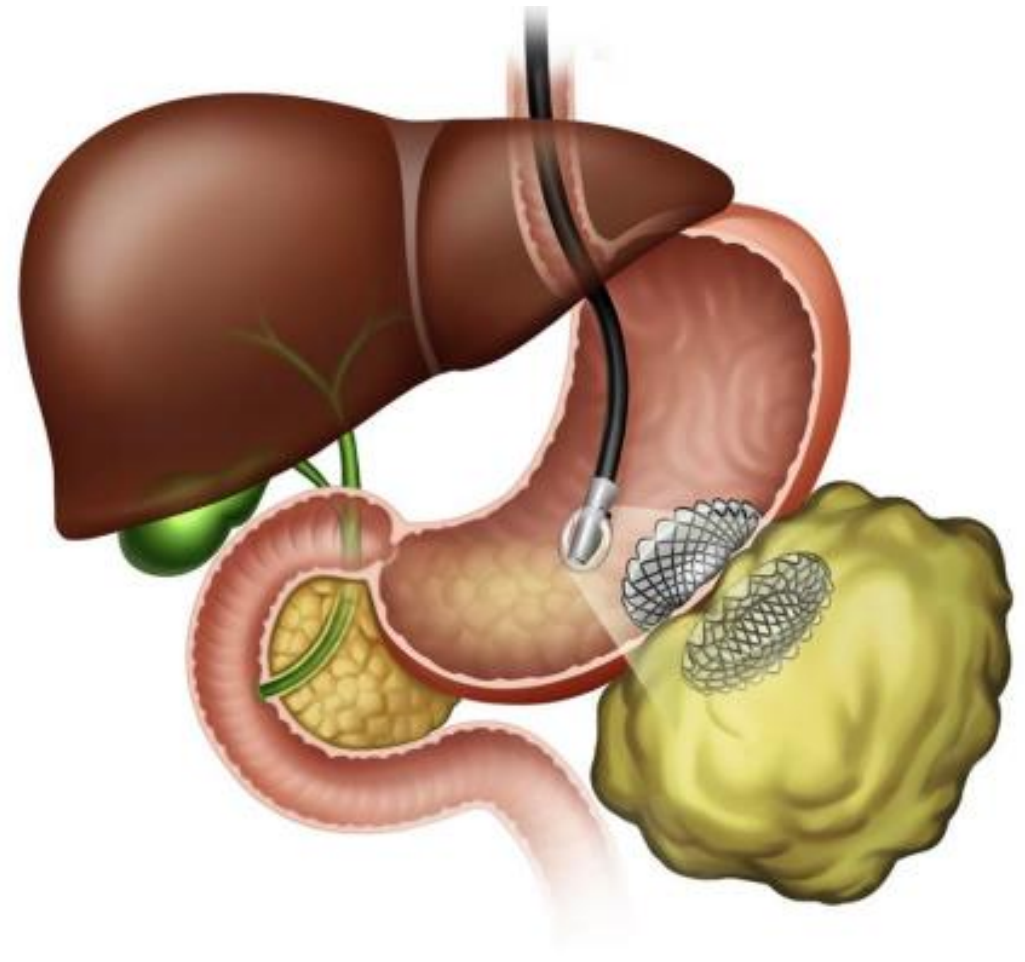
Gelijkaardig technisch succes, MAAR minder complicaties bij EUS-guided GBD

Table 2 Comparison of the clinical outcomes between the two groups

	EUS-GBD n=39	PT-GBD n=40	P value
1-year adverse events (%)	10 (25.6)	31 (77.5)	<0.001
Grading 1/2/3/4/5	1/1/6/0/2	13/6/8/0/4	
Recurrent acute cholecystitis (%)	1 (2.6)	8 (20)	0.029
Reinterventions after 30 days (%)	1 (2.6)	12 (30)	0.001
Reinsertion of PT-GBD	0	12	
Clearing blocked stent	1	0	
Unplanned admissions (%)	6 (15.4)	20 (50)	0.002
30-day adverse events (%)	5 (12.8)	19 (47.5)	0.001
Grading 1/2/3/4/5	0/1/2/0/2	6/4/5/0/4	
30-day mortality (%)	3 (7.7)	4 (10)	1
Technical success (%)	38 (97.4)	40 (100)	0.494
Clinical success (%)	36 (92.3)	37 (92.5)	1
Procedure time (minutes)	22.7 (13.0)	27.4 (12.0)	0.108
Analgesic requirements (total paracetamol in mg)	3345 (5663)	5165 (5068)	0.034
Hospital stay (days)*	8 (4–13)	9 (7–14)	0.181

Therapeutische EUS – courante klinische situaties

- ▶ Walled-off necrose
 - ▶ Necrotiserende pancreatitis
 - ▶ Plaatsing LAMS
 - ▶ Vervolgens uitvoeren necrosectomie



EUS conclusie

- Met de toename van kwaliteit van echobeeld forse meerwaarde als diagnostische tool
 - Beeldvorming
 - Weefsel sampling
- Recente forse evolutie van therapeutische EUS
 - Complementair met ERCP ('EUS-assisted')
 - Minimaal invasieve prodedures ('EUS-guided')
 - Galblaas en galwegen
 - Gastric outlet obstructie
 - Pancreas
- Keuze van procedure: afhankelijk van multipale patiënt-, ziekte-, en endoscopiegerelateerde factoren - multidisciplinair

Key points