

*12<sup>th</sup> Paris Hepatology Conference*

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# **Management of cholestatic diseases**

## **Today and tomorrow**

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**Paris**

15 January 2019

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Amsterdam University Medical Centers  
Location AMC  
Amsterdam, The Netherlands

# Disclosures

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## Grant support

German, Norwegian, American and South-African PSC patient foundations  
Netherlands Foundation for Gastroenterology & Hepatology  
EU Program ‘Liverhope’

## Lecture fees

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

## Consulting agreements

Intercept, NGM, Novartis

## Support for investigator-initiated studies

Falk, Intercept



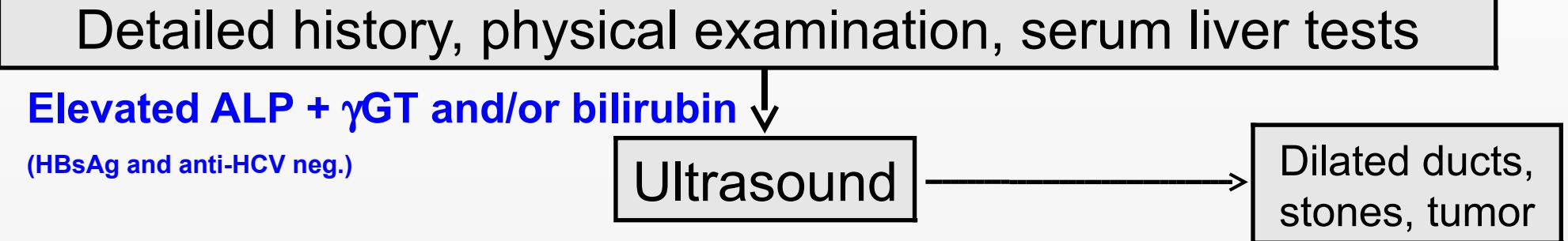
# Diagnostic approach to cholestasis

Detailed history, physical examination, serum liver tests

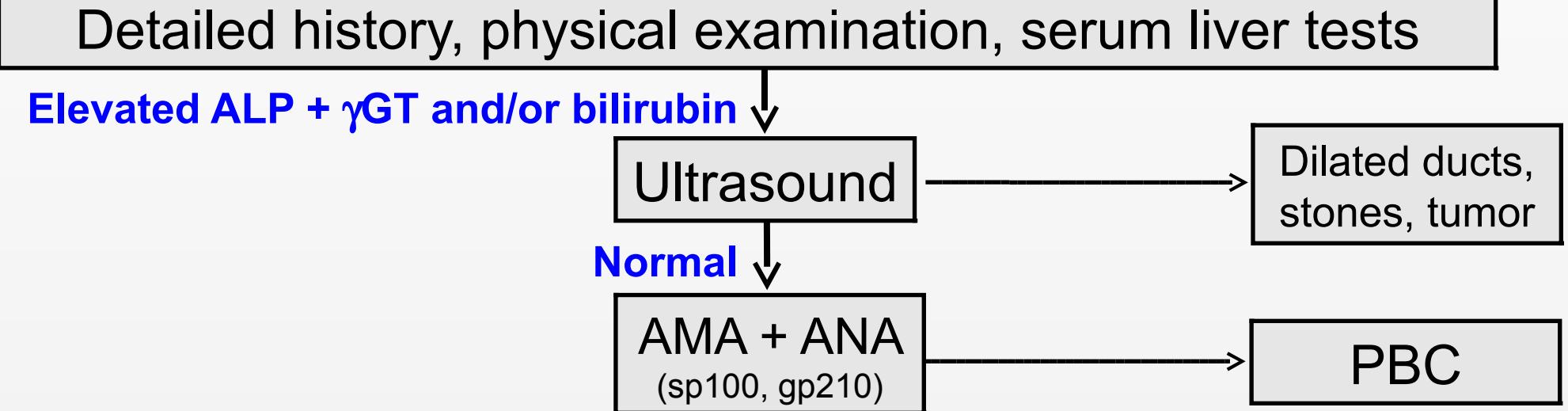
**Elevated ALP +  $\gamma$ GT and/or conjugated bilirubin**

(HBsAg and anti-HCV neg.)

