Verwezen vanwege leverenzymafwijkingen: wat nu?

Dutch Liver Week

21 juni 2017

J.T. Brouwer

Reinier de Graaf Groep Delft

Mw G, 41 jaar

- **Bekend bij reumatoloog ivm gewrichtsklachten**
- **Doorverwezen ivm verhoogde leverwaarden**
- **Gewicht 94.7 kg, lengte 1.75 m**
- **Geen alcohol, drugs, of andere risicofactoren**
- **Echo abd: steatosis hepatis**

	27-12-2011 09:22		10-02-2012 11:45	
Bilirubine ongeconj.				
Alkalische fosfatase	76		79	
ASAT(SGOT)	79	H	209	H
ALAT(SGPT)	108	H	209	H
Gamma-GT	175	H	258	H
Amylase			48	

Mw G, 41 jaar

Wat doet u?

1. **Behandelen als NAFLD / NASH; alleen verdere diagnostiek naar andere leverziekten indien geen verbetering**

2. **Stapsgewijze andere leveraandoeningen uitsluiten, op volgorde van waarschijnlijkheid**

3. **Eerst alle andere mogelijke leverziekten in 1x uitsluiten (non-directed testing)**

Mw G, 41 jaar

Bilirubine totaal	11
Bilirubine geconjugeerd	<Memo>
Bilirubine geconj.	
Bilirubine ongeconj.	
Alkalische fosfatase	79
ASAT(SGOT)	209 H
ALAT(SGPT)	209 H
Gamma-GT	258 H
Amylase	48
Melkzuur (lactaat)	
LD	332 H
CK	2158 H
Triglyceriden	
Cholesterol	
HDL cholesterol	
Chol:HDL-chol ratio	
LDL cholesterol	
Totaal eiwit	84 H
Ceruloplasmine	0.24
a1 Antitrypsine	1.17
Totaal IgG	19.3 H
Totaal IgA	2.50
Totaal IgM	0.95

ANA (ANF)	<Memo> *
- titer	320
- fluor. beeld	<Memo>
dsDNA as	3.1
ENA (SSA,SSB,RNP etc.) as	0.5
Reumafactor IgM	
Reumafactor IgA	
CCP as	
CCP as	
Gladspier as	<Memo>
- IgM titer	negatief
- IgG titer	160
- IgA titer	
LKM (liver, kidney, microsome) as	negatief
SLA (soluble liver antigen) as	positief *
Mitochondrien as	negatief
Gliadine (gluten) IgA as	0.8
Gliadine (gluten) IgG as	
Endomysium IgA as	negatief
TTG IgA as	1.8

Transferrine	2.54
IJzer	25
LIJBC	30
TIJBC	55
Verzadigingsperc.	45
Ferritine	1237 H
Vitamine B12	287
Foliumzuur	20.7

Mw G, 41 jaar

Wat is uw werkdiagnose?

1. **NAFLD / NASH**
2. **NAFLD / NASH + AIH**
3. **NAFLD / NASH + AIH + hemochromatose**
4. **Anders, namelijk…**

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TIJBC	55	
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Diagnostisch algoritme
bij leverziekten e.c.i.

Kans op diagnose ziekte A=

Pre-test kans op A
(prevalentie / incidentie)
X
Individueel profiel patiënt
X
Accuratesse diagnosticum

Reinier de Graaf Groep

Pre-test kans leverziekte
prevalentie / incidentie

- **NHANES III study (US)**
  - **elevated liver enzymes in 7.9% of subjects (n=1,238)**
- **BALLETS study (UK)**
  - **n=1,236 primary care patients with an abnormal LFT**
- **German ‘‘Check-Up 35+’’ Study**
  - **elevated liver enzymes in 13.2% of subjects (n=2,741)**

NHANES III study (US)

Elevated liver enzymes in 7.9% of subjects (n=1,238/15,670)

Table 1. Base-case disease prevalence estimates and true positives by confirmatory testing.

