10th Paris Hepatology Conference

Management of Cholestatic Diseases 2017

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Disclosures

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Lecture fees

Falk Foundation, Gilead, Intercept, Novartis, Roche, Shire, Zambon

Consulting agreements

Intercept, Novartis

Support for investigator-initiated studies

Falk, Intercept

Case report

♀ 34 yrs

2012 (11): Fever for 3 days, increasing pruritus and progressive jaundice

(Serum liver tests elevated, markers for viral hepatitis, AIH, hereditary metabolic disease neg.)

- No relevant diseases in the past
- Family: no liver disease
- Alcohol: 2 U / week
- Drugs: none
- Medication: oral contraceptives since 15 years
- Work: post office

Physical Examination 2013 (1)

♀ 34 yrs

- Icteric, exhausted, intermittently scratching woman
- 165 cm, 66 kg
- No other relevant diagnostic findings

Lab

♀ 34 yrs

		2013 (1)	
Bilirubin	(≤ 17 µmol/l)	565	(>90% conjugated)
ALT	(≤ 45 U/l)	55	
AST	(≤ 40 U/l)	70	
γGT	(≤ 60 U/l)	23	
ALP	(≤ 120 U/l)	347	

Diagnostic approach to cholestasis

♀ 34 y

Detailed history, physical examination, serum liver tests

Elevated ALP + γGT and/or bilirubin

(HBsAg and anti-HCV neg.)

Ultrasound → Dilated ducts, stones, tumor

EASL CP Guidelines management of cholestatic liver diseases. J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; under review

Abdominal Imaging

♀ 34 yrs

Ultrasound:

-Normal aspect of the liver, no focal lesions

-Sludge in the gallbladder

-No bile duct obstruction (by stones or mass)

Abdominal Imaging

♀ 34 yrs

Ultrasound:

-Normal aspect of the liver, no focal lesions

-Sludge in the gallbladder

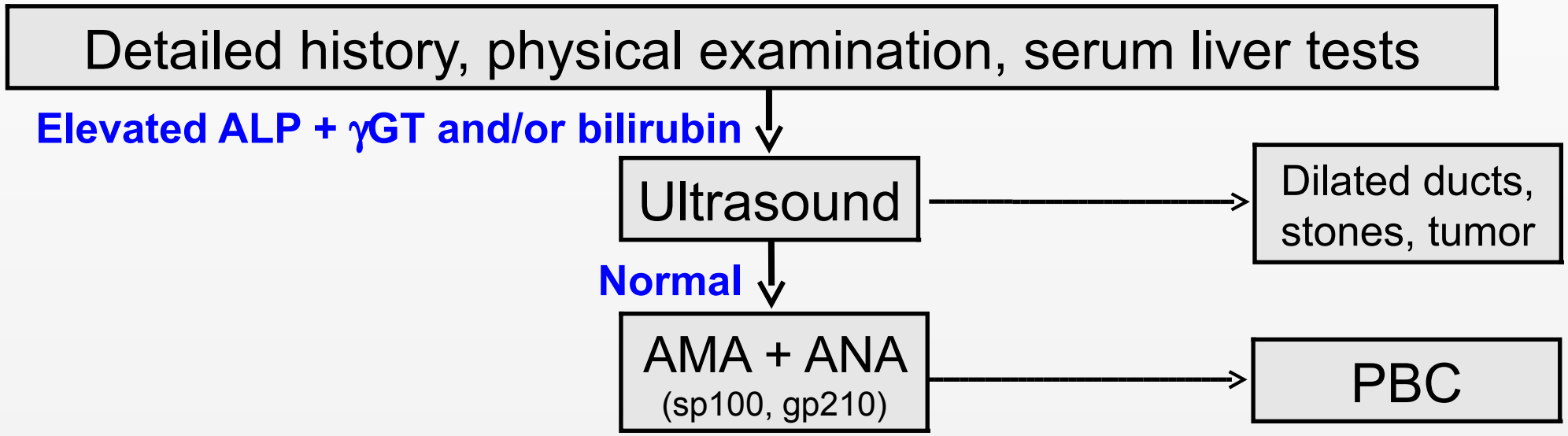
-No bile duct obstruction (by stones or mass)

Fibroscan: 17.7 kPa (IQR 3.3, success rate 100%)

CAP: 154 dB/m (IQR 23)

Diagnostic approach to cholestasis

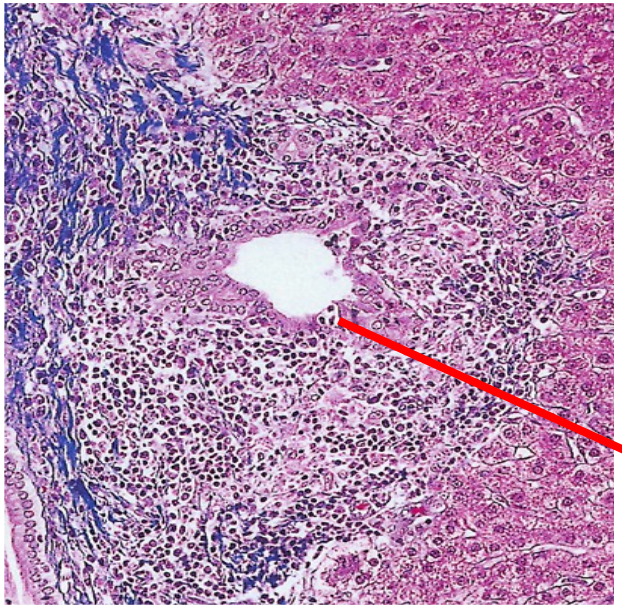
♀ 34 y



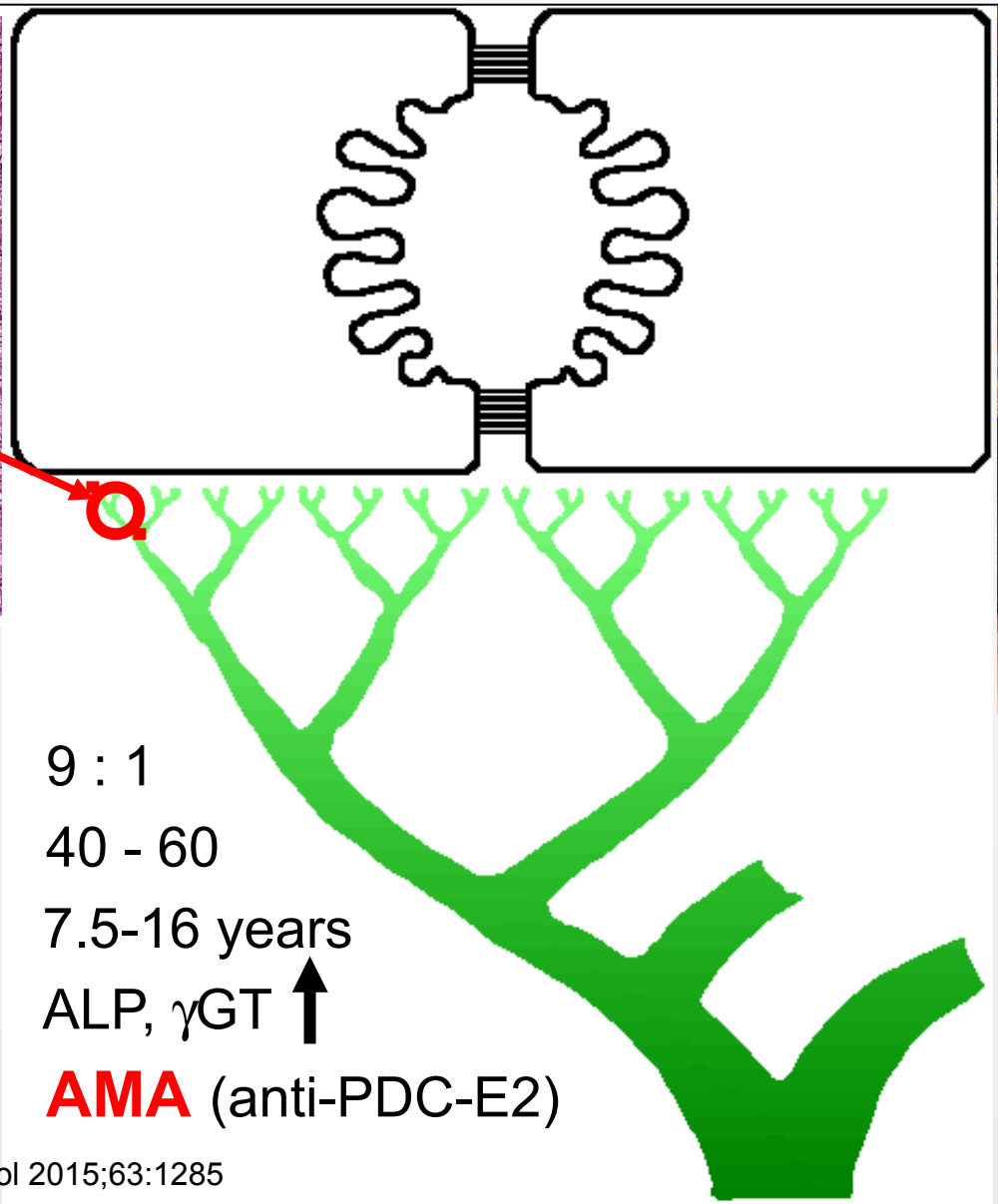
EASL CP Guidelines management of cholestatic liver diseases. J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; submitted

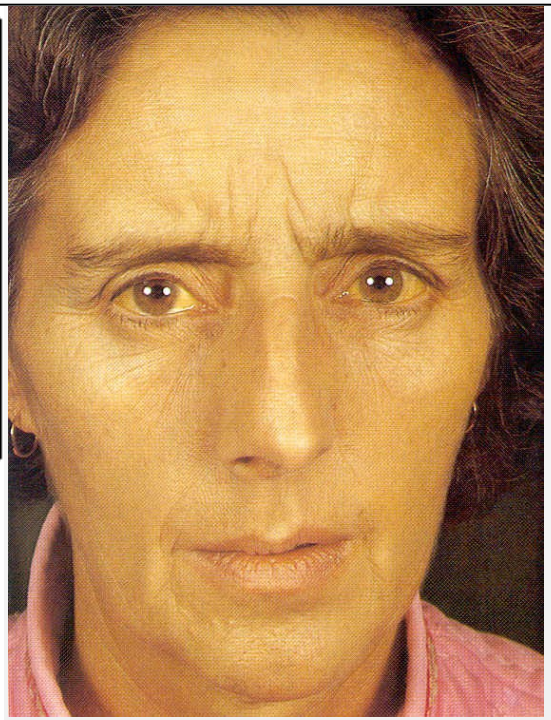
Primary biliary cholangitis* (PBC)

Characteristics



Florid, non-suppurative, destructive cholangitis





Sherlock and Summerfield, 1991

Women : Men	9 : 1
Age at diagnosis	40 - 60
Survival without treatment	7.5-16 years
Cholestasis	ALP, γGT ↑
Autoantibodies	**AMA** (anti-PDC-E2)

Symptoms

- Fatigue
- Pruritus
- Sicca syndrome
- …

* Beuers , Gershwin, …Poupon. J Hepatol 2015;63:1285

Primary biliary cholangitis:

Potential pathogenetic mechanisms

Immune-mediated bile duct injury

↓

Bile duct injury by hydrophobic bile acids

↓

Cholestasis with retention of hydrophobic bile acids in liver

↓

Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

↓

Liver failure

Genetic Predisposition

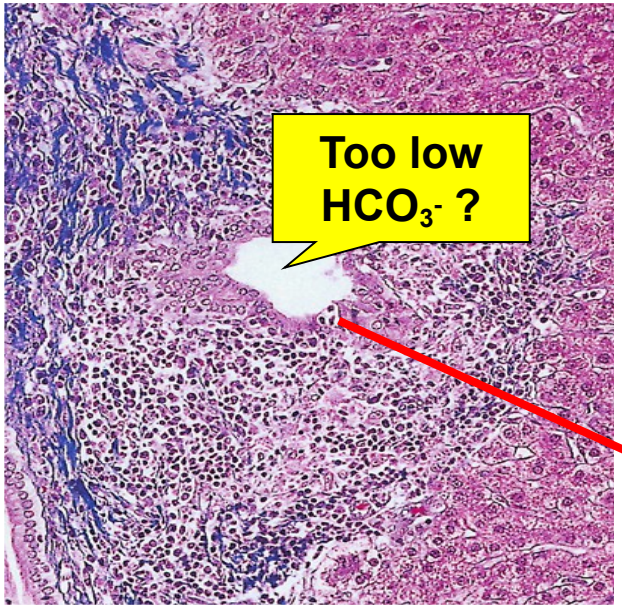
Environmental factors
(molecular mimicry)