# Diagnostic approach to cholestasis

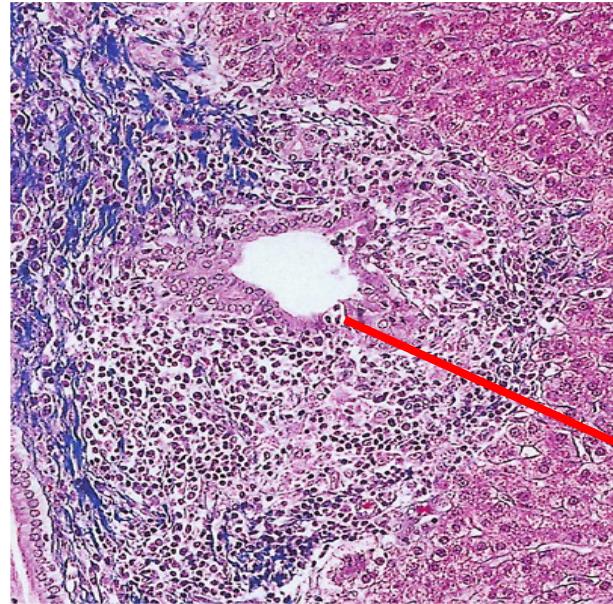


# Diagnostic approach to cholestasis



# Primary biliary cholangitis\* (PBC)

## Characteristics



Florid, non-suppurative, destructive cholangitis

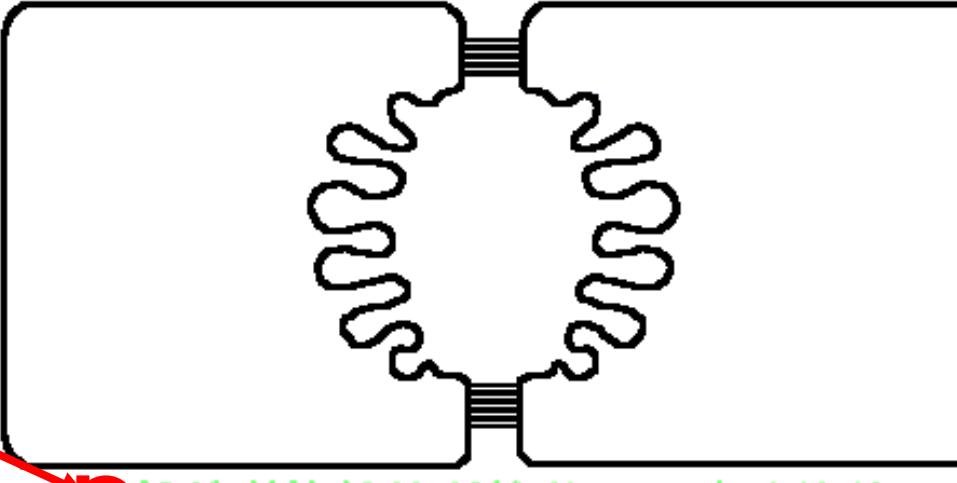
**Women : Men**

**Age at diagnosis**

**Survival** without treatment

**Cholestasis**

**Autoantibodies**



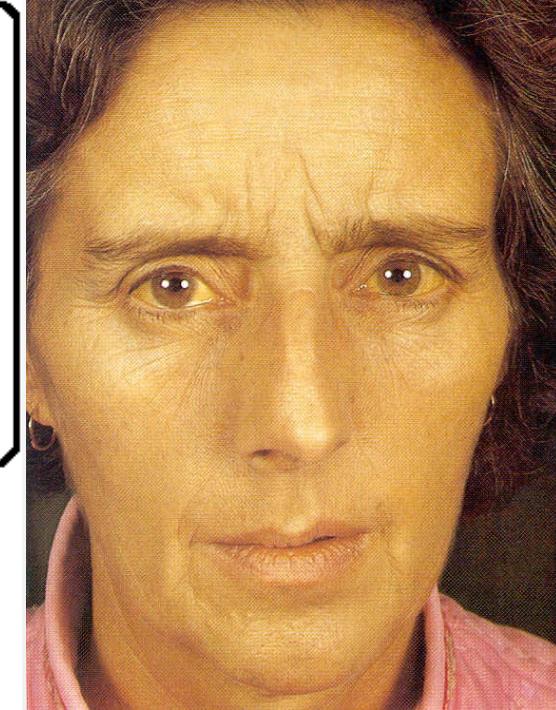
9 : 1

40 - 60

7.5-16 years

↑ ALP,  $\gamma$ GT

**AMA** (anti-PDC-E2)



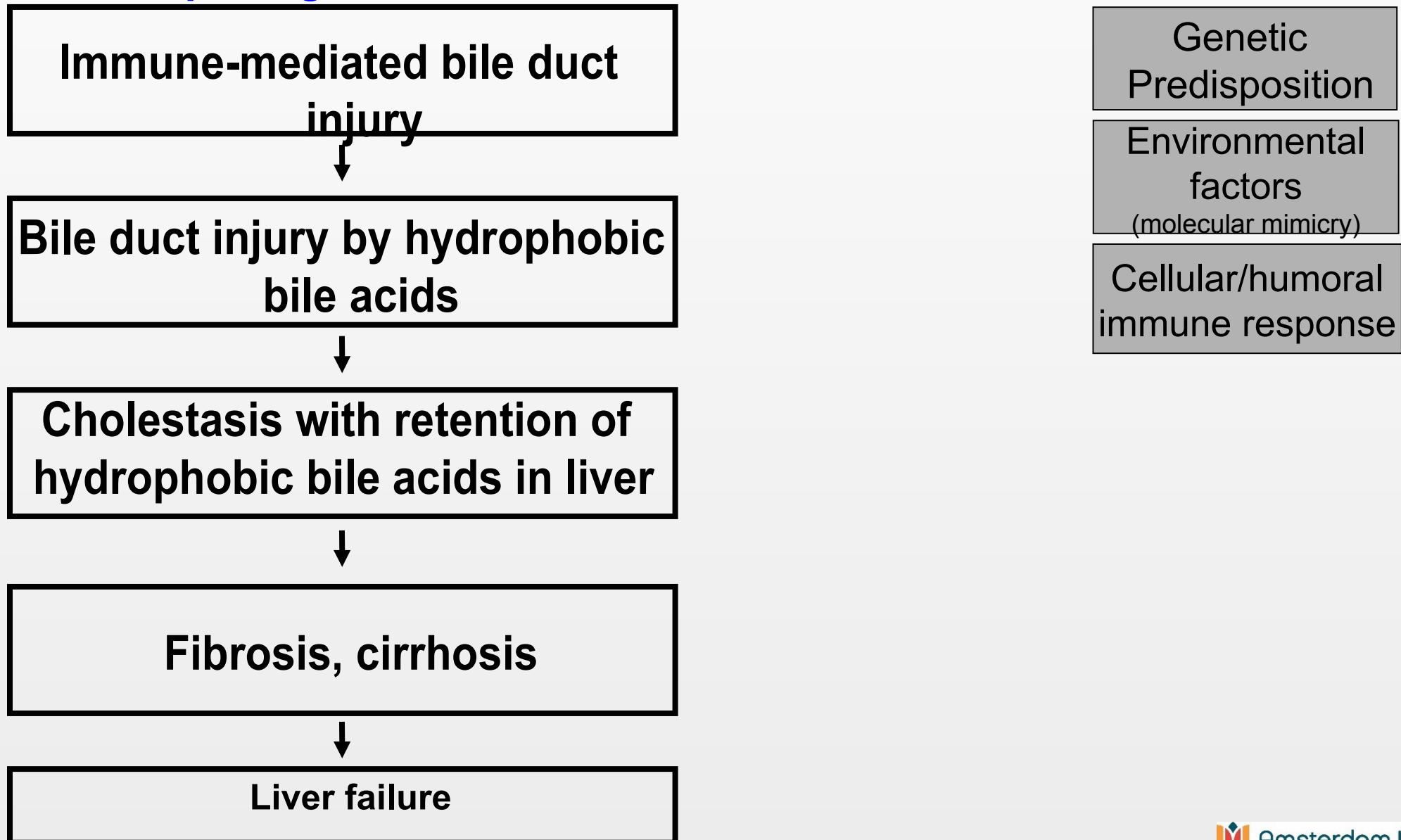
Sherlock and Summerfield, 1991

## Symptoms

- Fatigue
- Pruritus
- Sicca syndrome
- ...

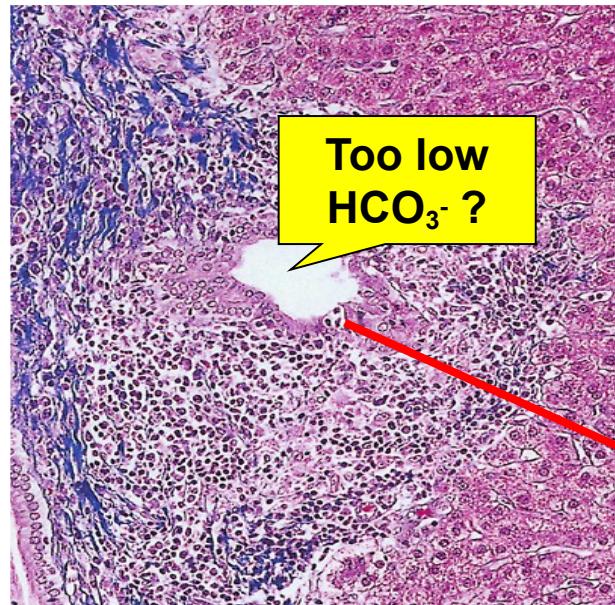
# Primary biliary cholangitis:

## Potential pathogenetic mechanisms



# Primary biliary cholangitis (PBC)

## Characteristics



Florid, non-suppurative, destructive cholangitis

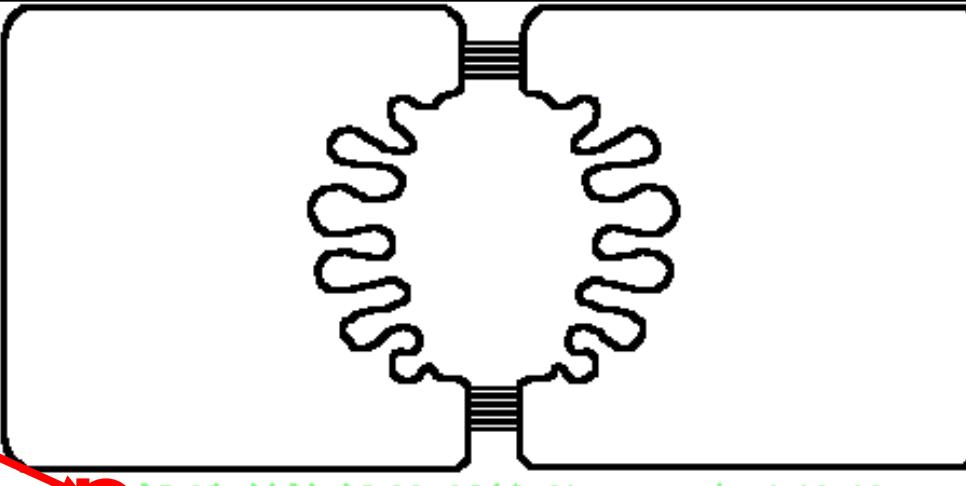
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9 : 1

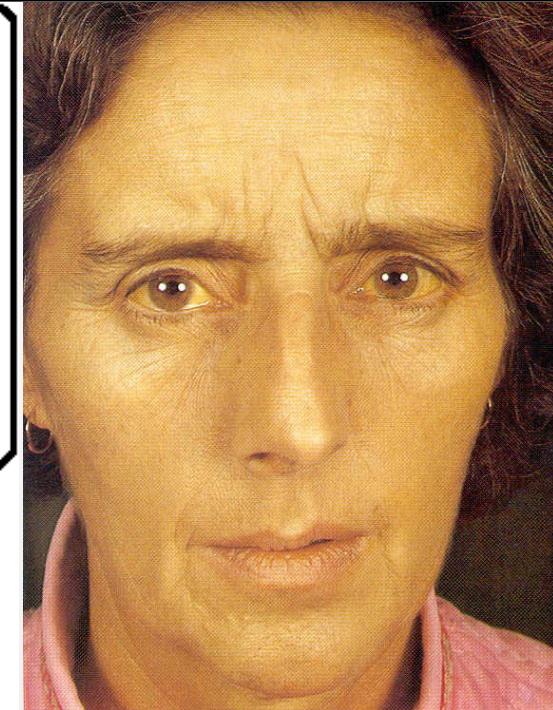
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**AMA** (anti-PDC-E2)

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  
Erice et al. Hepatology 2018;67:1420

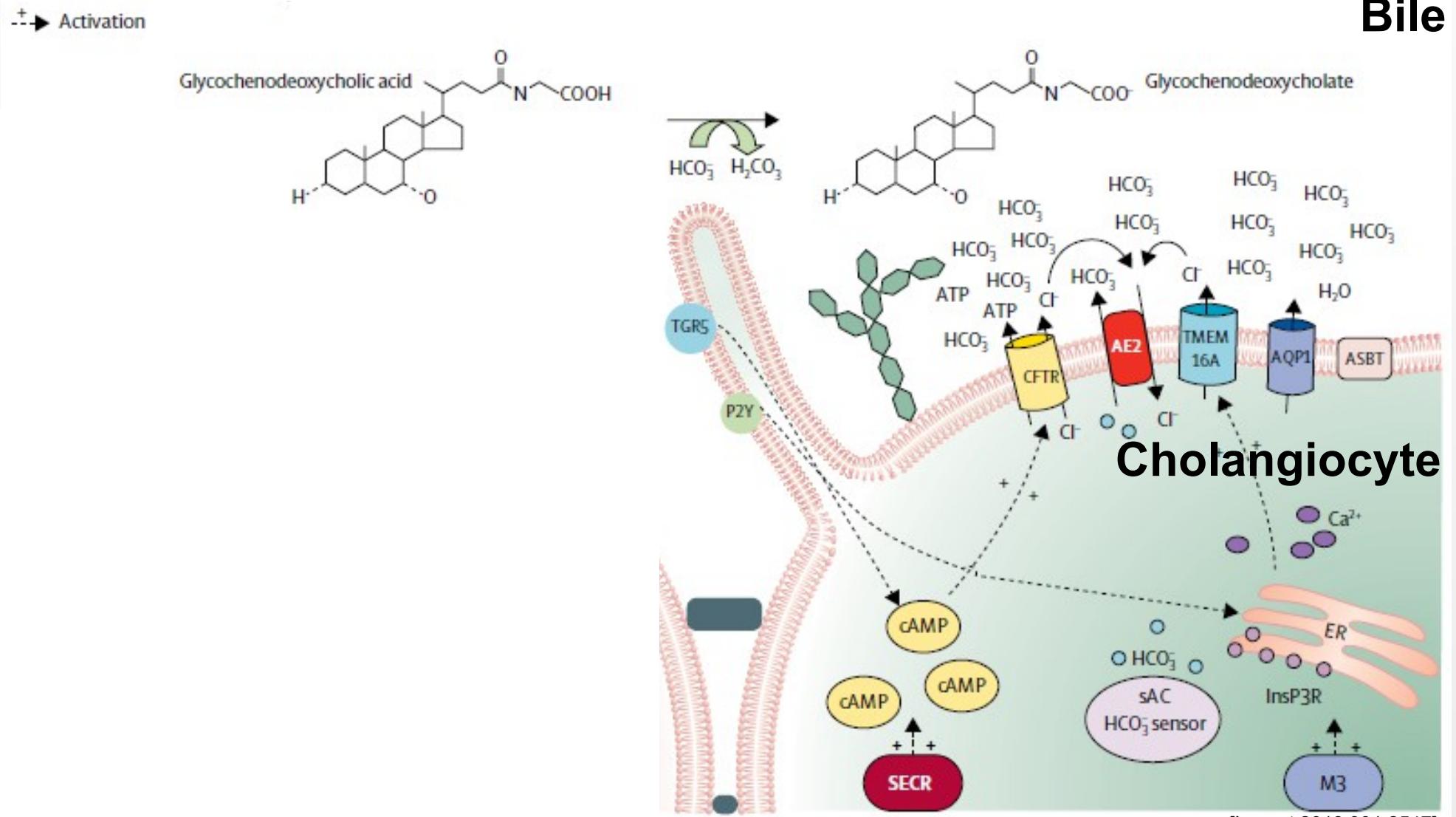


Sherlock and Summerfield, 1991

## Symptoms

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# The ‘Biliary $\text{HCO}_3^-$ - Umbrella’ Hypothesis