Disease	Positive by first test n (test)	True positives n (confirmatory test)
Hepatitis B (0.5-8%)	11 (hepatitis B surface antigen)	11 (viral load)
Hepatitis C (0.5-8%)	87 (hepatitis C antibody)	69 (viral load)
Hemochromatosis 0.03-0.3%	42 (transferrin saturation >50%)	12 (homozygous C282Y genotype)
Primary biliary cholangitis 0.02%	15 (AMA >1:20)	11 (biopsy)
Primary sclerosing cholangitis 0.01%	17 (suggestive ultrasound)	11 (MRCP)
Alpha-1 antitrypsin deficiency 0.04%	Range 0–18* (AAT level <80 mg/dl)	0 (PiZZ phenotype)
Alcoholic liver disease 2-18%	167 (patient reported history)	–
Non-alcoholic fatty liver disease 3-40%	508 (steatosis seen on ultrasound)	–
Autoimmune hepatitis 0.02%	Range 22–248* (ASMA >1:20)	22 (biopsy)
Wilson disease 0.01%	Range 0–104 (ceruloplasmin <20 mg/dl)*	0 (24 h urine copper >100 μg/L)
Total*	1238	–

DILI 0.01-0.1% (reported prevelance)

Am J Gastroenterol 2003 / J Hepatol 2017

Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) study

Estimated prevalence of liver diseases in the British population

Table 1 Viral, genetic, and autoimmune diseases of the liver (tested for by a "liver panel"), their prevalence in the British population and diagnostic algorithms*

Disease	Prevalence amongst adult population (%)	Blood tests done on all members of the cohort (to diagnose or screen for the disease)	Diagnostic algorithm
Chronic viral hepatitis C	0.42 [46]	Hepatitis C virus antibody (HCV Ab)	Viral marker positive.
Chronic viral hepatitis B	0.3 [47]	Hepatitis B viral markers (HBV Surface Ag)	Viral marker positive.
Metal storage disease: Iron	0.25 (prevalence of phenotype; homozygous plus complex heterozygous) [48]	Iron saturation	Genotype if iron saturation >50%.
Primary biliary cirrhosis (PBC)	0.024 [49]	Antimitochondrial Ab	Raised antibodies and raised ALP level.
Autoimmune hepatitis	0.001 [50]	Smooth Muscle Ab	Raised antibodies and raised ALT, AST or globulin exceeding twice the upper limit of normal. Confirmed by hepatologist.
Metal storage disease: Copper	<0.025 [51]	Caeruloplasmin	Low levels of caeruloplasmin.
Alpha-1 antitrypsin deficiency	<0.025 [52]	Alpha-1 antitrypsin	Low Alpha-1antitrypsin levels followed by phenotype testing.

*Method by which the diagnosis was made.