Cellular/humoral immune response

Beuers, Boyer, Paumgartner. Hepatology 1998;28:1449

Primary biliary cholangitis (PBC)

Characteristics



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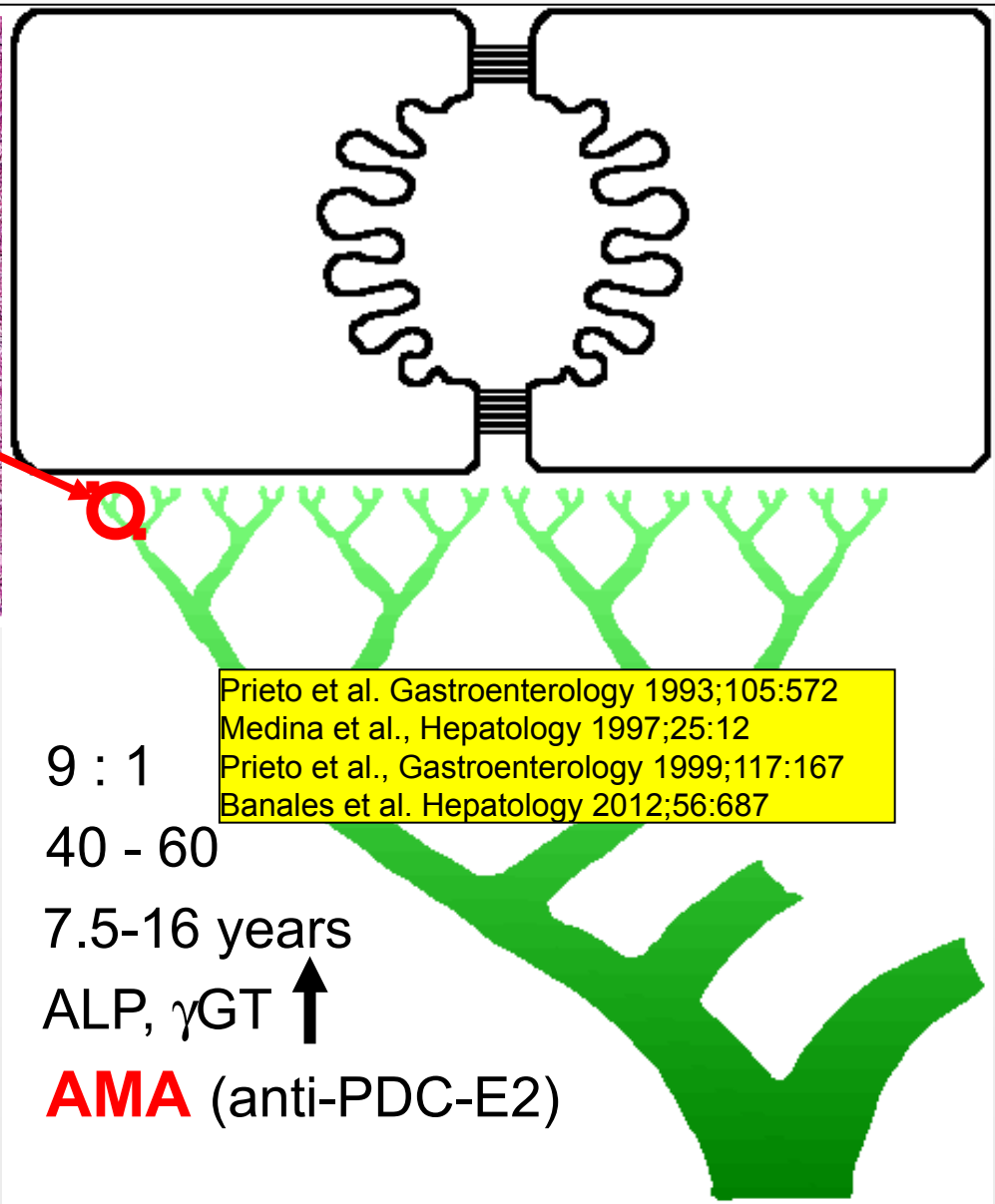

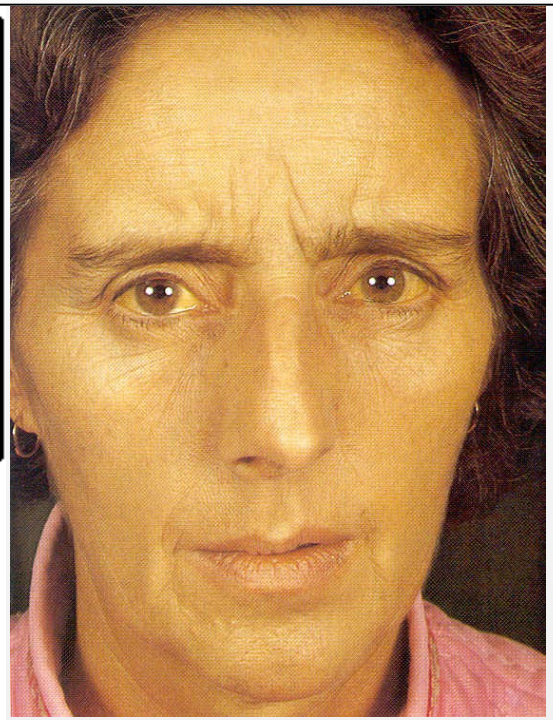

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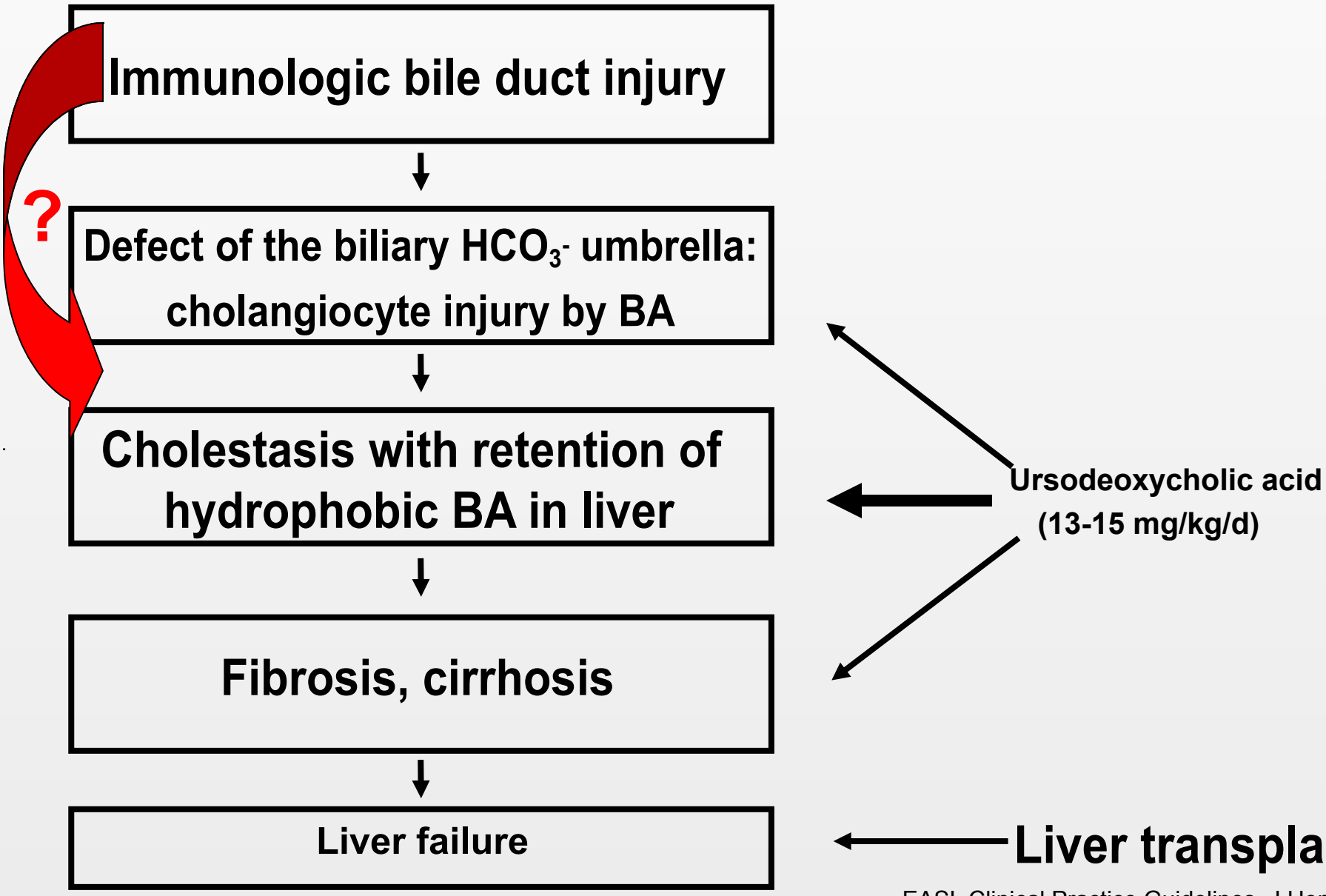
Prieto et al. Gastroenterology 1993;105:572
Medina et al., Hepatology 1997;25:12
Prieto et al., Gastroenterology 1999;117:167
Banales et al. Hepatology 2012;56:687