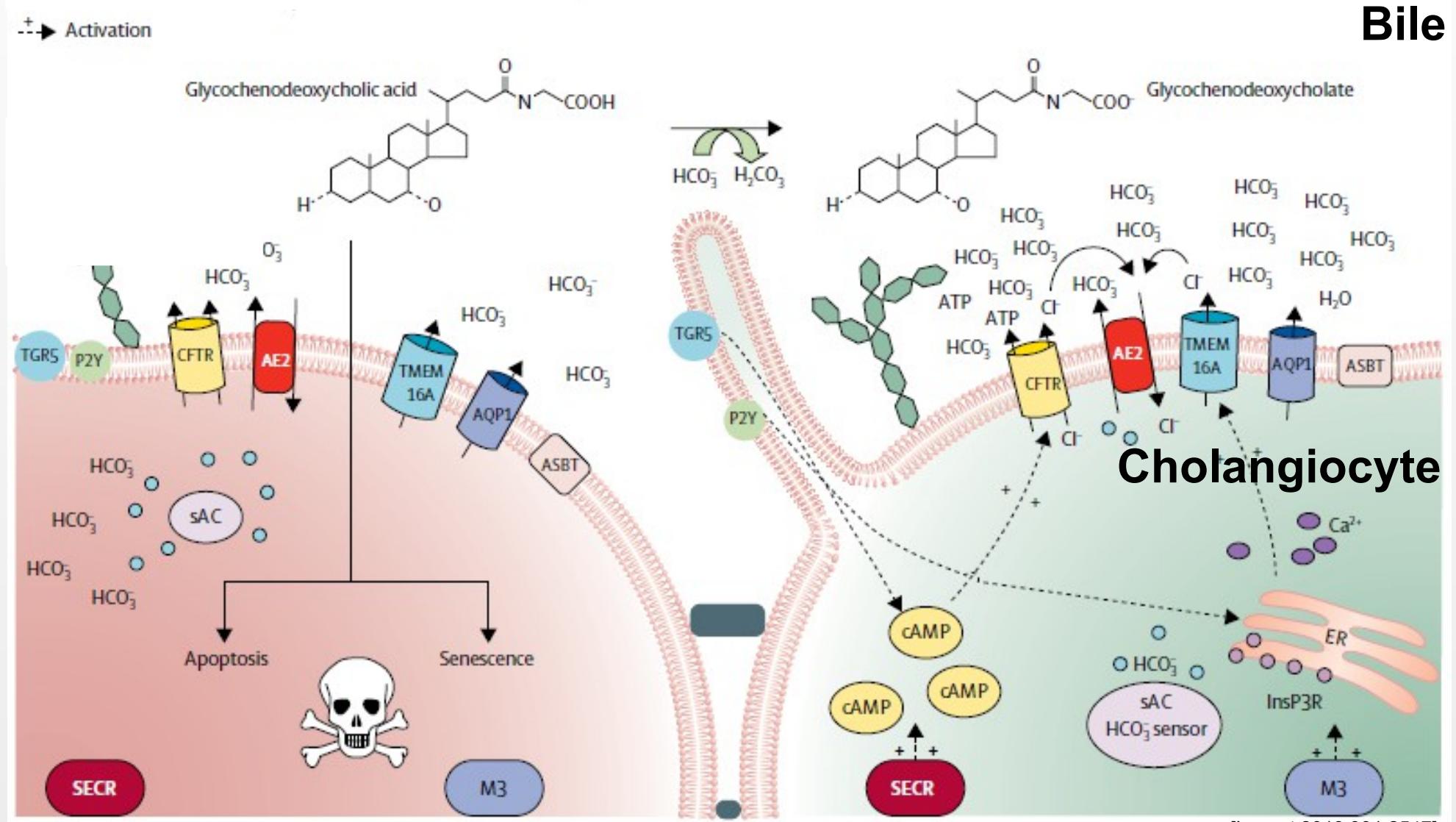
Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

Chang et al., Hepatology 2016;64:522

[Lancet 2018;391:2547]

# The ‘Biliary $\text{HCO}_3^-$ - Umbrella’ Hypothesis

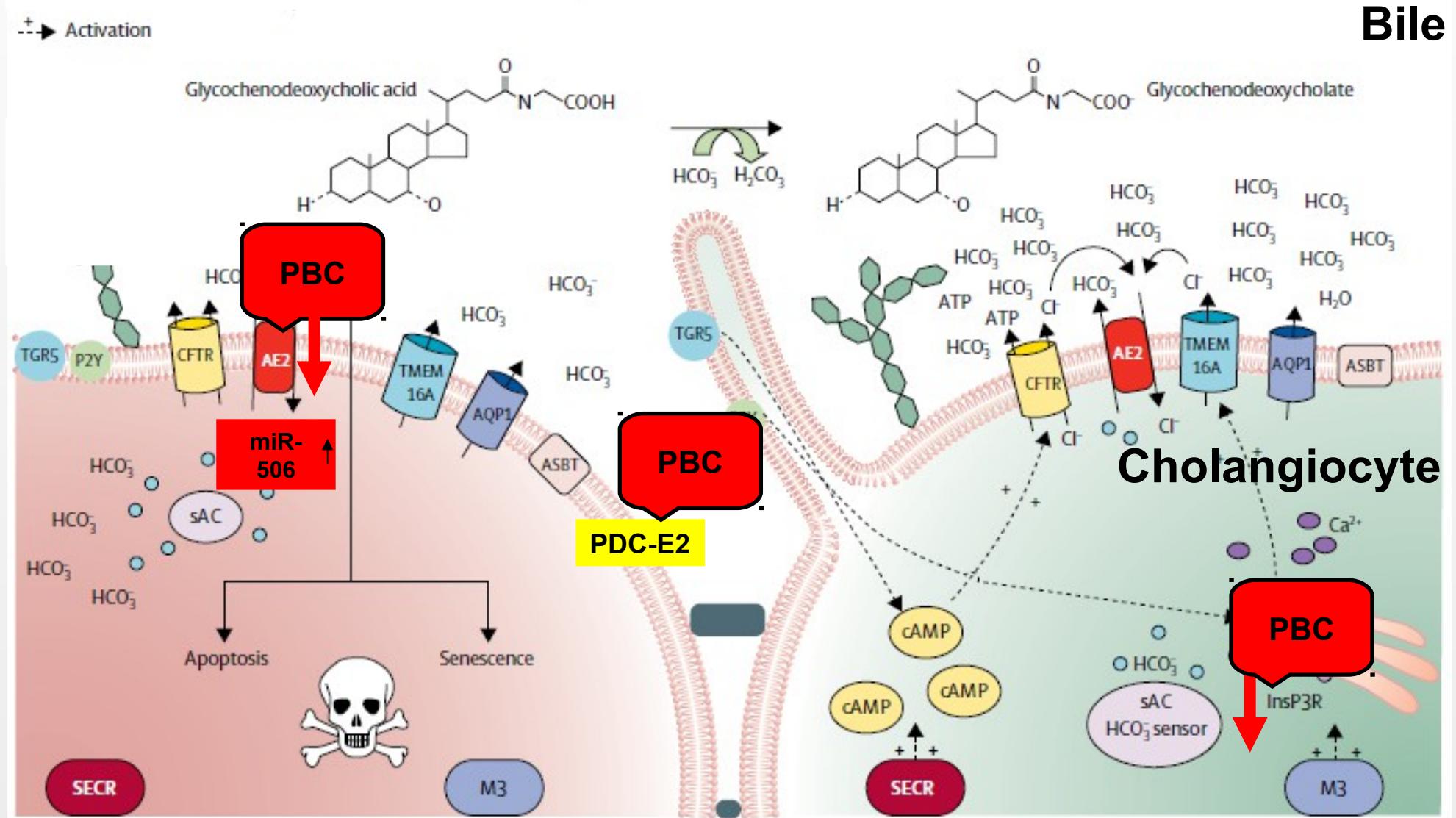


Beuers et al., Hepatology 2010;52:1489

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Chang et al., Hepatology 2016;64:522