Arnold et al. BMC Family Practice 2011

Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) study

N= 1,236 primary care patients with an abnormal LFT

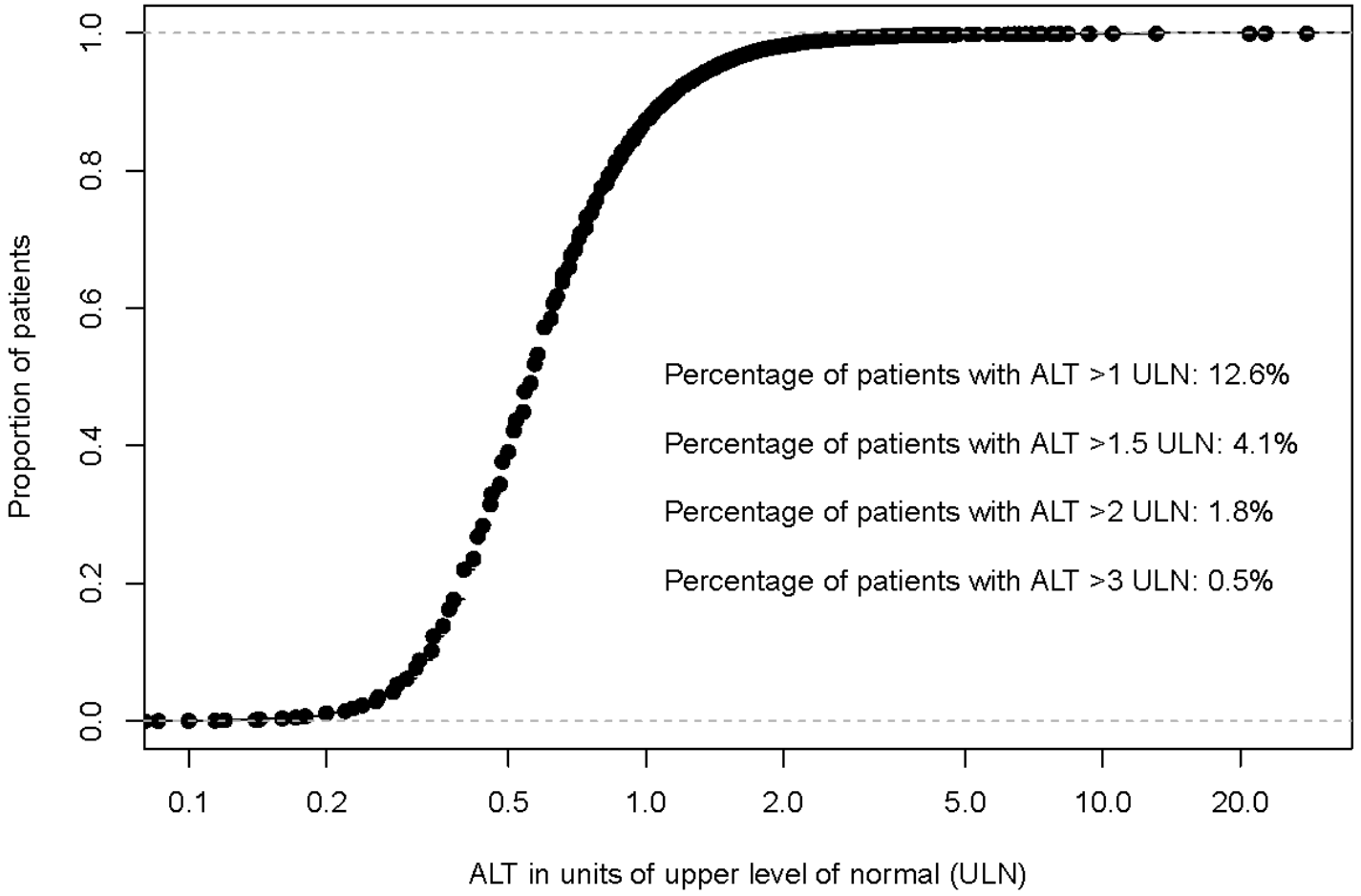
Table 5 Yield, sensitivity and Positive Predictive Values (PPV) of different detection strategies

Strategy for viral testing	No. of patients*	Hepatitis cases*	Viral tests	Cases detected	Sensitivity (%)	PPV (%) 95% Confidence Limits
A. If repeat LFT panel is abnormal	1124	11	955	11	100	1.15 (0.64-2.05)
B. If ALT abnormal on primary test	1064	12	418	8	67	1.91 (0.97-3.73)
C. If ALT > 2 upper limit of normal on primary test	1064	12	77	6	50	7.79 (3.62-15.98)
D. If patient born in a country of intermediate to high viral hepatitis prevalence.	1208	13	170	11	85	6.47 (3.65-11.21)
E. If patient born in a country of intermediate to high viral hepatitis prevalence *and* ALT > 2 upper limit of normal on primary test.	1041	12	16	5	42	31.25 (14.16-55.60)
F. If patient born in a country of intermediate to high viral hepatitis prevalence, *or* ALT > 2 upper limit of normal on primary test.	1041	12	215	11	92	5.12 (2.88-8.93)
G. Test all cases	1236	13	1236	13	100	1.05 (0.62-1.79)

Arnold et al. BMC Family Practice 2011

German "Check-Up 35+" Study

N= 21,008 patients recruited by 51 primary care private practices.



Wolffram et.al., J Hepatol 2015; personal communication SW Schalm – J Wiegand

German "Check-Up 35+" Study

N= 21,008 patients recruited by 51 primary care private practices.