Symptoms

- Fatigue
- Pruritus
- Sicca syndrome
- …

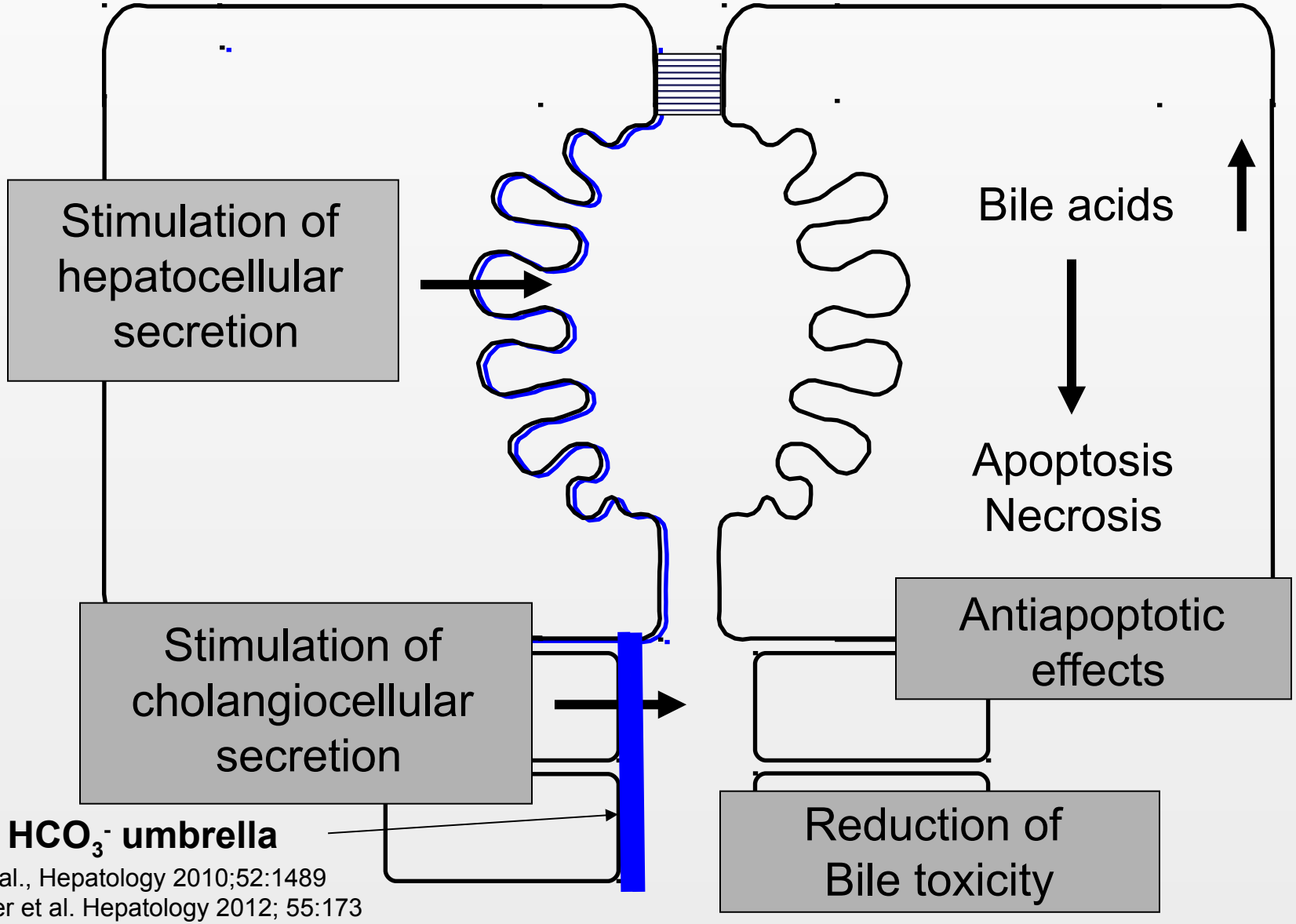
Primary biliary cholangitis: Therapy

Potential pathogenetic mechanisms



EASL Clinical Practice Guidelines, J Hepatol 2009;51:237

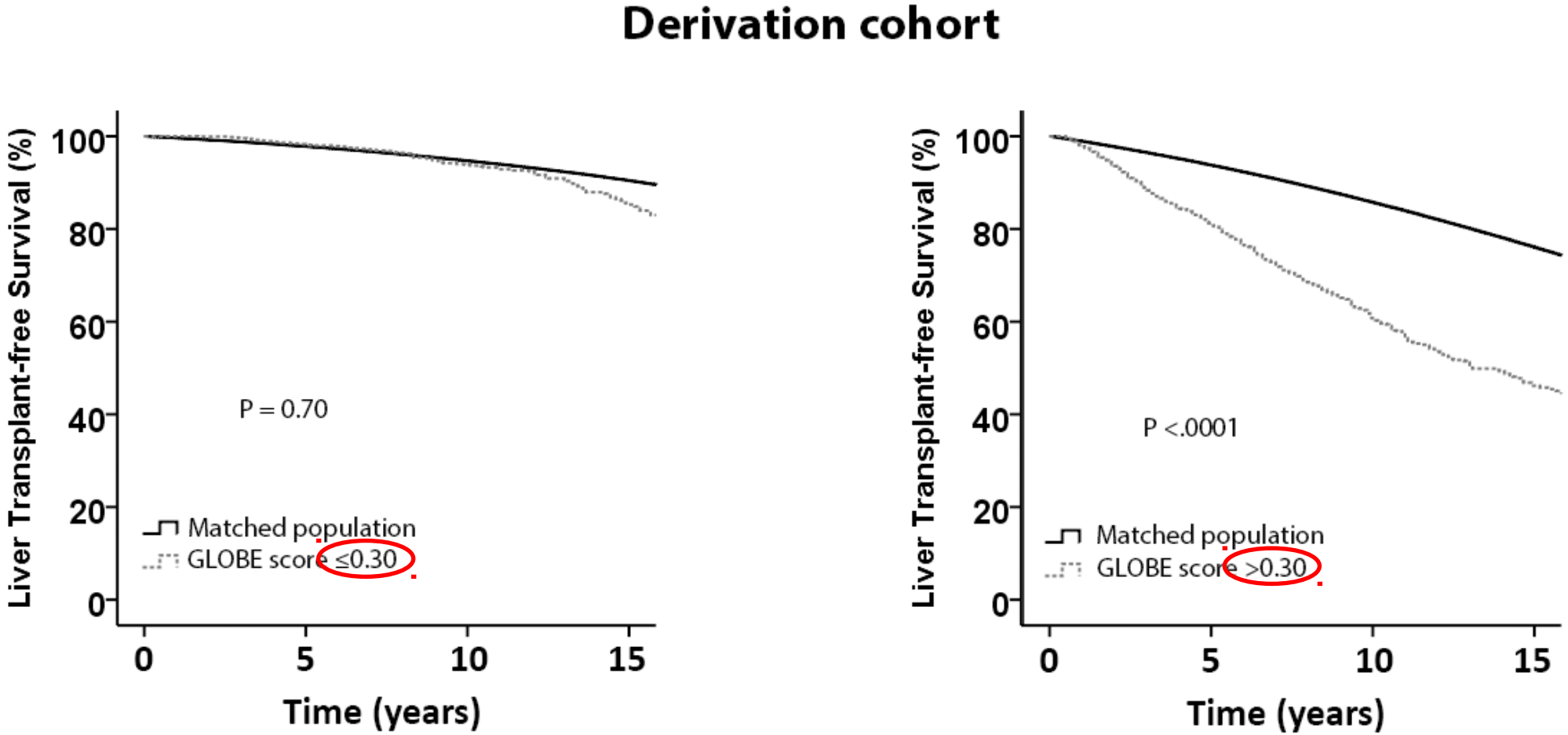
Putative mechanisms and sites of action of UDCA in cholestatic liver diseases



Beuers et al., Hepatology 2010;52:1489
Hohenester et al. Hepatology 2012; 55:173
Chang JC et al. Hepatology 2016; 64:522

Beuers. Trauner, Jansen, Poupon. J Hepatol 2015;62:S35

The PBC GLOBE score predicts outcome after 1 year of UDCA



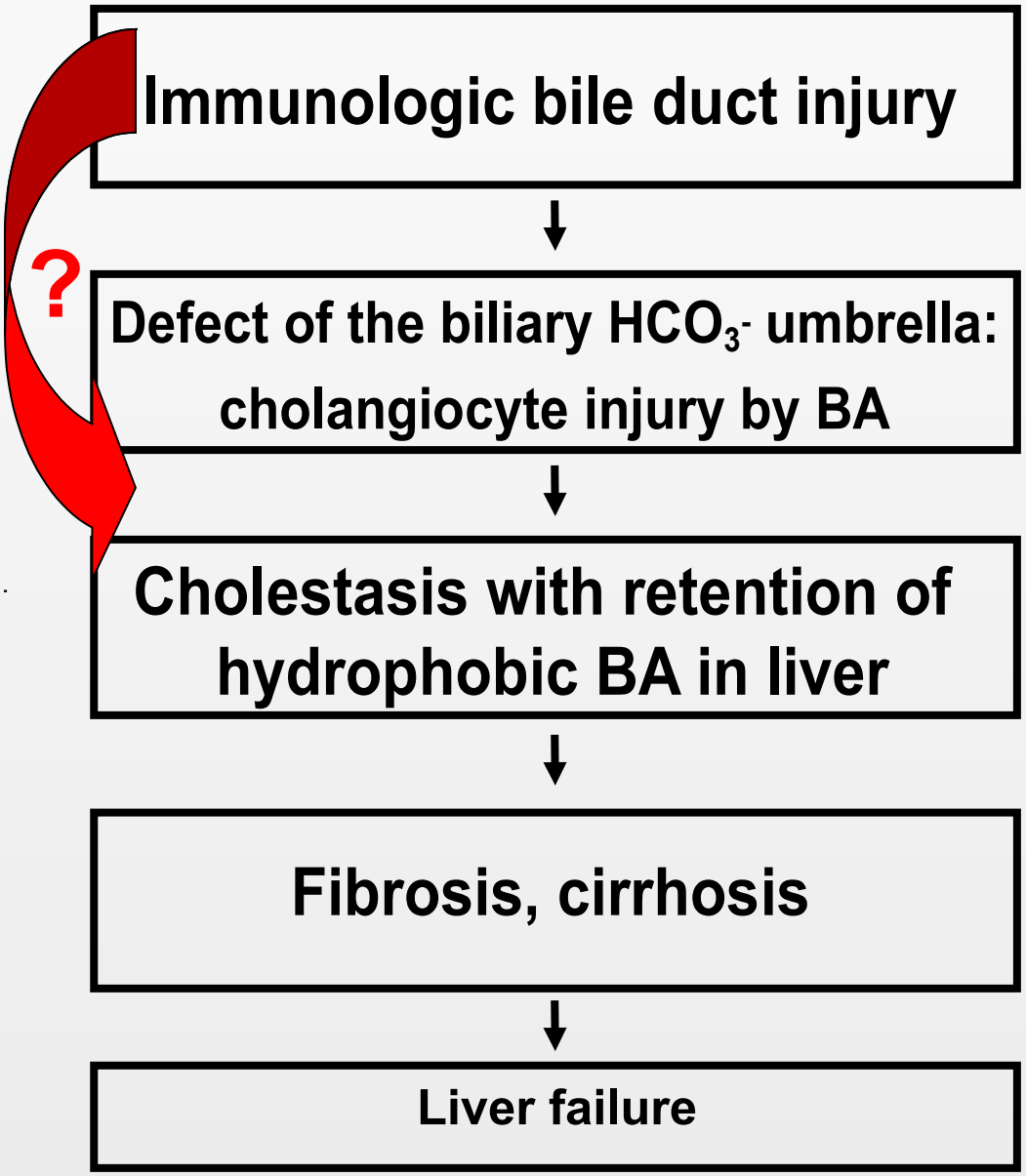
GLOBE score: Age, bilrubin, alkaline phosphatase, albumin, platelets

n=4111 PBC patients

Lammers et al., Gastroenterology 2015;149:1804

Primary biliary cholangitis: *Potentially new* Therapy

Potential pathogenetic mechanisms



RCT (Phase 3)

FXR agonists**: e.g. **obeticholic acid

GR/PXR agonists: e.g. budesonide?

PPARα agonists: e.g. bezafibrate?

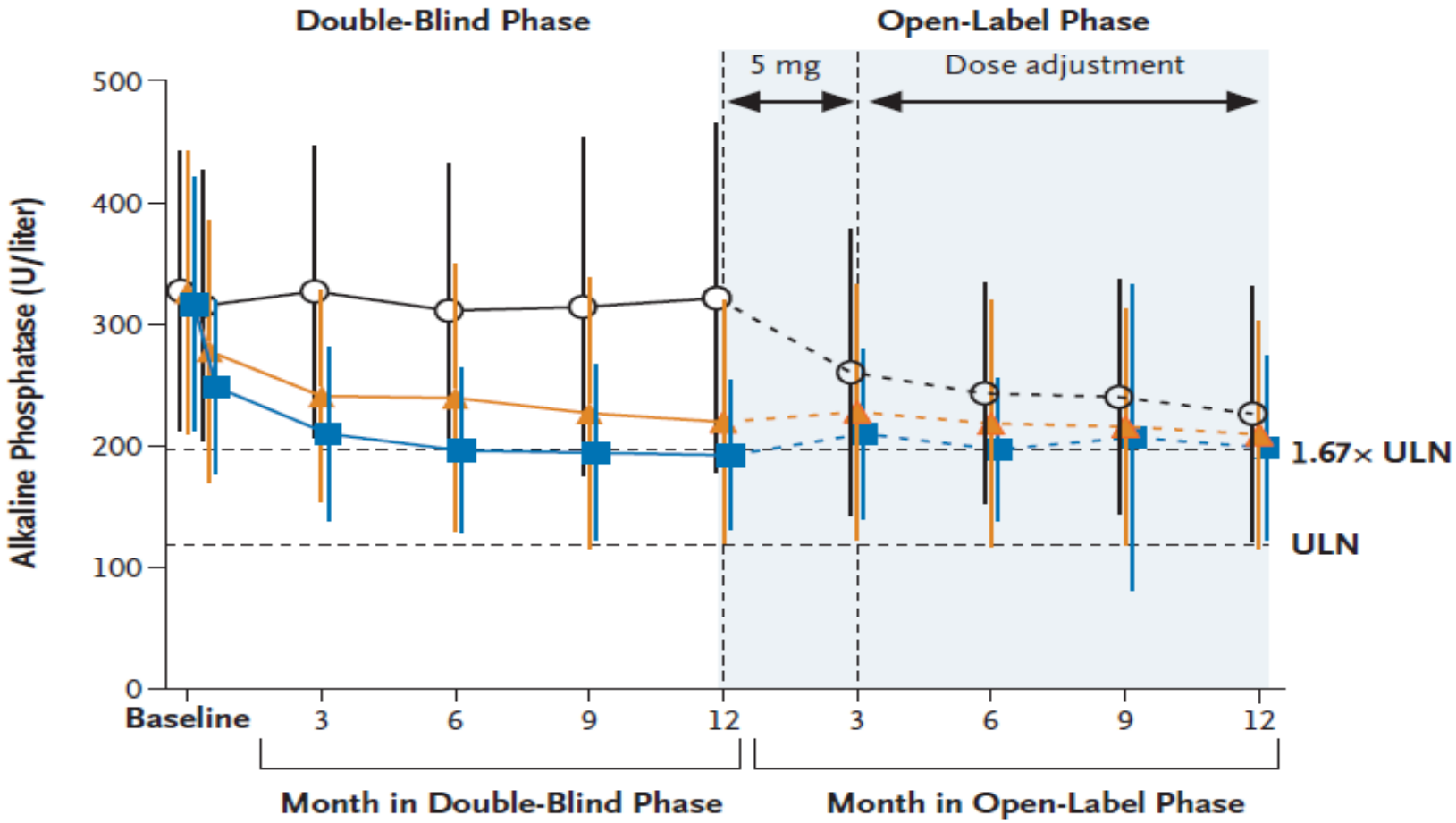
Ursodeoxycholic acid (13-15 mg/kg/d)