# Defects of the ‘Biliary HCO<sub>3</sub><sup>-</sup> Umbrella’ in PBC



Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

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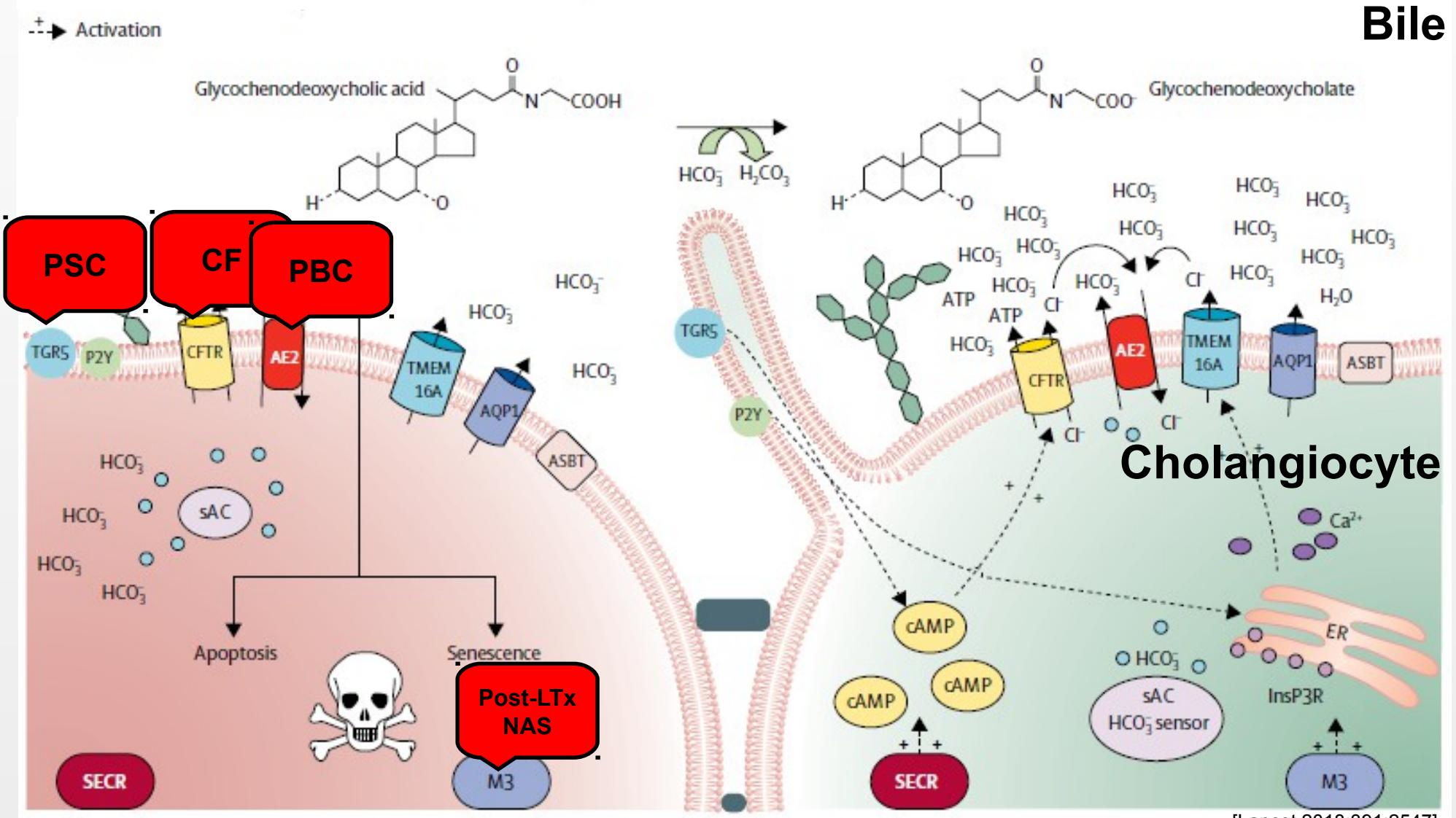
Banales et al. Hepatology 2012;56:687

Ananthanarayanan et al. JBC 2015;290:184

Erice et al. Hepatology 2018;67:1420

[Lancet 2018;391:2547]

# Defects of the 'Biliary $\text{HCO}_3^-$ Umbrella' in fibrosing cholangiopathies?



Beuers et al., Hepatology 2010;52:1489

Hohenester, Wenniger et al., Hepatology 2012; 55: 173

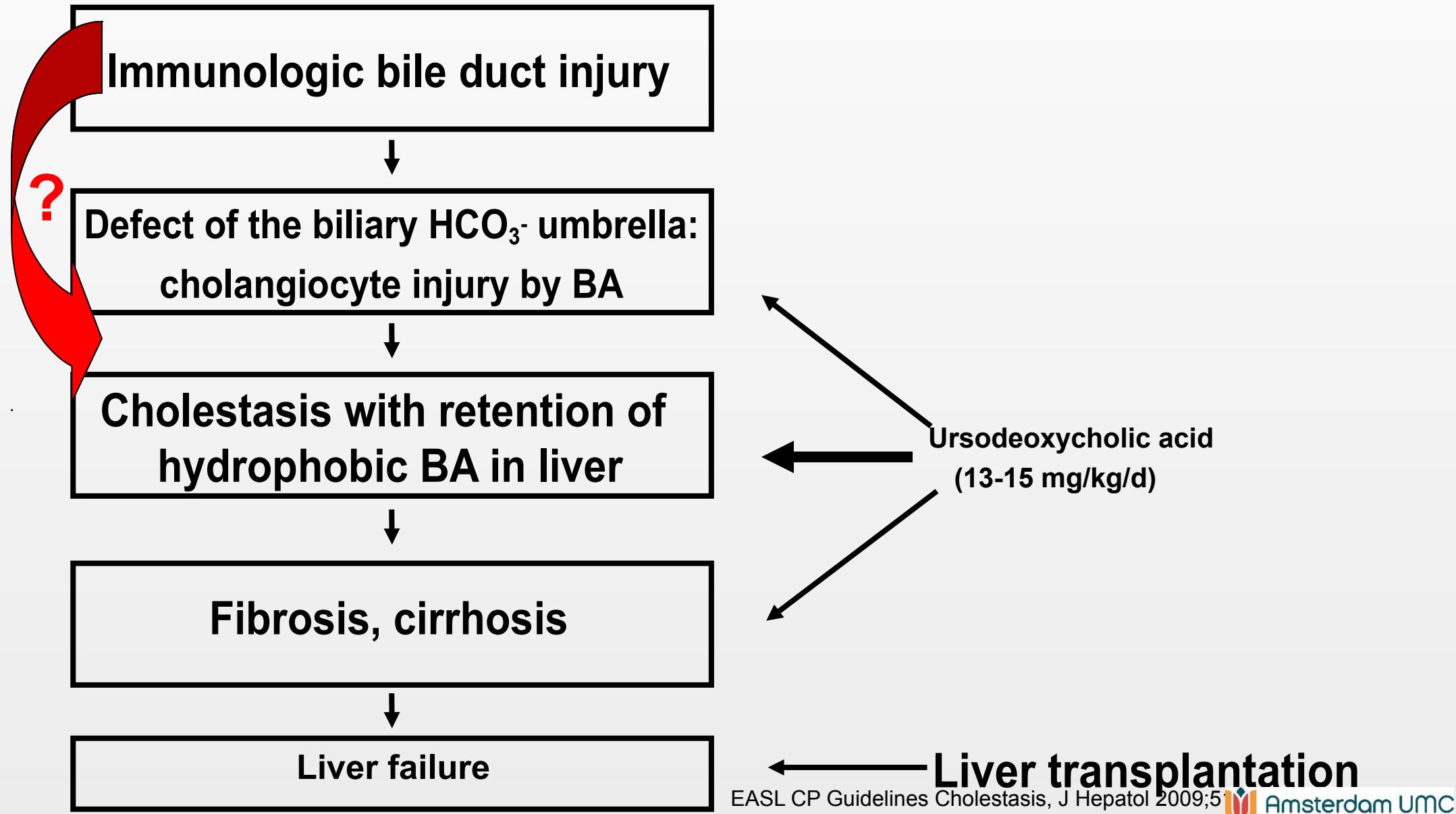
Chang et al., Hepatology 2016;64:522

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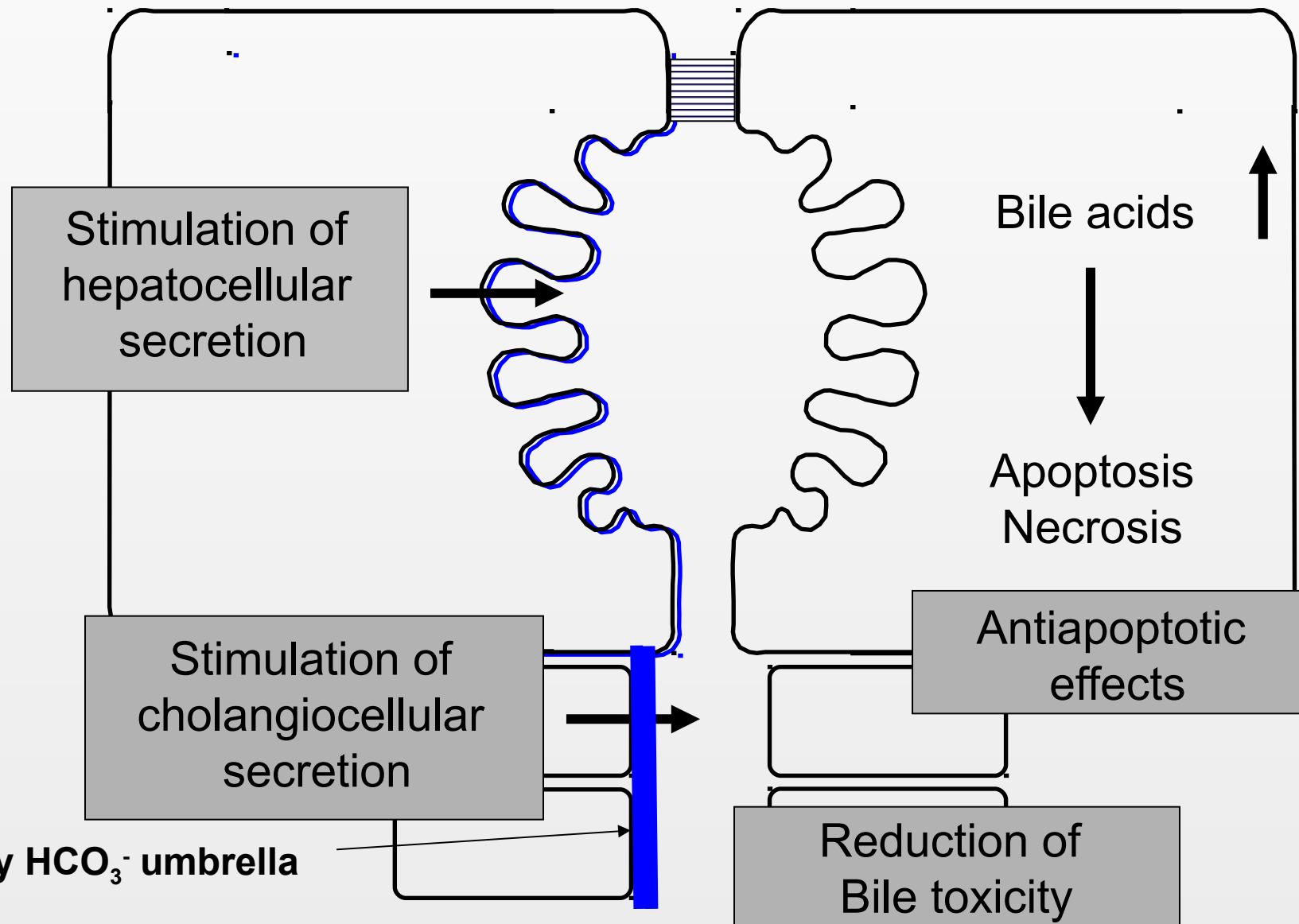
# Primary biliary cholangitis:

# Therapy

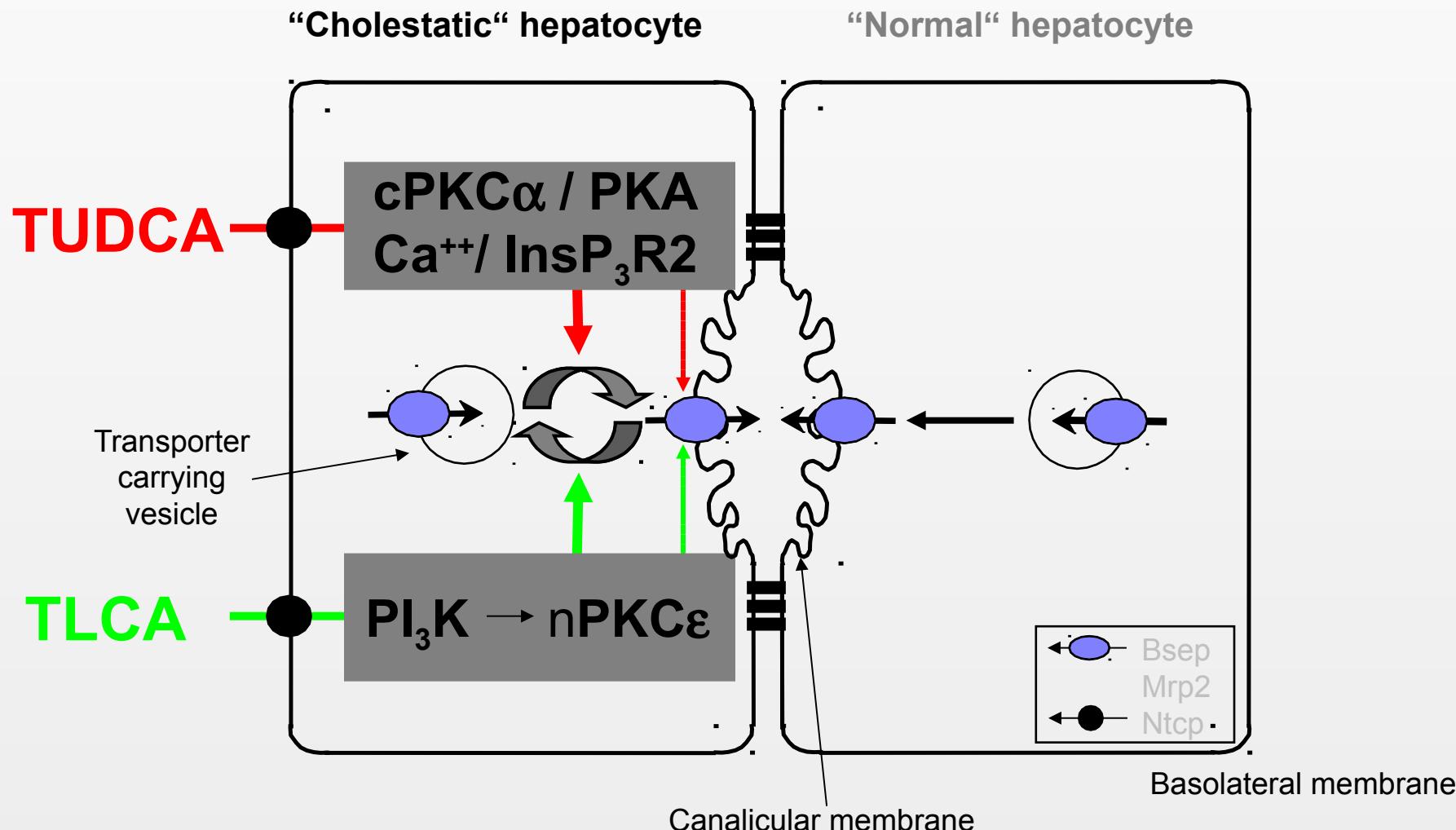
## Potential pathogenetic mechanisms



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



# UDCA conjugates act as posttranscriptional secretagogues in experimental cholestasis



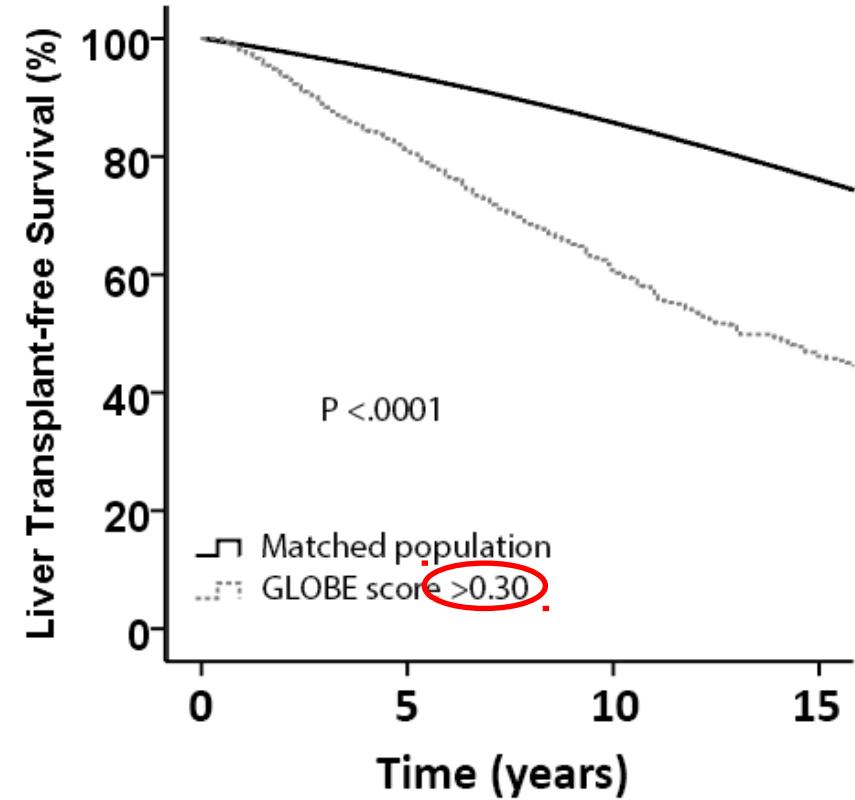
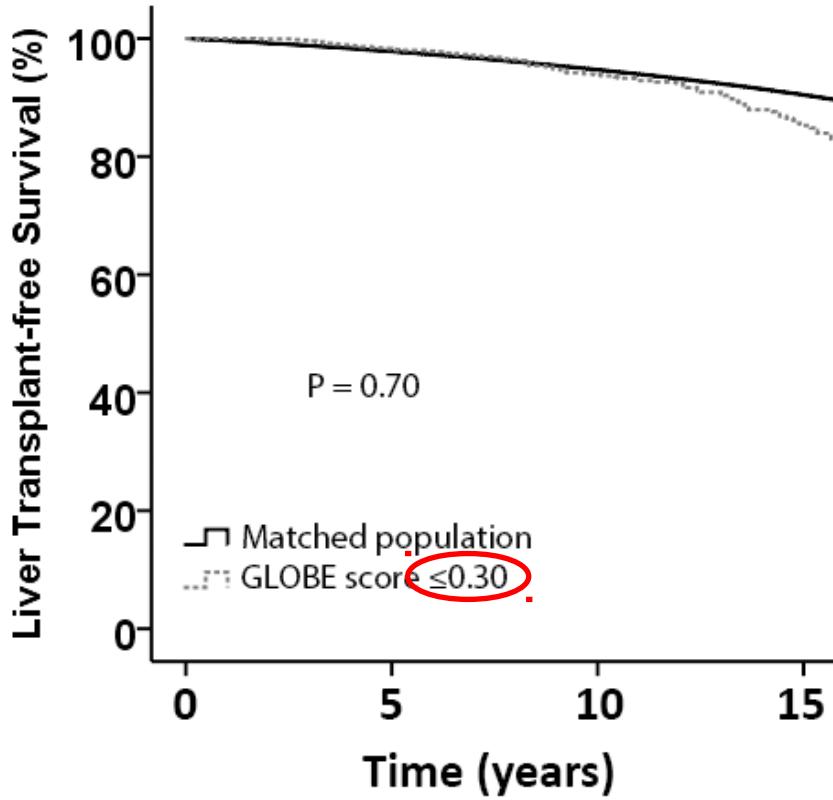
Beuers. Nature CP Gastroenterol Hepatol 2006;3:318 (references 1990-2006)