	Healthy individuals	HBsAg positive patients	Anti-HCV positive patients
		n = 110 (0.52%) (60% DNA+)	n = 199 (0.95%) (43% RNA+)
Age (years)	57.5 ± 14.5	52.3 ± 12.4	54.8 ± 15.3
Male (n)	9092 (43.9%)	60 (54.5%)	91 (45.7%)
IV drug abuse (n)	29 (0.1%)	1 (0.9%)	56 (28.1%)
Blood transfusion before 1992 (n)	1125 (5.8%)	4 (4.1%)	33 (18.2%)
Immigration (n)	1951 (10.0%)	37 (35.6%)	29 (15.7%)
Infection in household (n)	763 (4.0%)	11 (11.0%)	16 (8.7%)
Elevated ALT (n)	2741 (13.2%)	24 (21.8%)	70 (35.4%)

Wolffram et.al., J Hepatol 2015

Pre-test kans leverziekte
prevalentie / incidentie

- **NHANES III study (US)**
  - elevated liver enzymes in 7.9% of subjects (n=1,238)
  - NAFLD 40%, ALD 25%, HBV/HCV 8%, DILI 4.4%, other < 0.1%
- **BALLETS study (UK)**
  - n=1,236 primary care pts with an abnormal LFT
  - HBV/HCV 1.05%
  - Sensitivity 92% PPV 5.12% if restrict to ALT > 2x ULN or high prevelance background
- **German ‘‘Check-Up 35+’’ Study**
  - HBsAg 0.52% HCV RNA 0.41% of *all* subjects (n=21,008)
  - elevated liver enzymes in 13.2% of subjects (n=2,741)
  - limited correlation HBV/HCV with liver enzymes

Individueel profiel patiënt

- **Patroon leverwaarden**
  - **Cholestatisch vs hepatocellulair, ast/alt ratio en hoogte**
- **Familiaire belasting**
  - **Hereditaire leverziekten (vaak recessief), HBV**
- **Afkomst**
  - **Migratie uit hoog-risico gebieden**
- **Risicogedrag**
  - **Sex, drugs en (para)medici**
- **Comorbiditeit**
  - **Metabool syndroom**
- **Expositie**
  - **Alcohol, medicatie, OTC, toxische stoffen**

Serum levertesten

Function Assessed	Test	Physiological Function	Site Found
"Hepatocellular Arrangement"	Aspartate Aminotransferase	Important enzymes in amino-acid metabolism, allowing for entrance to Krebs Cycle	Liver, skeletal muscle, heart, kidney, brain
	Alanine Aminotransferase		Greatest concentration in the Liver
"Cholestatic Arrangement"	Alkaline Phosphatase	Enzyme that transports metabolites across cell membranes. Is present in the bile duct epithelial cells, therefore: biliary stasis = release of the enzyme	Liver, Bone > intestine, placenta, kidney
	γ – Glutamyl transpeptidase	Catalyzes the transfer of a γ – Glutamyl group between amino acids. Important for the synthesis and breakdown of glutathione.	Hepatocytes, biliary epithelial cells and renal tubules
	Bilirubin	Catabolic product of hemoglobin which is released in the unconjugated form, and conjugated to a water soluble product by hepatic cells.	Serum and Liver. Comparison of 'conjugated' and 'unconjugated' bilirubin elevations will determine whether intrahepatic.
Functional Liver Mass	Albumin	Main protein of human blood plasma.	Liver or dietary
	Prothrombin Time	Assay of the extrinsic pathway of coagulation. Assesses factors I, II, V, VII, and X.	Liver (synthesizes vitamin k dependent clotting factors)

http://dx.doi.org/10.1016/j.jemermed.2016.10.016

Causes of Elevated Serum Aminotransferase Levels

ALT > AST

(Chronic, Mild < 5 fold)

HEPATIC CAUSES

α_1-antitrypsin deficiency
Autoimmune hepatitis
Chronic viral hepatitis (B, C, and D)
Hemochromatosis
Steatosis and steatohepatitis
Wilson disease
medication and toxins

NON HEPATIC CAUSES

Celiac disease
Hyperthyroidism

(Acute severe>20 fold)

Acute bile duct obstruction
Acute Budd-Chiari syndrome
Acute viral hepatitis
Autoimmune hepatitis
Ischemic hepatitis
Medications/toxins
Wilson disease

AST > ALT

(Chronic, Mild < 5 fold)

Hepatic Causes

Alcohol-related liver injury
Cirrhosis.