Liver transplantation

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237

Obeticholic acid improves serum alkaline phosphatase (ALP) in PBC

Phase 3



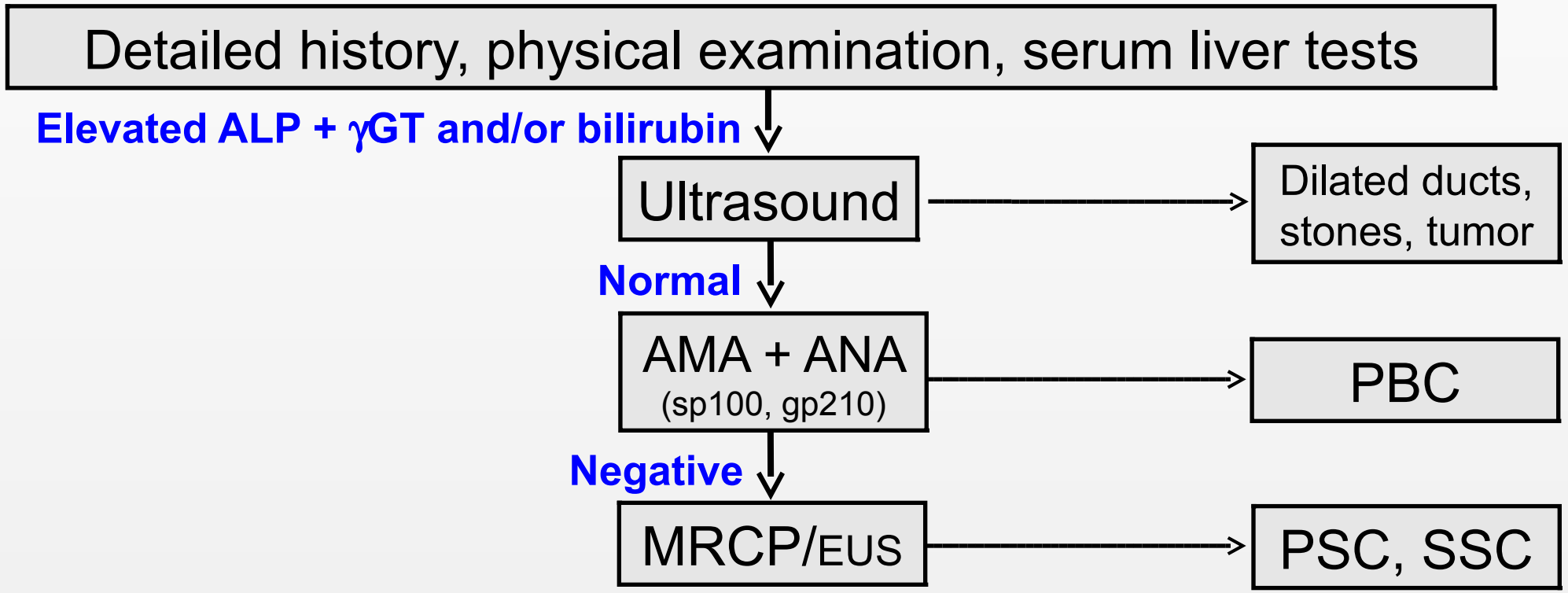
No. of Patients									
Placebo	73	69	71	69	70	64	60	59	59
Obeticholic acid, 5–10 mg	70	69	69	66	64	63	62	62	60
Obeticholic acid, 10 mg	73	66	64	64	62	64	59	61	59

Nevens et al., New Engl J Med 2016; 375: 631

Mean ± SEM

Diagnostic approach to cholestasis

♀ 34 y



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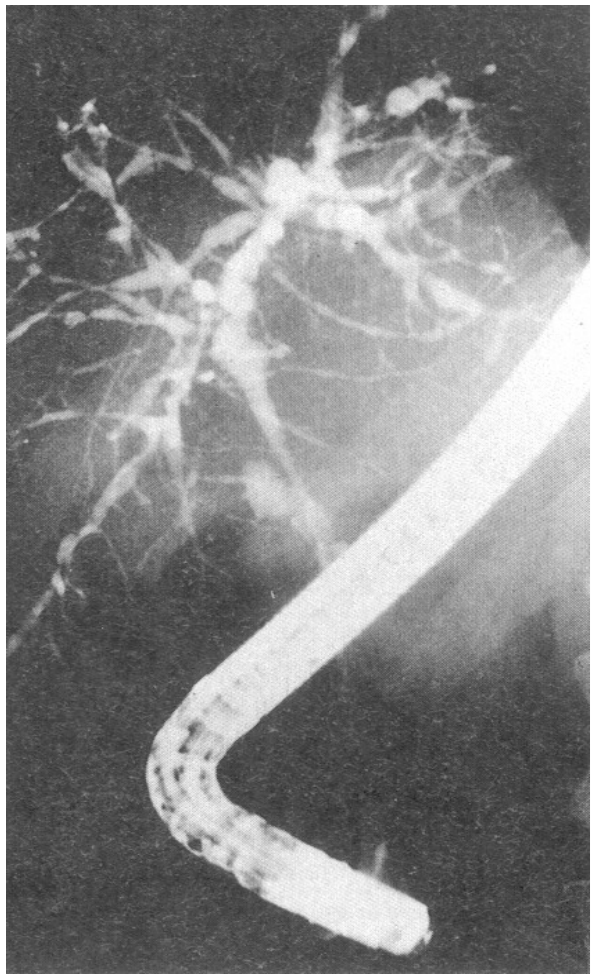
Primary sclerosing cholangitis

The typical patient in the Netherlands

Point prevalence	(per 100.000)	6.0
Incidence	(per 100.000/year)	0.5
Age at manifestation	(yrs, mean)	38.9
Male gender		64%
Inflammatory bowel disease		68%
UDCA treatment		92%
LTx-free survival	(yrs, mean)	**21.2**
(LTx-free survival of 450 patients at 3 LTx centres		13.2)
Cholangiocarcinoma		7%
Colorectal carcinoma		3%

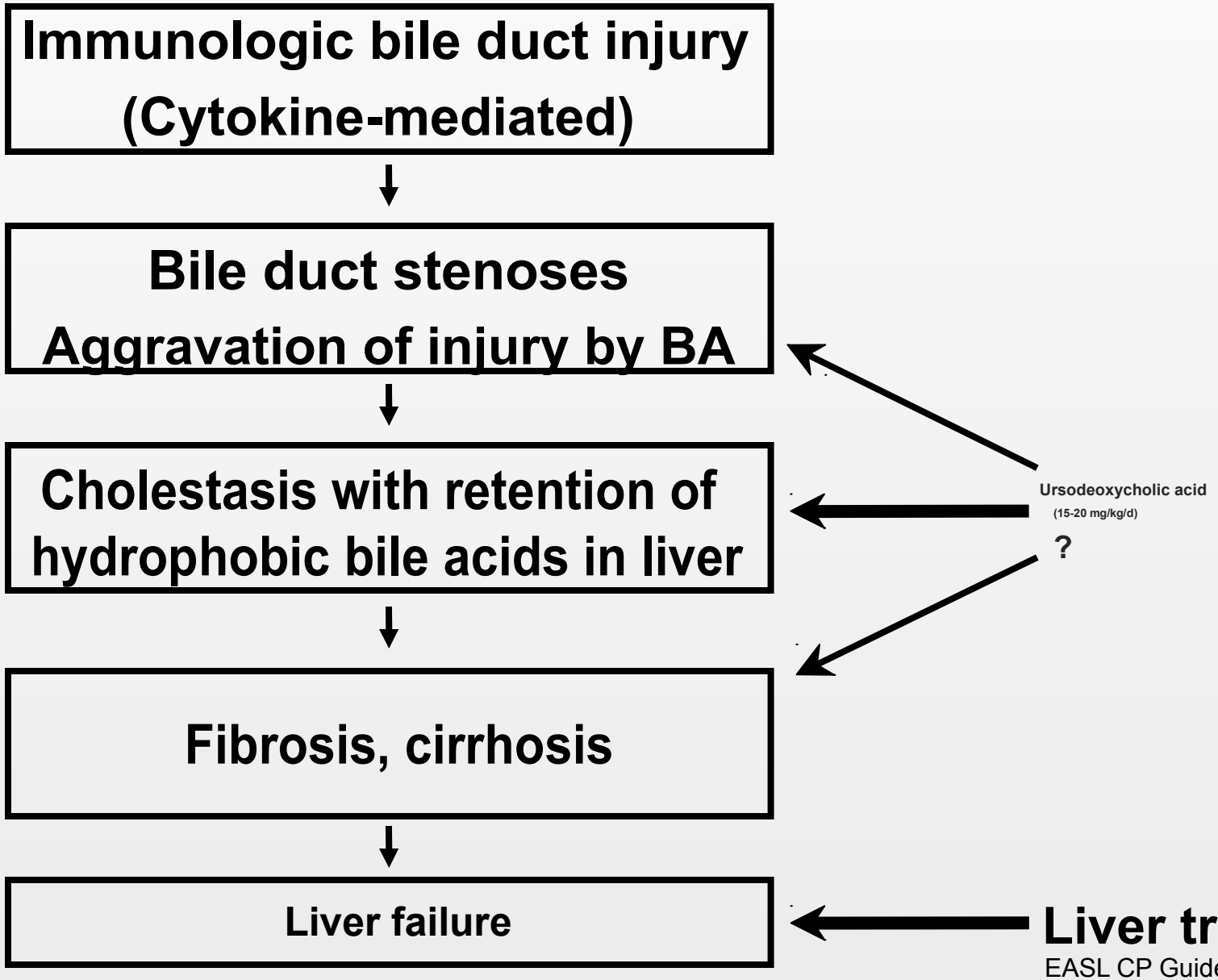


m, 42 years

Boonstra, Ponsioen et al., Hepatology 2013;58:2045 (population-based cohort [n=590, follow-up 92 months] covering the Northern half of the Netherlands)