Wimmer, Hohenester et al., Gut 2008; 57: 1448

Cruz et al., Hepatology 2010; 52: 327

# The PBC GLOBE score predicts outcome after 1 year of UDCA

## Derivation cohort



**GLOBE score:** Age, bilirubin, alkaline phosphatase, albumin, platelets

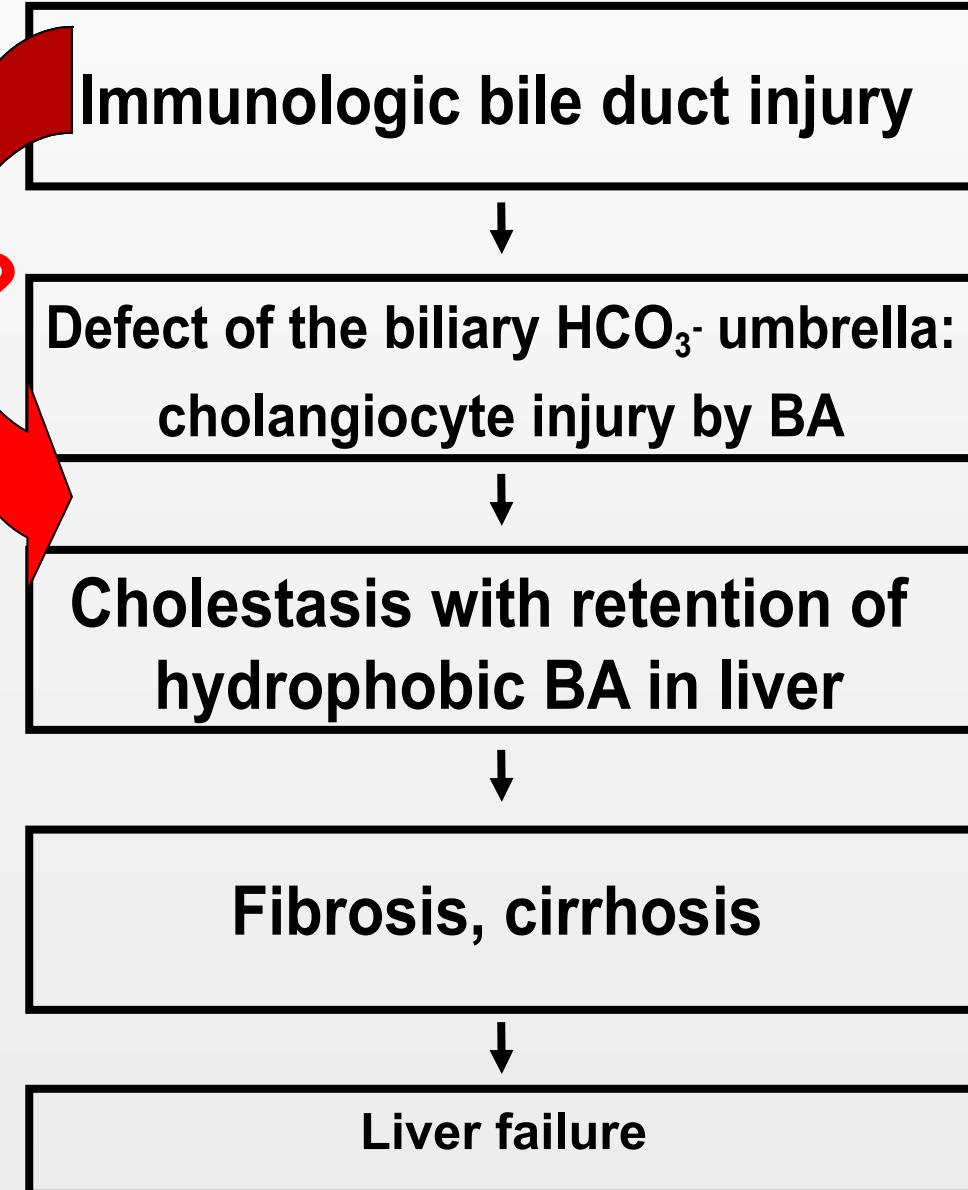
n=4111 PBC patients

Lammers et al., Gastroenterology 2015;149:1804

# Primary biliary cholangitis:

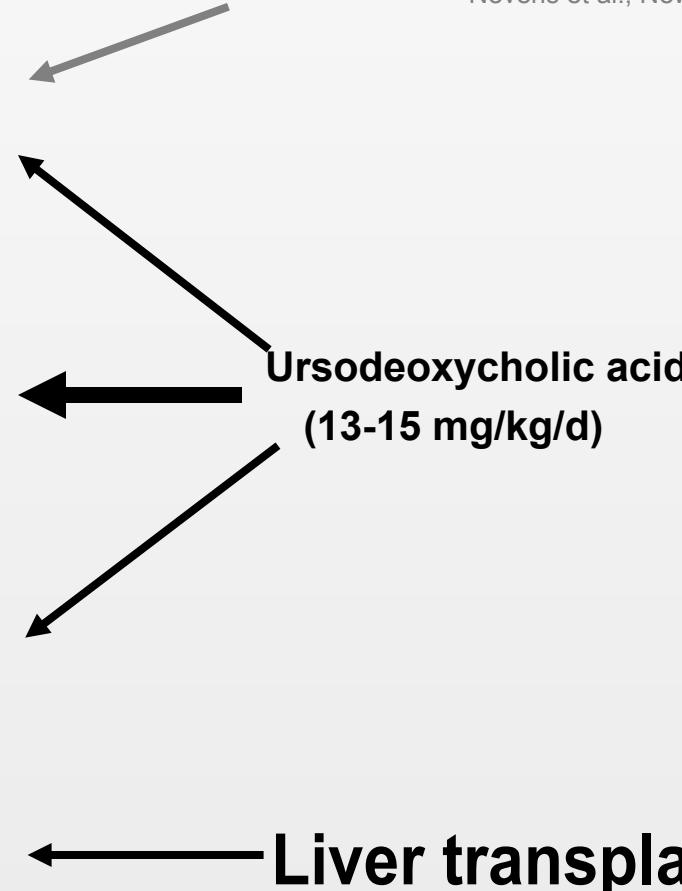
Potentially new Therapy

## Potential pathogenetic mechanisms

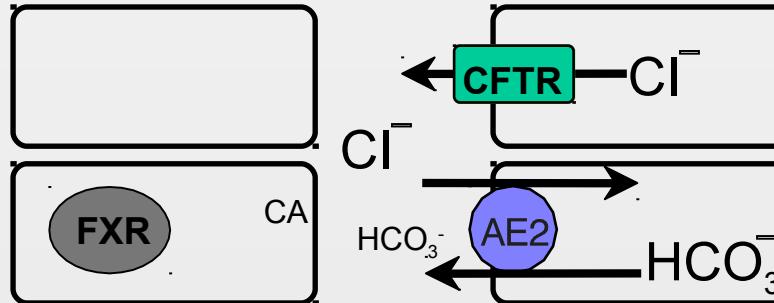
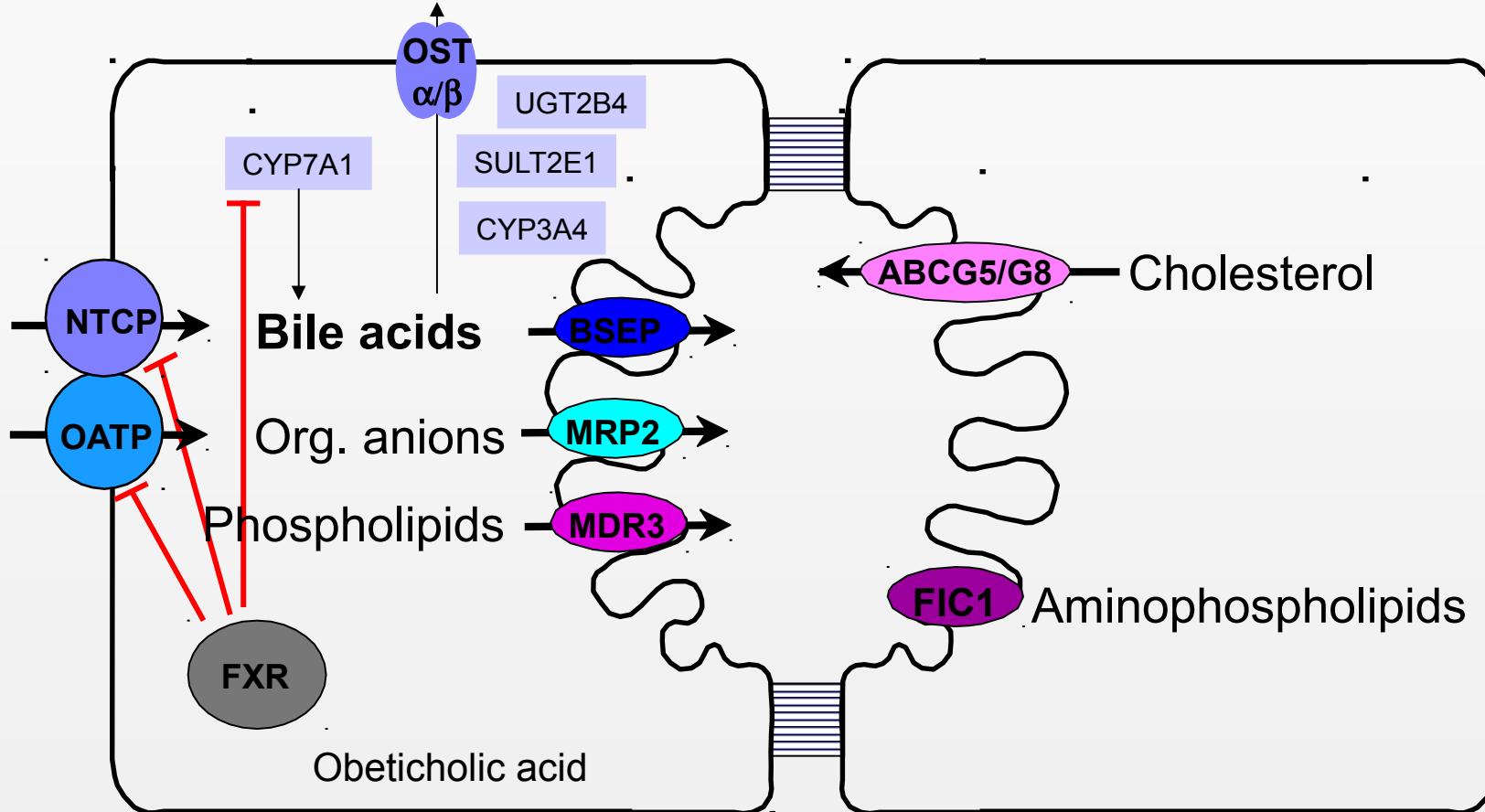