Nonhepatic Causes

Hypothyroidism
Myopathy
Strenuous exercise

(Acute severe>20 fold)

Hepatic Cause

Medications or toxins in a patient with underlying alcoholic liver injury

Nonhepatic Cause

Acute rhabdomyolysis

ALT & AST levels

American College of Gastroenterology guidelines

- ALT and/or AST levels <5X ULN
  - assess for viral hepatitis B and C, alcoholic and NAFLD, hemochromatosis, Wilson's disease, alpha-1-anti-trypsin deficiency, autoimmune hepatitis and consider drugs/supplement related injury
- ALT and/or AST levels 5–15X ULN
  - also assess for acute hepatitis A, B, C (and E)
- ALT and/or AST levels >15X ULN
  - also assess for acetaminophen toxicity and ischemic hepatopathy (shock liver)
- Acute hepatitis with elevated prothrombin time / encephalopathy
  - immediate referral to liver specialist

Am J Gastroenterol 2017; 112:18–35; doi: 10.1038/ajg.2016.517

Alkaline phosphatase & GGT levels

American College of Gastroenterology guidelines

- An elevation of alkaline phosphatase should be confirmed with an elevation in GGT
- Given its lack of specificity for liver disease, GGT should not be used as a screening test for underlying liver disease in the absence of other abnormal liver chemistries
- Patients with alkaline phosphatase elevation with or without elevation of bilirubin should undergo testing for
  - PBC with testing for anti-mitochondrial antibody
  - PSC with MR cholangiography in conjunction with IgG4

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NHC
NATIONAAL HEPATITIS CENTRUM
Kenniscentrum voor hepatitis

Reinier de Graaf Groep

Bij wie komt (chronische) hepatitis vaak voor in Nederland?

Chronische hepatitis B	
	Prevalentie
1e generatie migranten	**3,8 %**
overige Nederlanders	**0,2 %**
aandeel 1e generatie migranten CHB 65 %	

http://www.rivm.nl

NHC
NATIONAAL HEPATITIS CENTRUM
Kenniscentrum voor hepatitis

Reinier de Graaf Groep

Bij wie komt (chronische) hepatitis vaak voor in Nederland?

Chronische hepatitis C	
	Prevalentie
1e generatie migranten	**2,2 %**
overige Nederlanders	**0,1 %**
aandeel 1e generatie migranten CHC 56 %	

http://www.rivm.nl

Diagnostisch algoritme
bij leverziekten e.c.i.

Kans op diagnose ziekte A=

Pre-test kans op A
(prevalentie / incidentie)
X
Individueel profiel patiënt
X
Accuratesse diagnosticum