PSC : Therapy

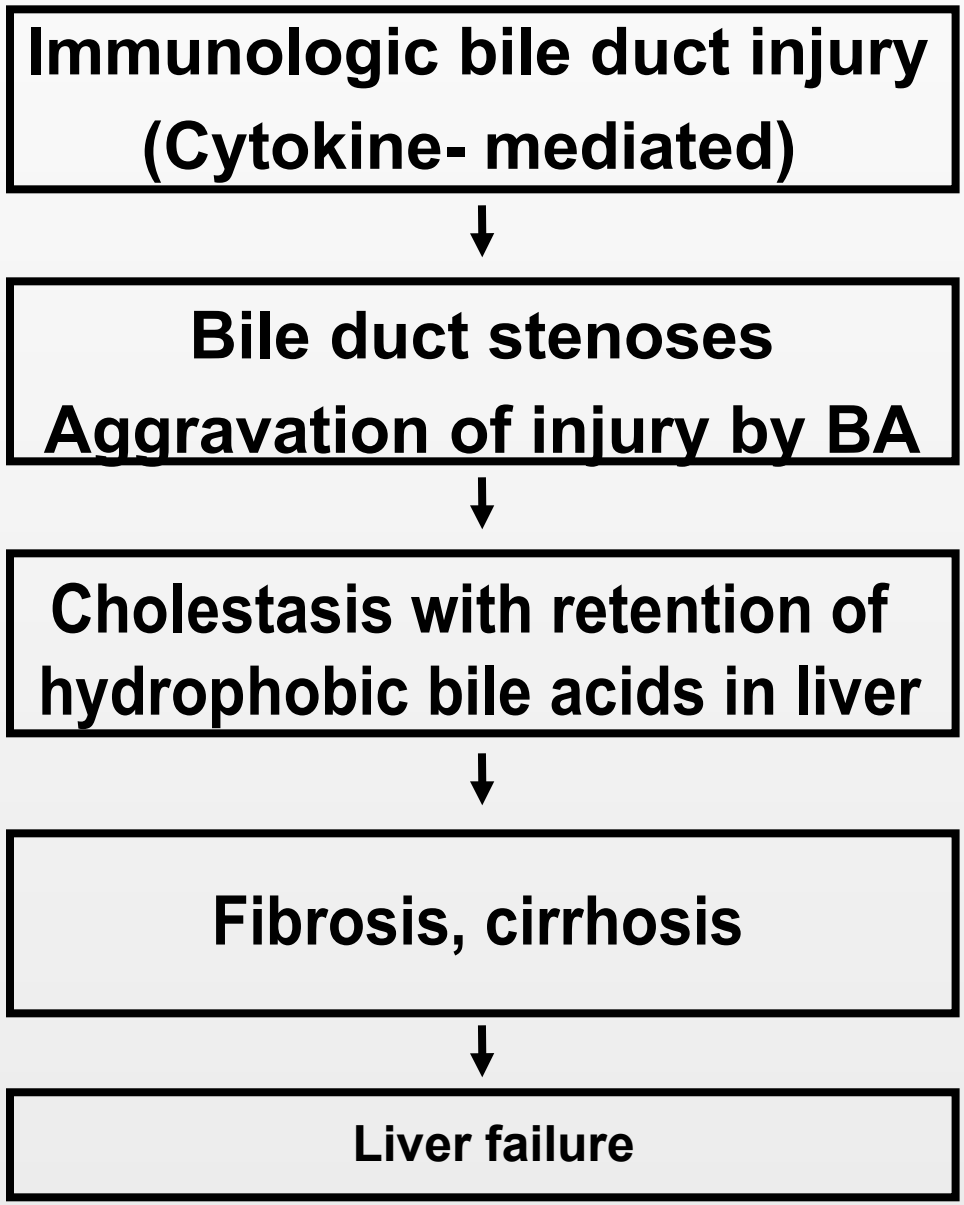
Pathogenetic model



EASL CP Guidelines, J Hepatol 2009;51:237

PSC : Therapy *under evaluation*

Pathogenetic model



Vedolizumab ?
norUDCA ?

RCT (Phase 2)

Endoscopic dilatation

RCT (Phase 3)

Ursodeoxycholic acid
(15-20 mg/kg/d)

Nuclear receptor agonists ?
- PPARα

RCT (Phase 2)

FGF19 homologues ?

Liver transplantation

The Patient with Sclerosing Cholangitis

Diagnostic Algorithm

Sclerosing Cholangitis

↓

History, additional diagnostic procedures:
Causes of secondary sclerosing cholangitis ?

↓ no

Primary sclerosing cholangitis

yes ↓

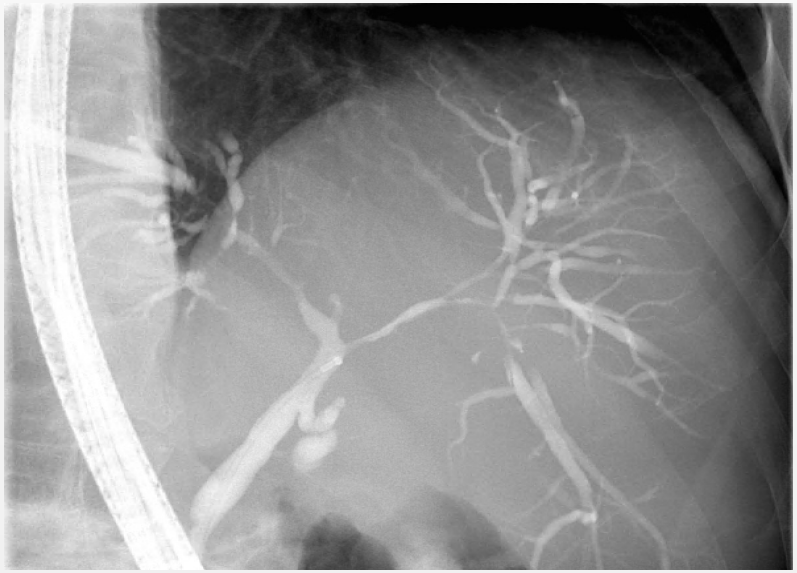
- Bile duct surgery
- Abdominal trauma
- Choledocholithiasis *
- Cholangiocarcinoma *
- Recurrent pancreatitis
- Ischemic cholangitis
- Eosinophilic cholangitis
- Mastcell cholangiopathy
- AIDS cholangiopathy
- Recurrent pyogenic cholangitis
- Portal hypertensive biliopathy
- **IgG4-assoc. cholangitis (IAC)**
- *ABCB4* deficiency
- others

Secondary sclerosing cholangitis

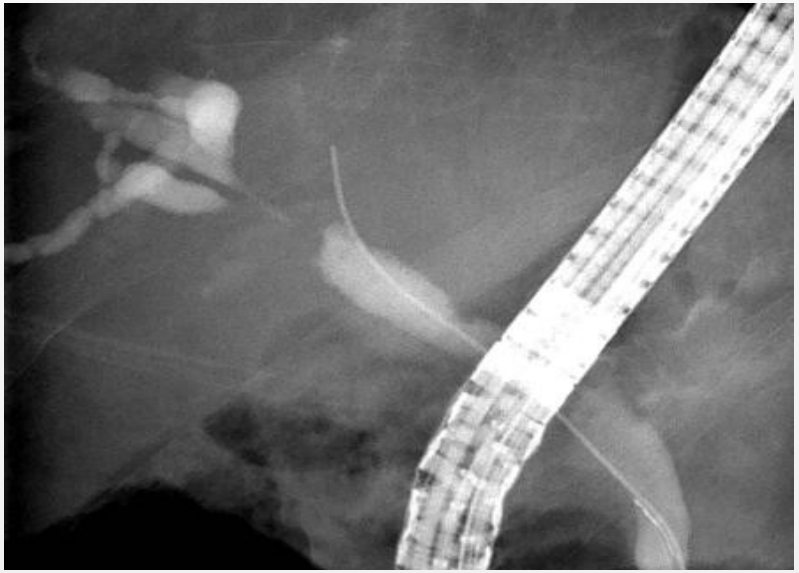
*** may be consequence of PSC**

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237

IgG4-associated cholangitis mimics PSC and CCA



Cholangiographic appearance mimicking primary sclerosing cholangitis (**PSC**)

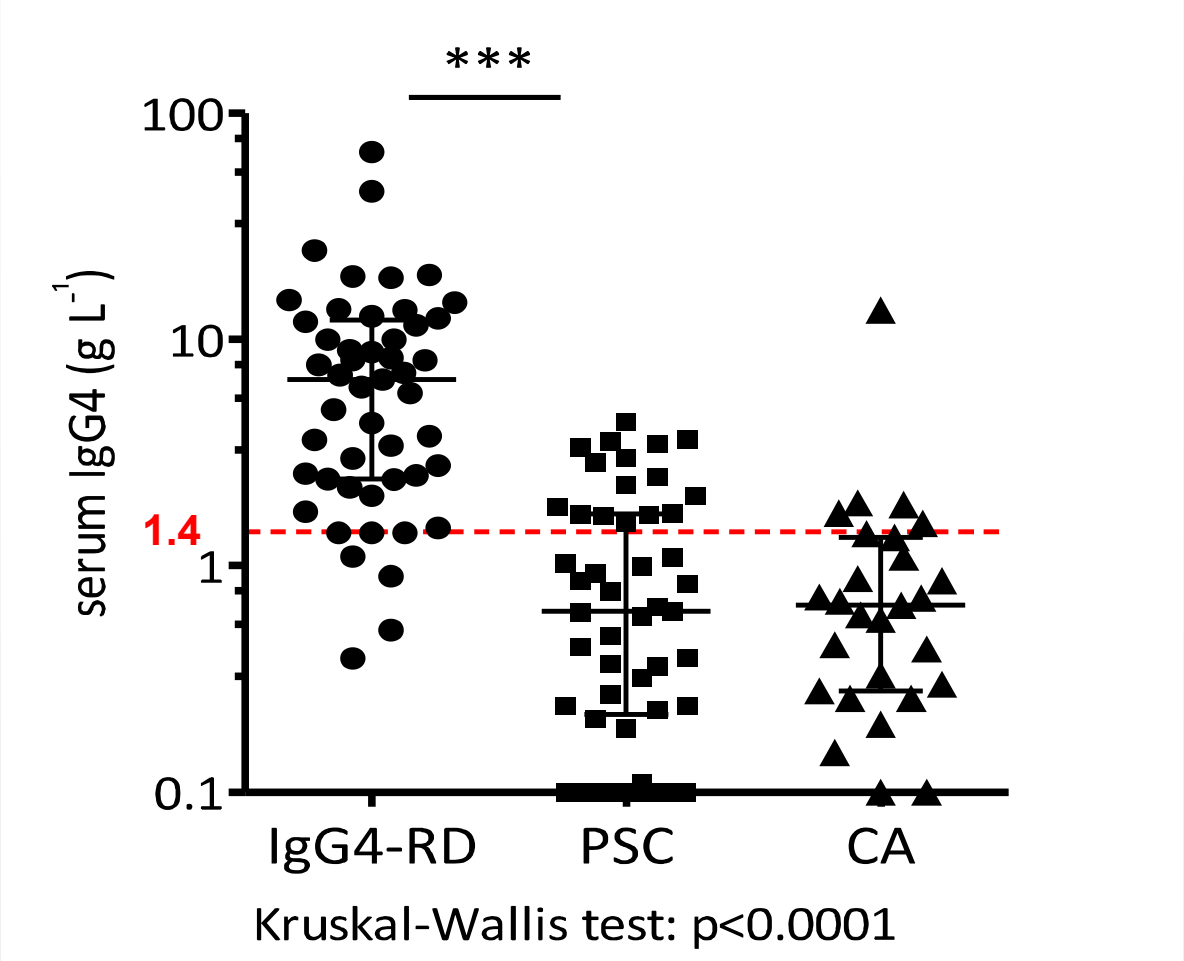


Cholangiographic appearance mimicking cholangiocarcinoma (**CCA**)

Misdiagnosis is common!

Hubers & Beuers, Viszeralmedizin 2015;31:185

Diagnostic value of serum IgG4 is limited



Sensitivity = 86%
Specificity = 75%

Doorenspleet, Hubers et al. Hepatology. 2016; 64: 501

n=125

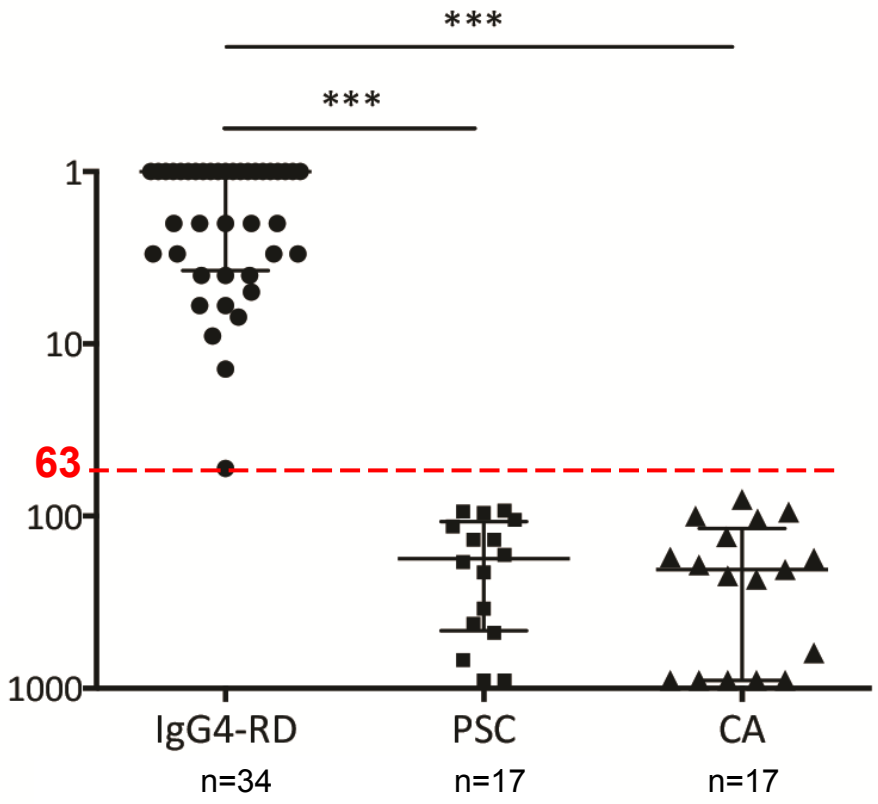
CA: Biliary and pancreatic malignancies

Distinguishing PSC and IgG4-associated cholangitis

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than PSC

Rank of the most prominent IgG4+ BCR clone
(detected by NGS)