FXR agonist: Obeticholic acid

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



# The Farnesoid X receptor (FXR) protects against toxic effects of hydrophobic bile acids

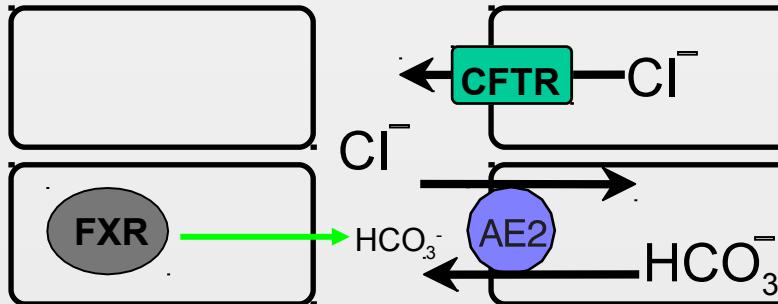
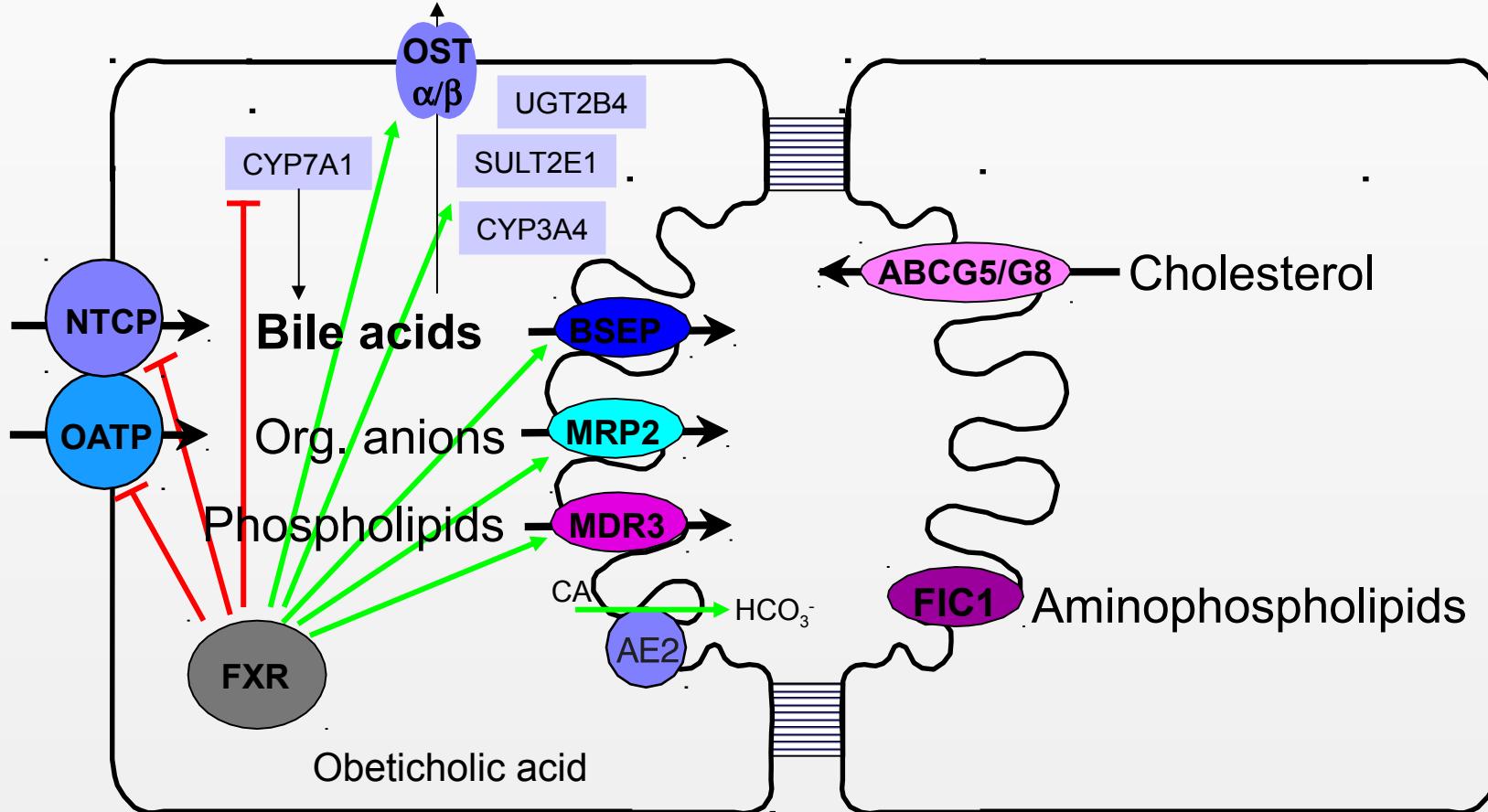


BSEP: ABCB11  
MRP2: ABCC2  
MDR3: ABCB4  
FIC1: ATP8B1

CA, Carboanhydrase

For details, see:  
Trauner et al., Hepatology 2017;65:1393

# The Farnesoid X receptor (FXR) protects against toxic effects of hydrophobic bile acids



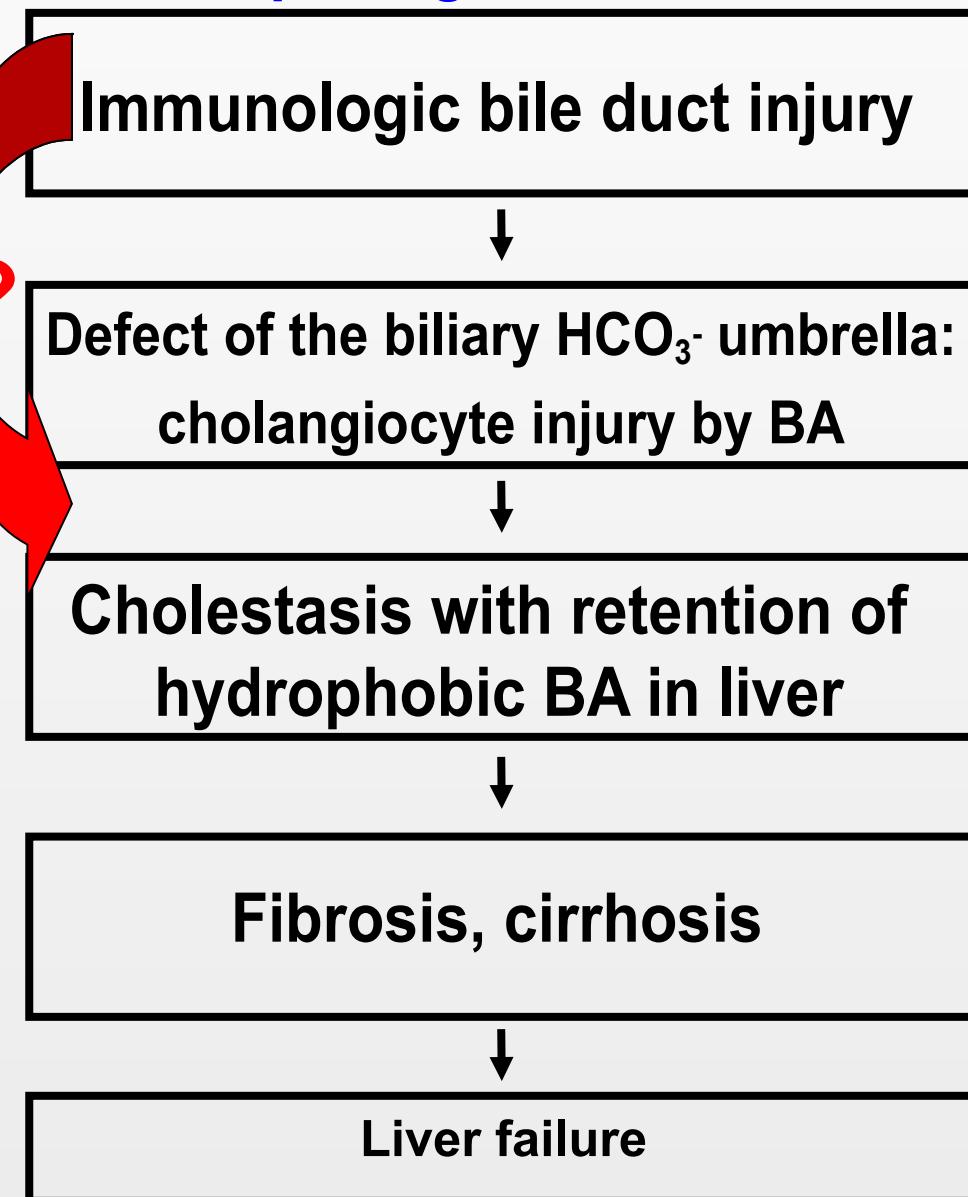
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# Primary biliary cholangitis:

Potentially new Therapy

## Potential pathogenetic mechanisms



**FXR agonist: Obeticholic acid**

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**PPAR agonist: Bezafibrate**