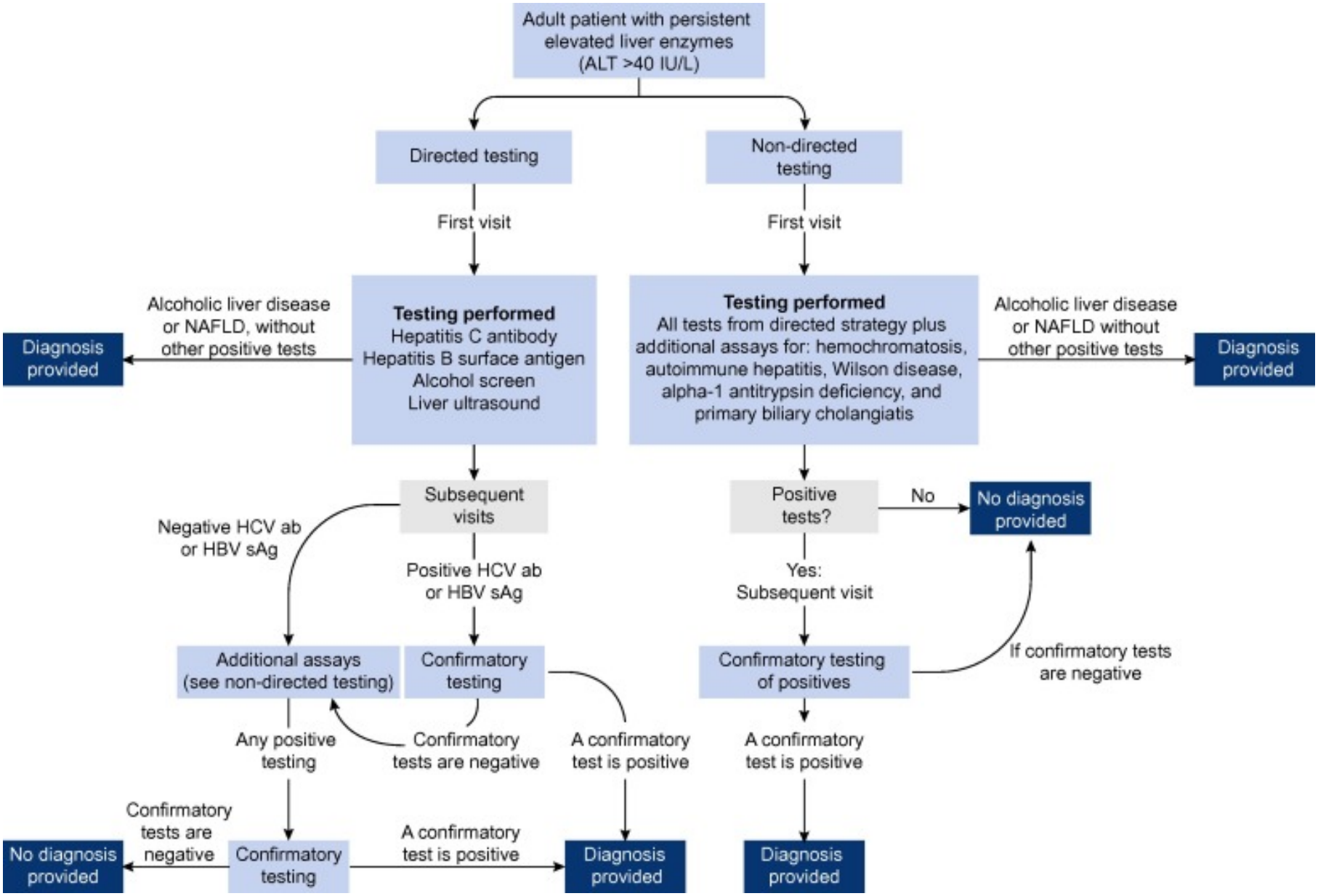
Reinier de Graaf Groep

Diagnostisch algoritme
bij leverziekten e.c.i.

One size fits all…..,
or tailor made?

Extensive testing or focused testing of patients with elevated liver enzymes. Tapper et al., J Hepatol 2017

- Simulation of 10.000 adult outpatients
- Model based on NHANES III and Ballets population
- Directed versus non-directed testing
- Primary outcome: US dollars per diagnosis
- Secondary: doctor visits, false positives, liver biopsies ordered per diagnosis



Tapper et al., J Hepatol 2017

Extensive testing or focused testing of patients with elevated liver enzymes.