among all IgG clones



Sensitivity = 100%
Specificity = 100%

Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

BCR: B-cell receptor

CA: Biliary and pancreatic malignancies

Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340

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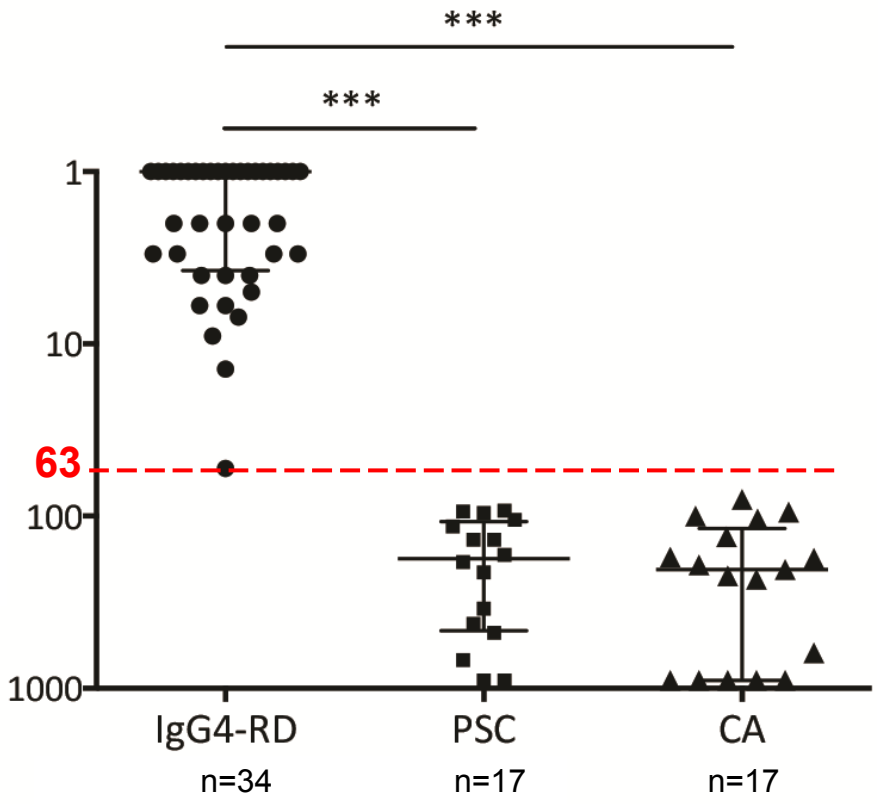

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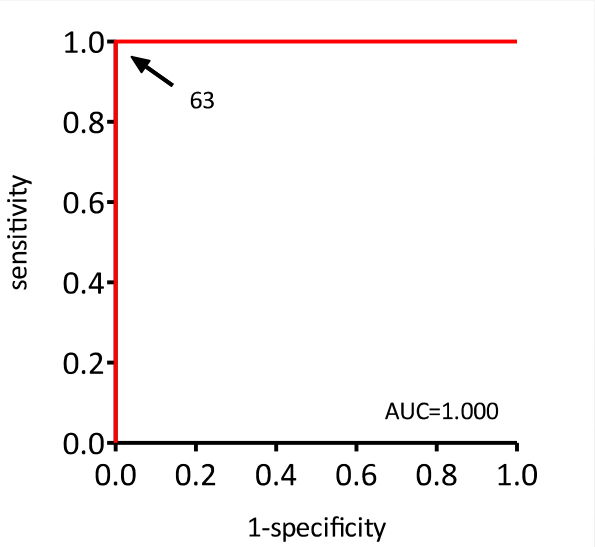

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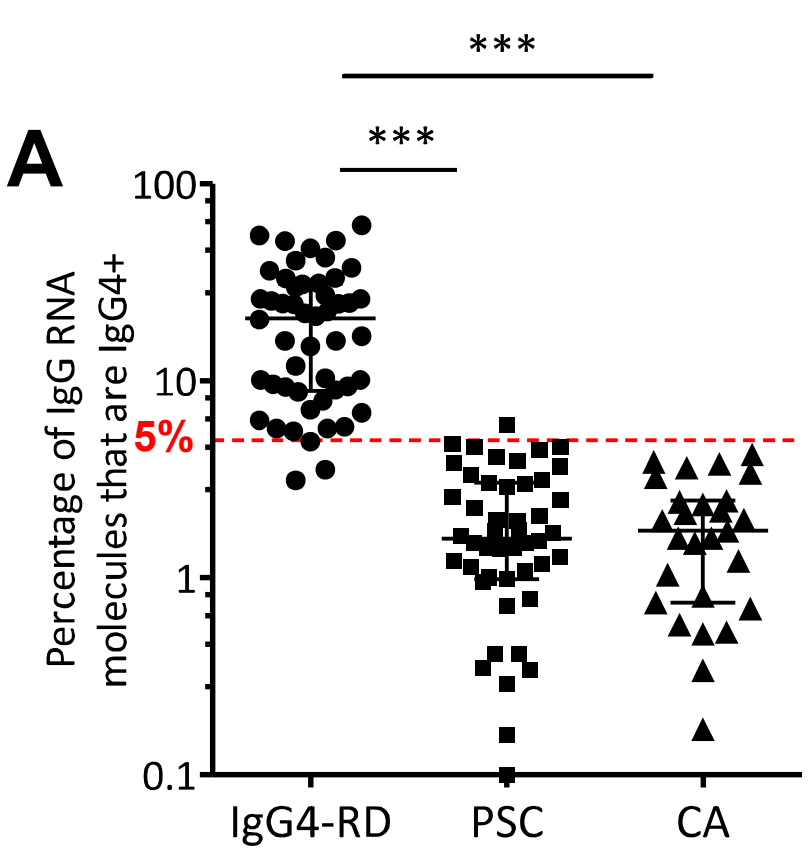
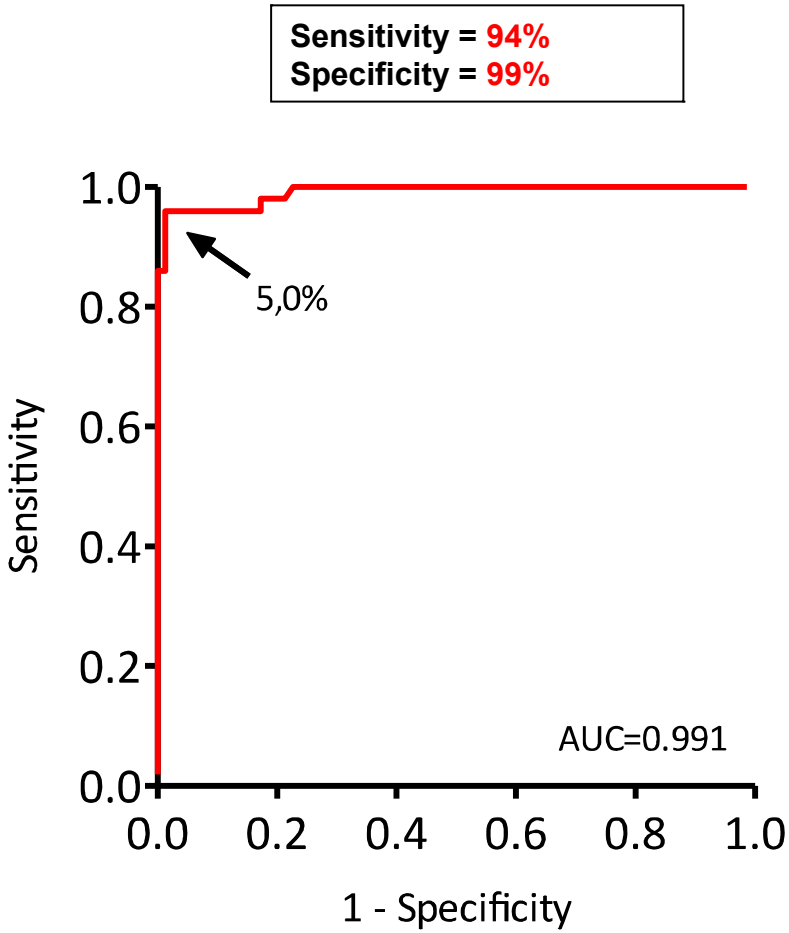
CA: Biliary and pancreatic malignancies

Distinguishing PSC and IgG4-Related Disease

An affordable IgG4/IgG RNA qPCR is almost as accurate as NGS technology





Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

n=125

CA: Biliary and pancreatic malignancies

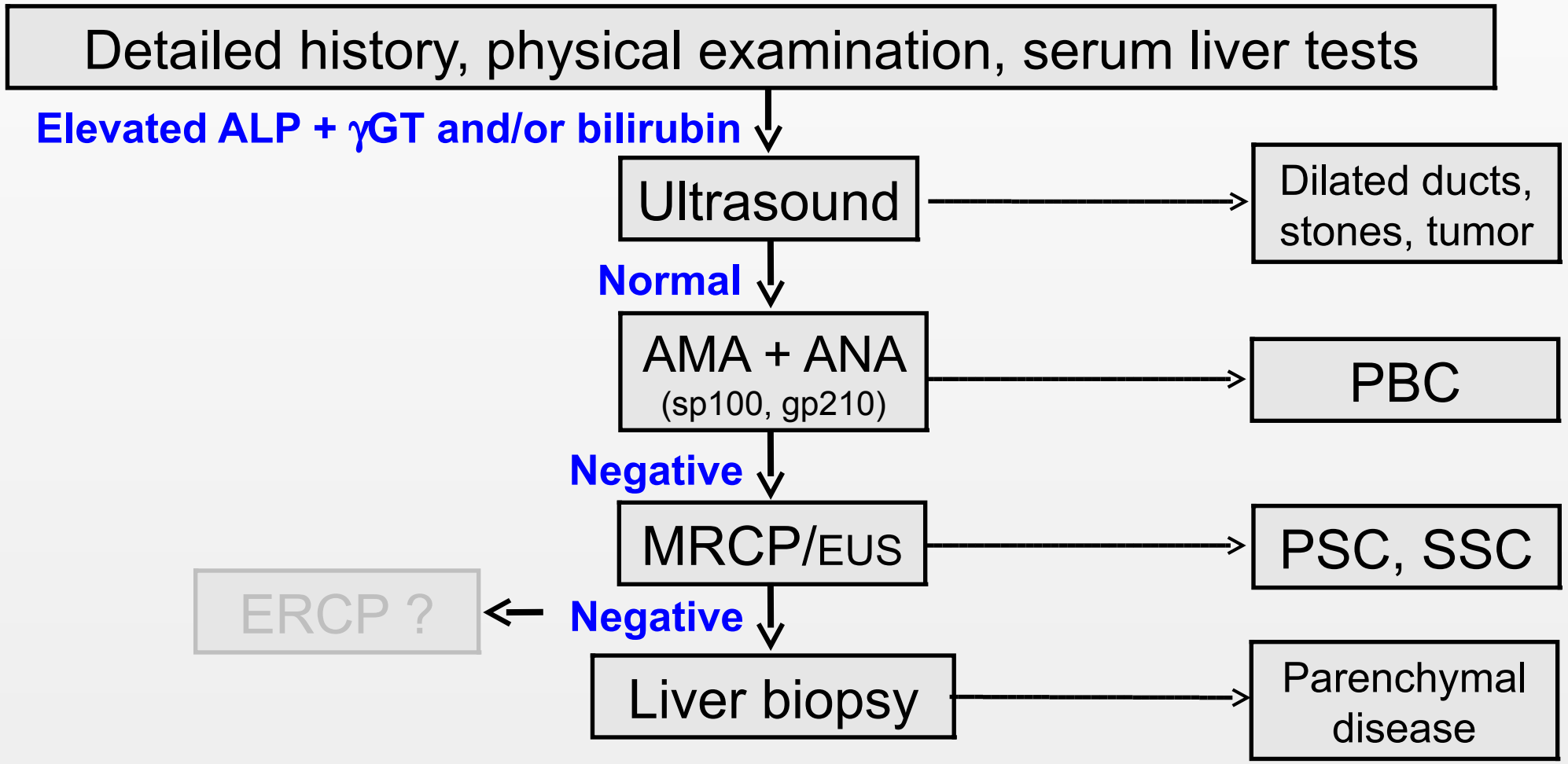
Chronic Exposure to Occupational Antigens May Play a Key Role in the Initiation and/or Maintenance of IgG4-Related Disease

"Blue collar" work (> 1 year, mostly lifelong)	Amsterdam	Oxford
IAC/AIP (n=25 and 44, resp.)	88 %	61 %
PSC (n=21 and 22, resp.)	16 %	22 %

Maillette de Buy Wenniger, Curver, Beuers. Hepatology 2014: 60:1453

Diagnostic approach to cholestasis

♀ 34 yrs



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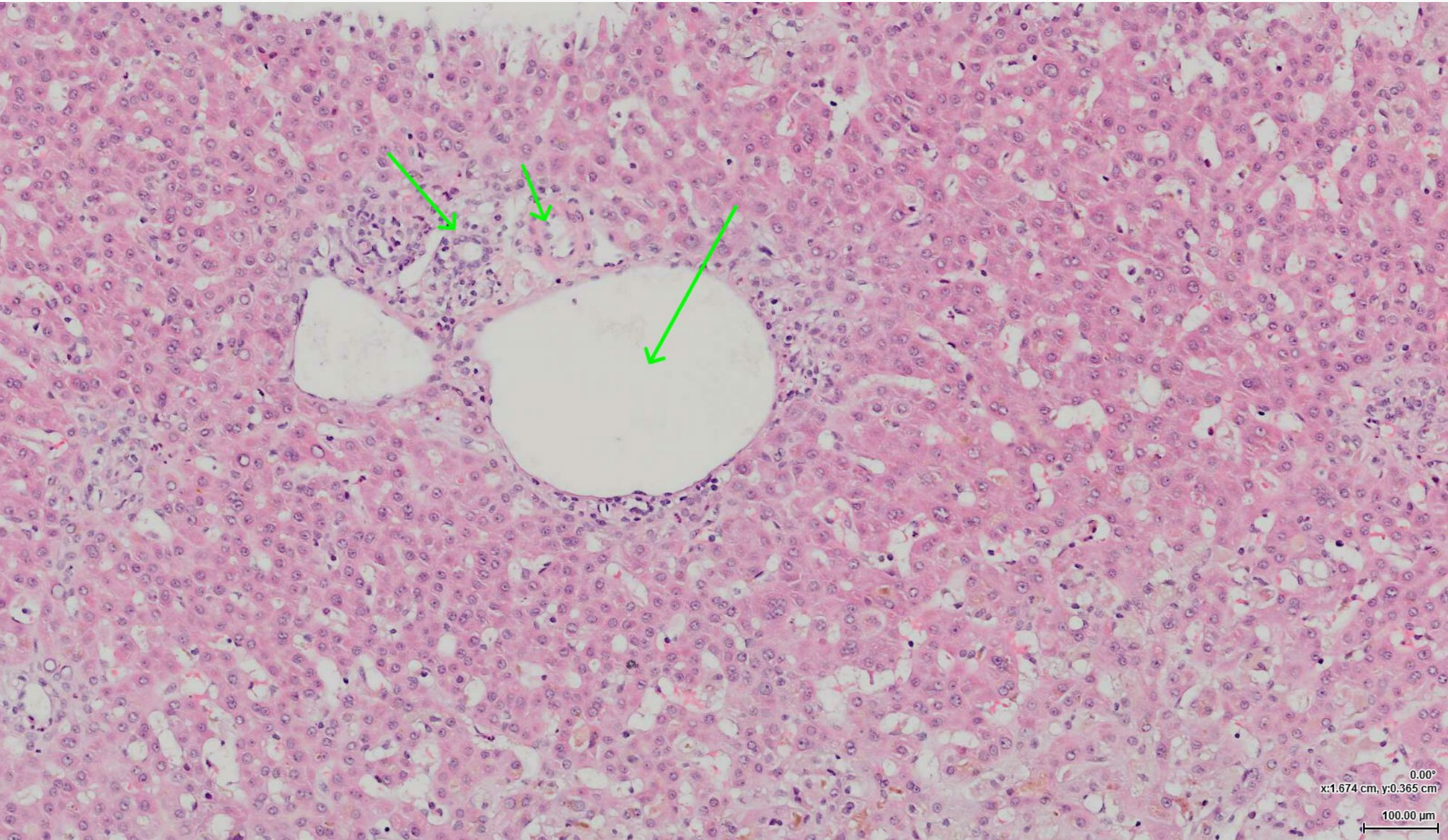
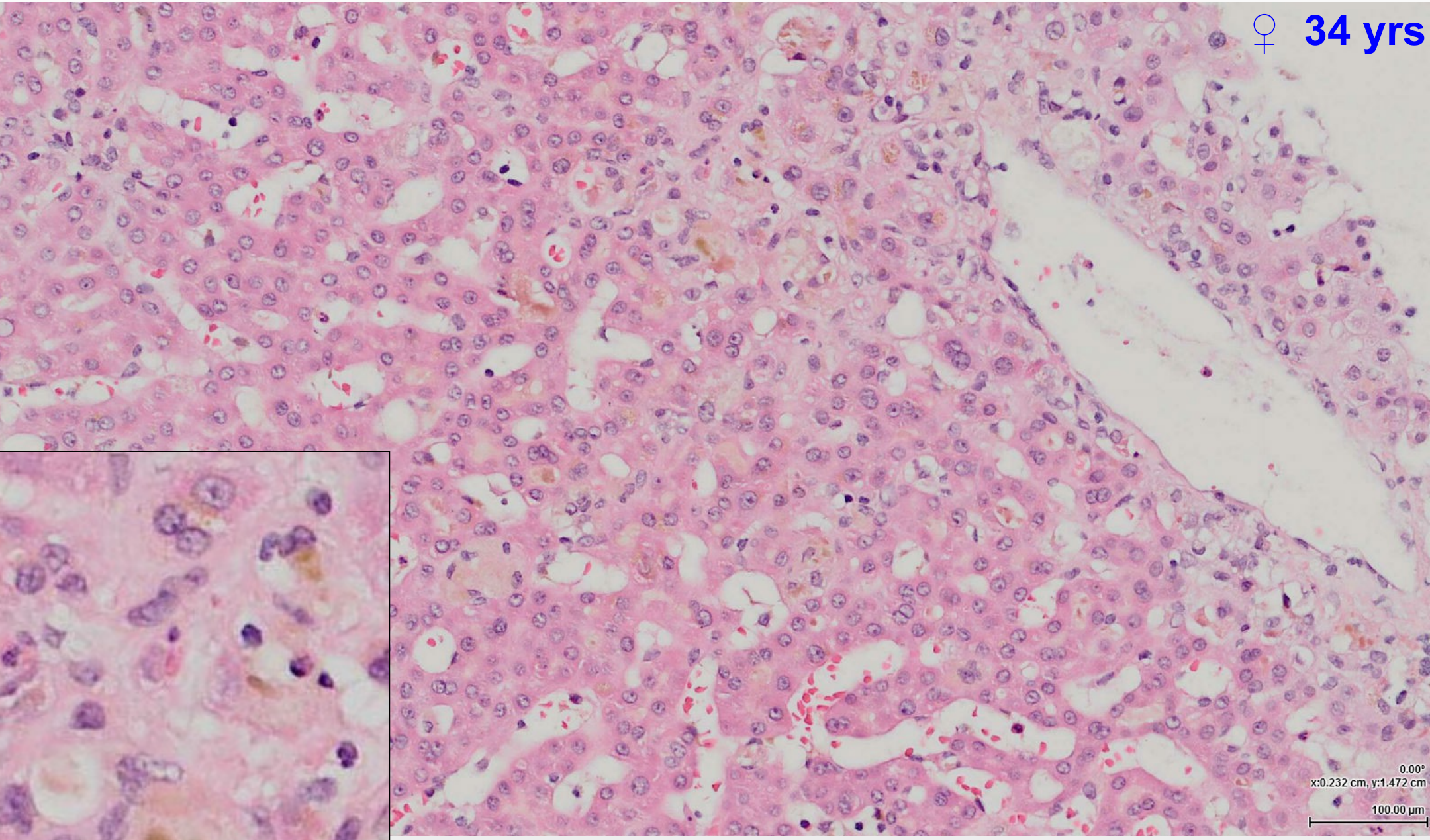
Liver biopsy

♀ 34 yrs



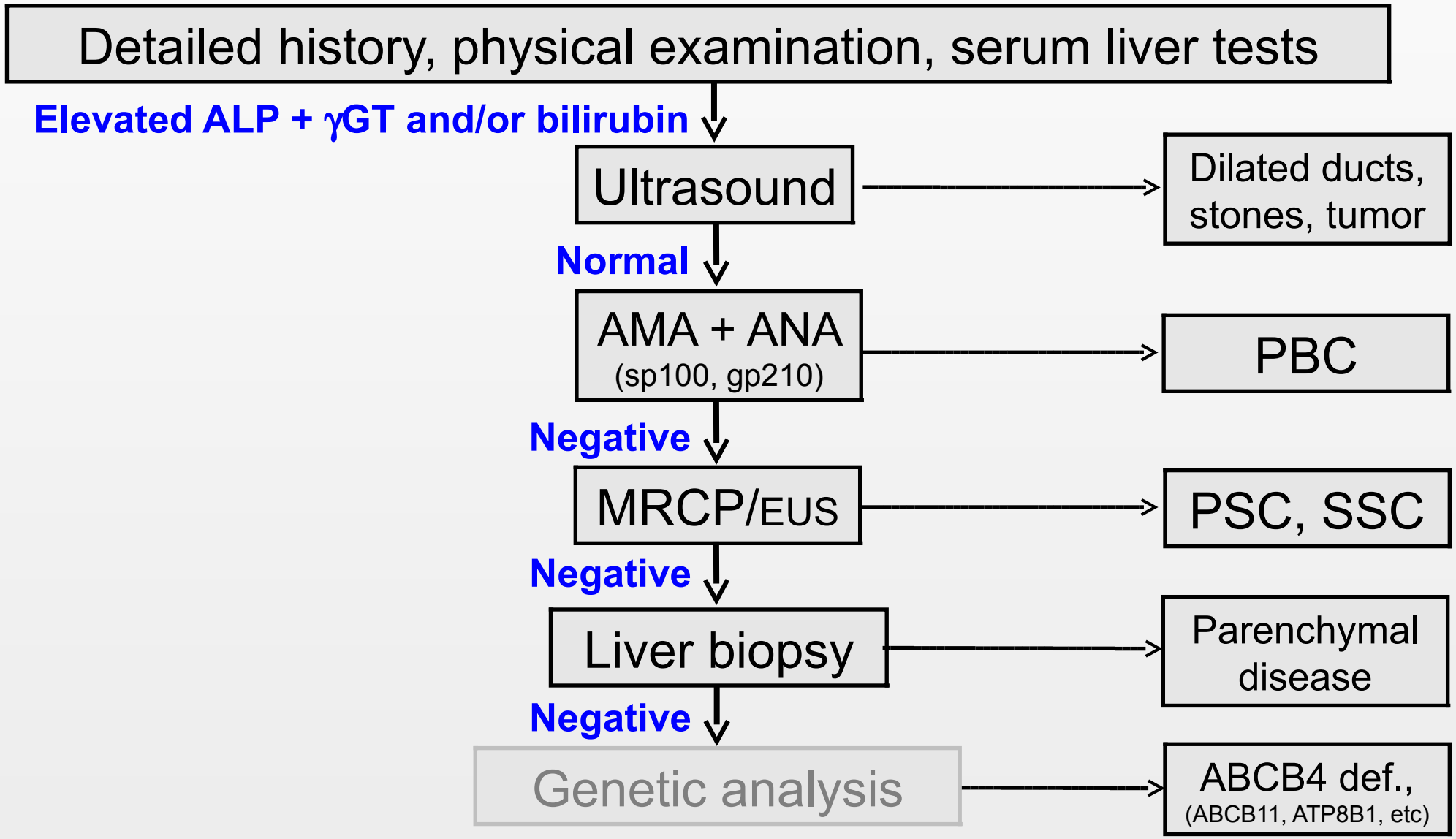


dd toxic / canalicular transport defect?