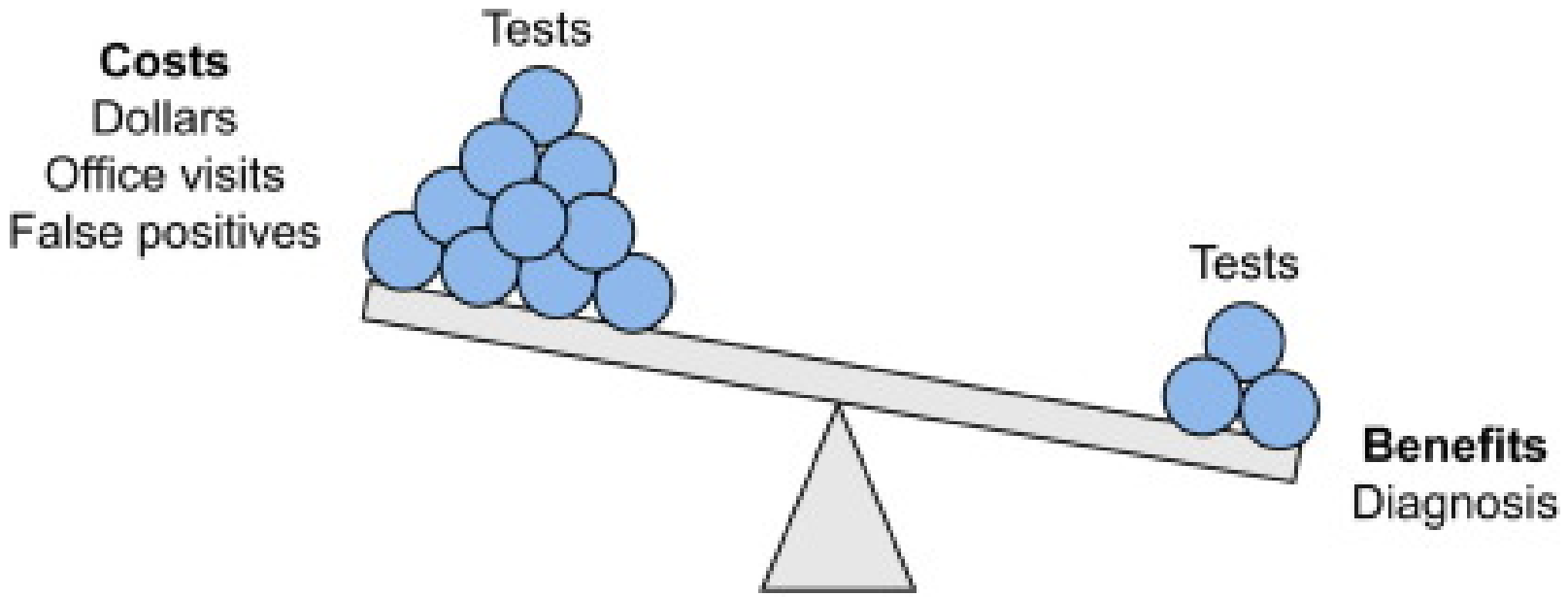
Outcome	Strategy	Average 'cost' per patient	Average diagnoses per patient	Incremental 'cost-diagnosis' ratio
Dollars (2014 USD) per diagnosis	Non-directed testing	447.84	0.54	n.a.
	Directed testing	502.40	0.53	
Visits ('cost') per diagnosis	Non-directed testing	1.35	0.54	n.a.
	Directed testing	1.61	0.53	
False positives ('cost') per diagnosis	Directed testing	0.10	0.53	8.45
	Non-directed testing	0.19	0.54	

Tapper et al., J Hepatol 2017

Extensive testing or focused testing of patients with elevated liver enzymes.

- Extensive testing required lowest monitary cost and fewer doctor visits per diagnosis
- Focused strategy generated fewer false-positives and ordered less liver biopsies (4 vs 8 per 100 pts)
- Focused testing most cost-effective strategy when accounting for pretest probabilities (e.g. when ALD, NAFLD or DILI > 51.1%, 53.0% or 13.0% resp.)

Tapper et al., J Hepatol 2017



When it comes to liver disease testing, less is more
when the pre-test probability of a common disease is high

Diagnostisch algoritme
bij leverziekten e.c.i.

- **Beoordeel de pretest kans op een specifieke leverziekte, toegespitst op het profiel van de patiënt**
- **Sluit de meest voorkomende leverziekten uit: NAFLD, ALD, HBV/HCV, DILI**
- **Indien geen aanknopingspunten of indien haast geboden is, dan non-directed testing inclusief zeldzamere leverziekten**

Referenties

- **Tapper EB, Saini SD, Sengupta N. Extensive testing or focused testing of patients with elevated liver enzymes. J Hepatol. 2017 Feb;66(2):313-319. doi: 10.1016/j.jhep.2016.09.017.**
- **Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol 2017; 112:18-35. doi: 10.1038/ajg.2016.517.**