Courtesy of Dr. J.Verheij

Diagnostic approach to cholestasis

♀ 34 yrs



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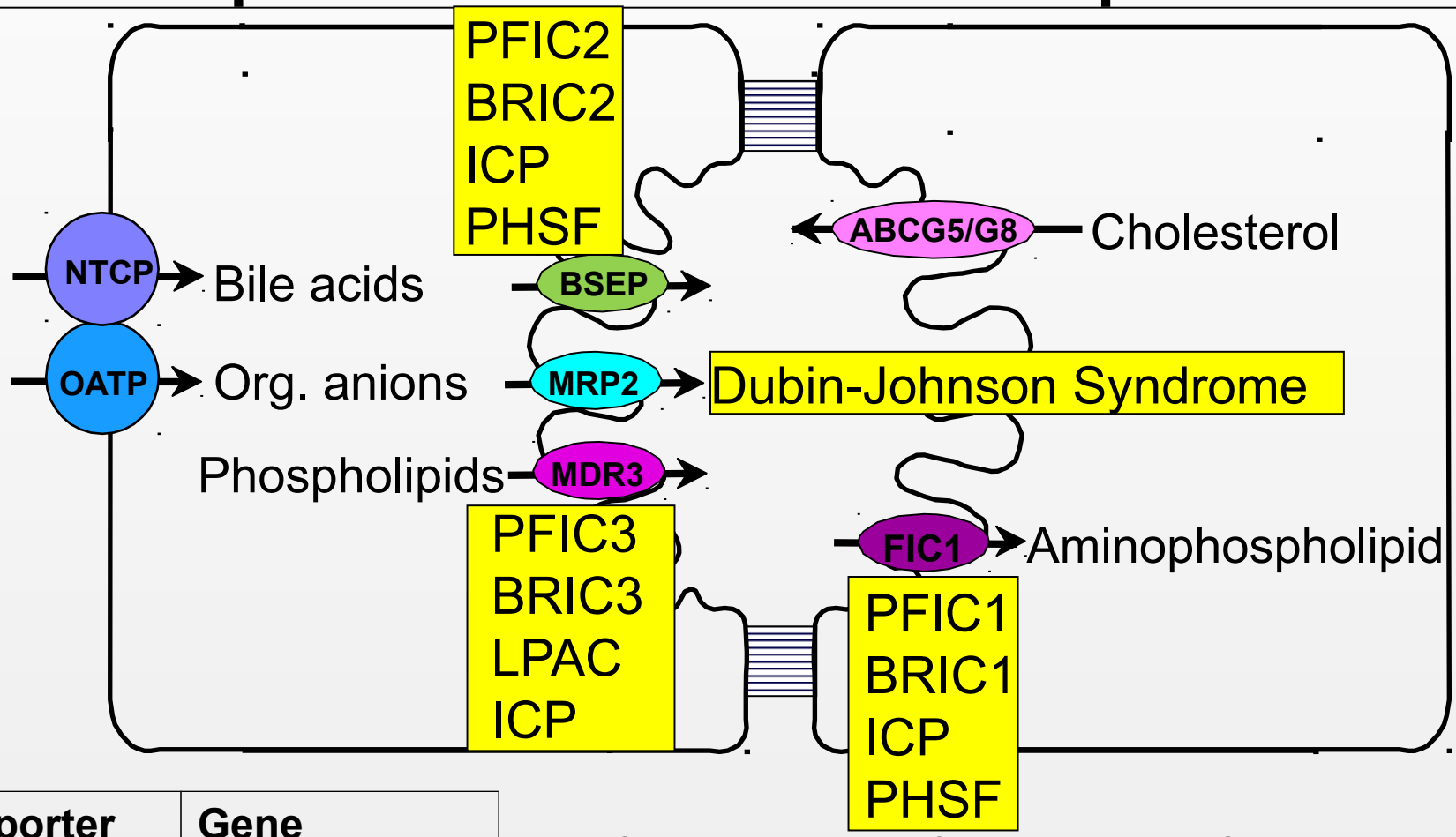
Consequences of canalicular transporter defects



Transporter	Gene
FIC1	*ATP8B1*
BSEP	*ABCB11*
MDR3	*ABCB4*

PFIC: Progressive familial intrahepatic cholestasis

BRIC: Benign recurrent intrahepatic cholestasis

PHSF: Persistent hepatocellular secretory failure

LPAC: Low phospholipid associated cholelithiasis

ICP: Intrahepatic cholestasis of pregnancy

Genetic analysis

♀ 34 yrs

Heterozygote mutation in the *ABCB11* gene (c.2809G>A)

compatible with:

Persistent hepatocellular secretory failure (PHSF)

(i) Serum bilirubin >255 μmol/L

(ii) Persistently elevated bilirubin (>1 week) after removal of the underlying cause (medication, toxin, transient mechanical obstruction)

(iii) Exclusion of bile duct obstruction by imaging

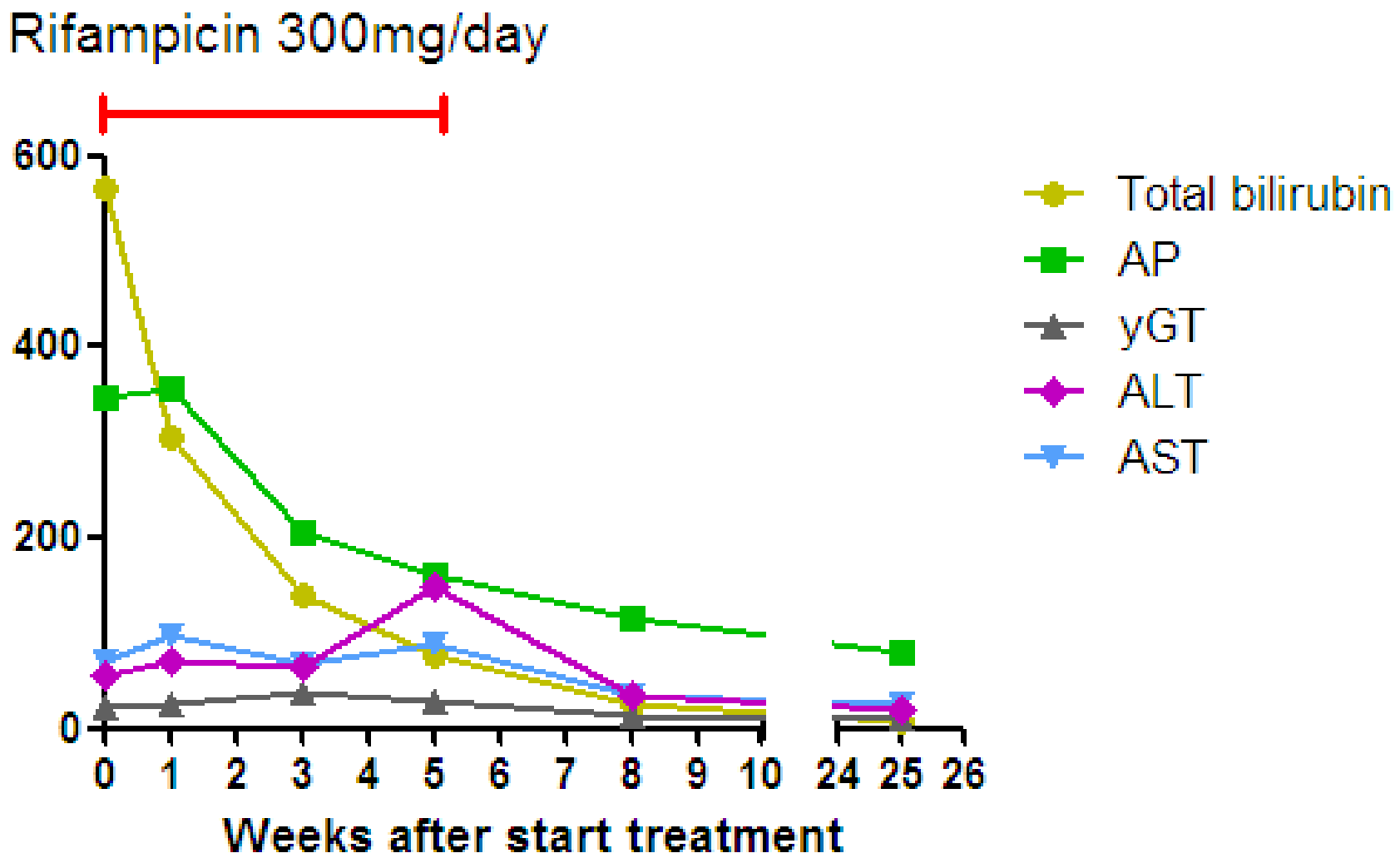
(iv) No underlying liver disease

van Dijk et al. Liver Int 2015; 35:1478

amc

Treatment of PHSF

♀ 34 yrs



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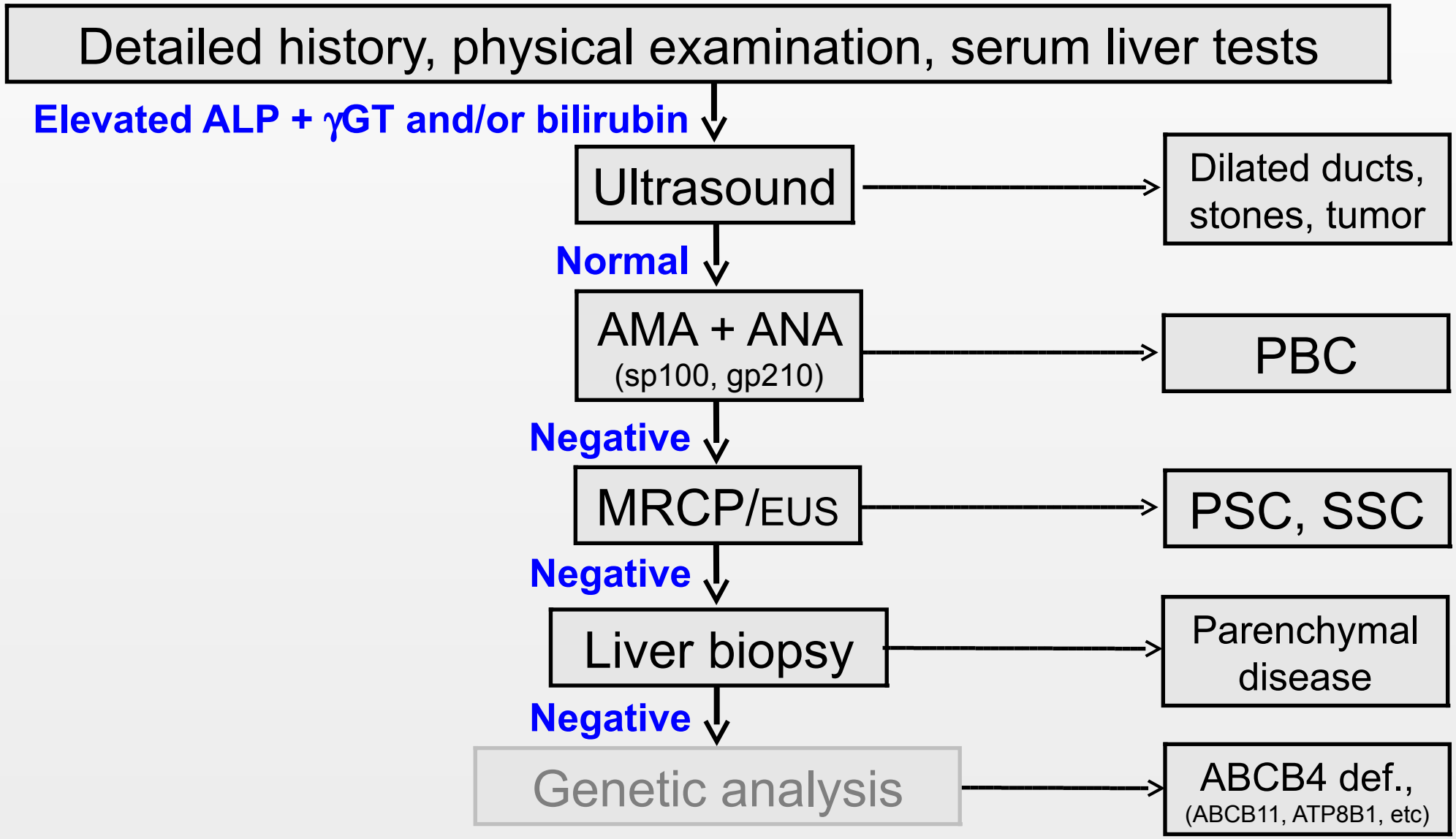

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