Corpechot et al., New Engl J Med 2018;378:217

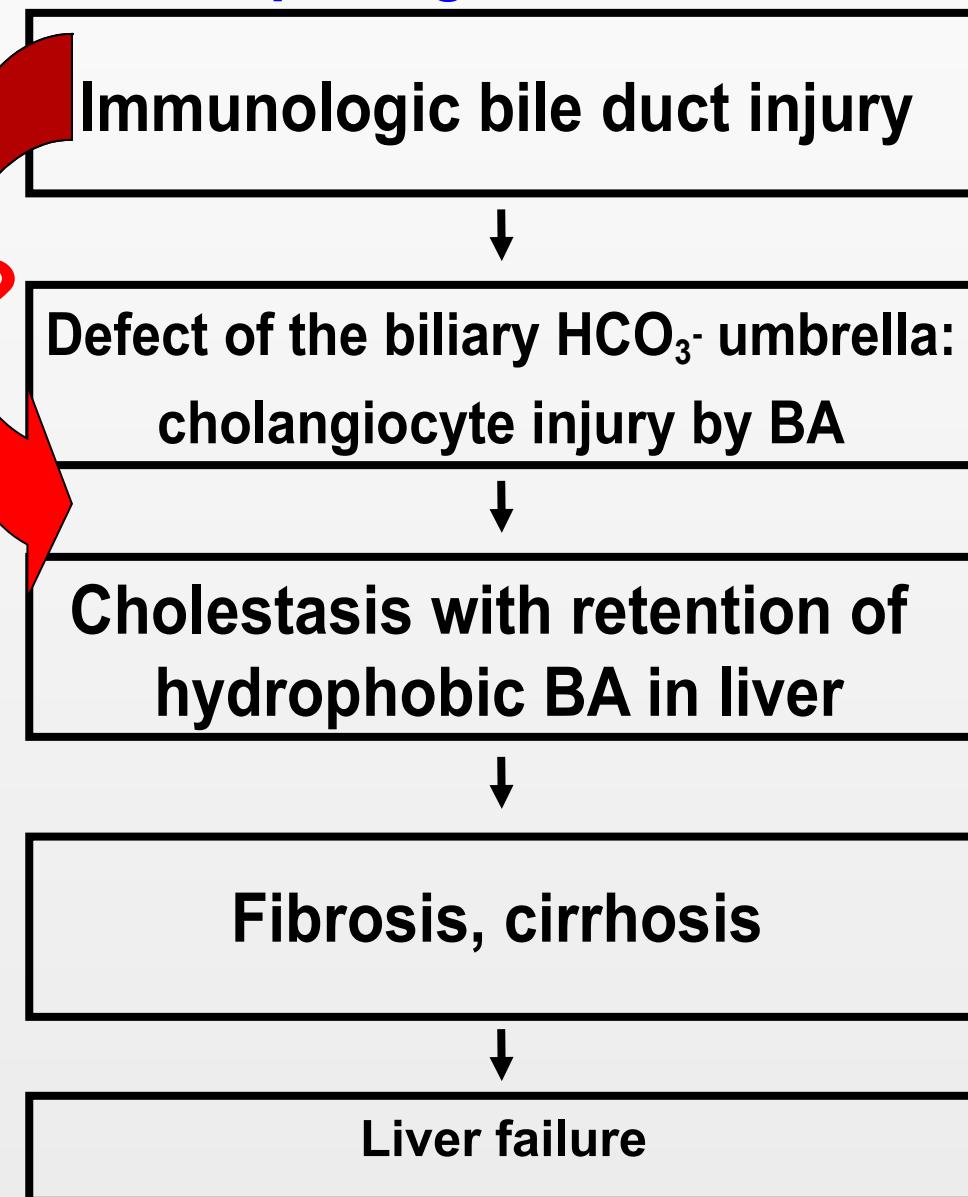
Ursodeoxycholic acid  
(13-15 mg/kg/d)

Liver transplantation

# Primary biliary cholangitis:

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## Potential pathogenetic mechanisms



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

**PPAR agonist: Bezafibrate**

Corpechot et al., New Engl J Med 2018;378:217

**GR/PXR-Agonists: e.g., Budesonide?**

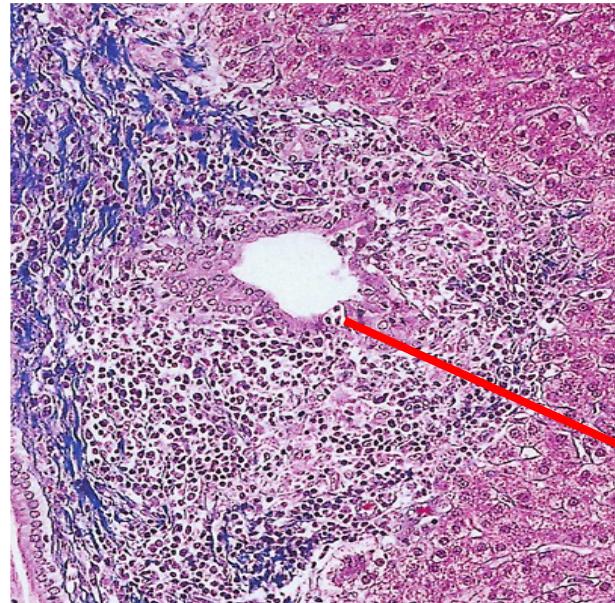
Hirschfield et al, in preparation

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

**Liver transplantation**

# Primary biliary cholangitis

## Characteristics



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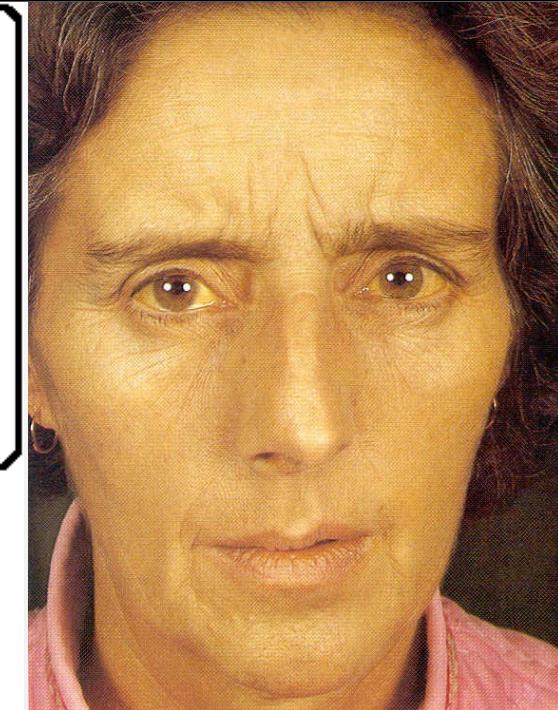
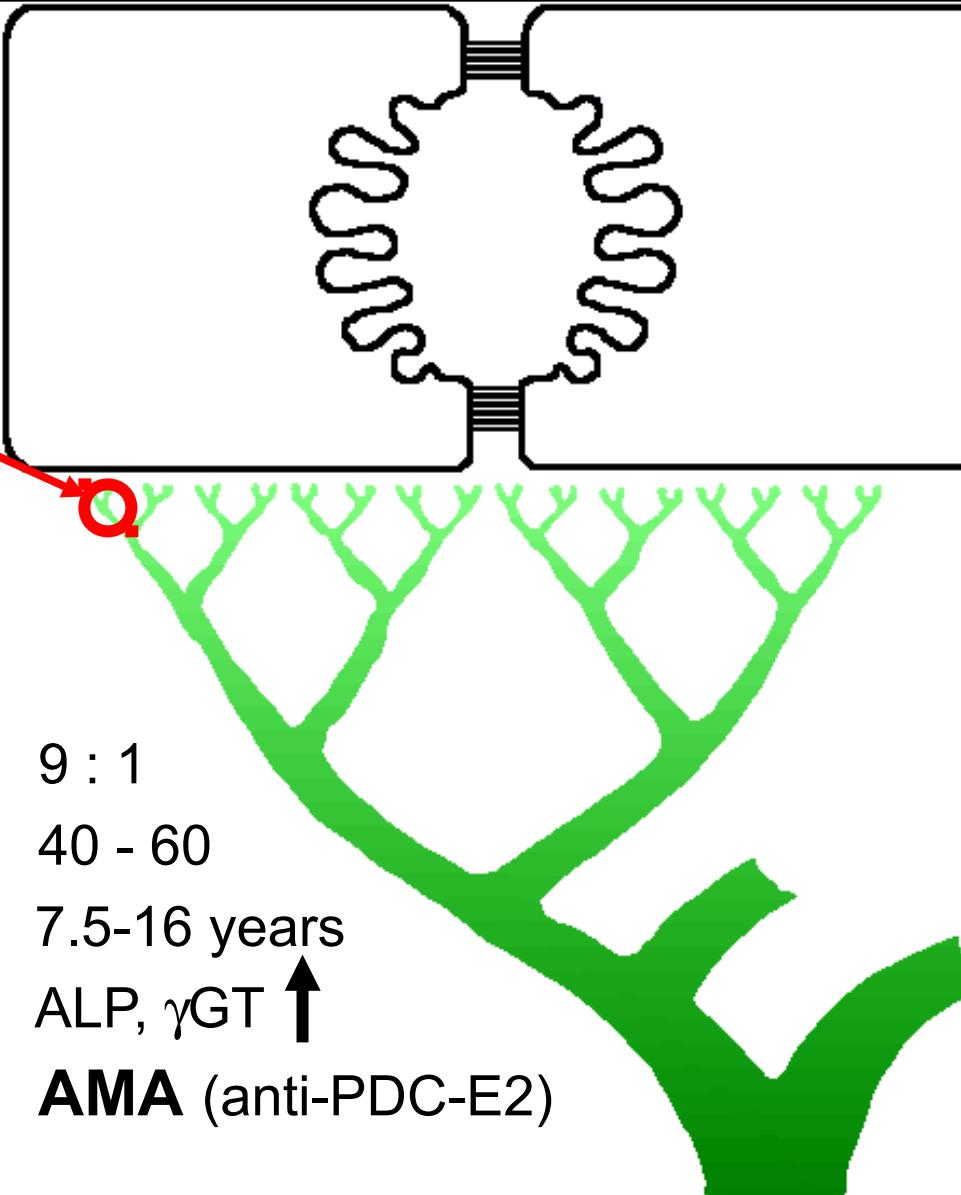
**Women : Men**

**Age at diagnosis**

**Survival** without treatment

**Cholestasis**

**Autoantibodies**



Sherlock and Summerfield, 1991

### **Symptoms**

- Fatigue
- **Pruritus**
- Sicca syndrome
- ...

# Therapeutic Targets in Pruritus of Cholestasis

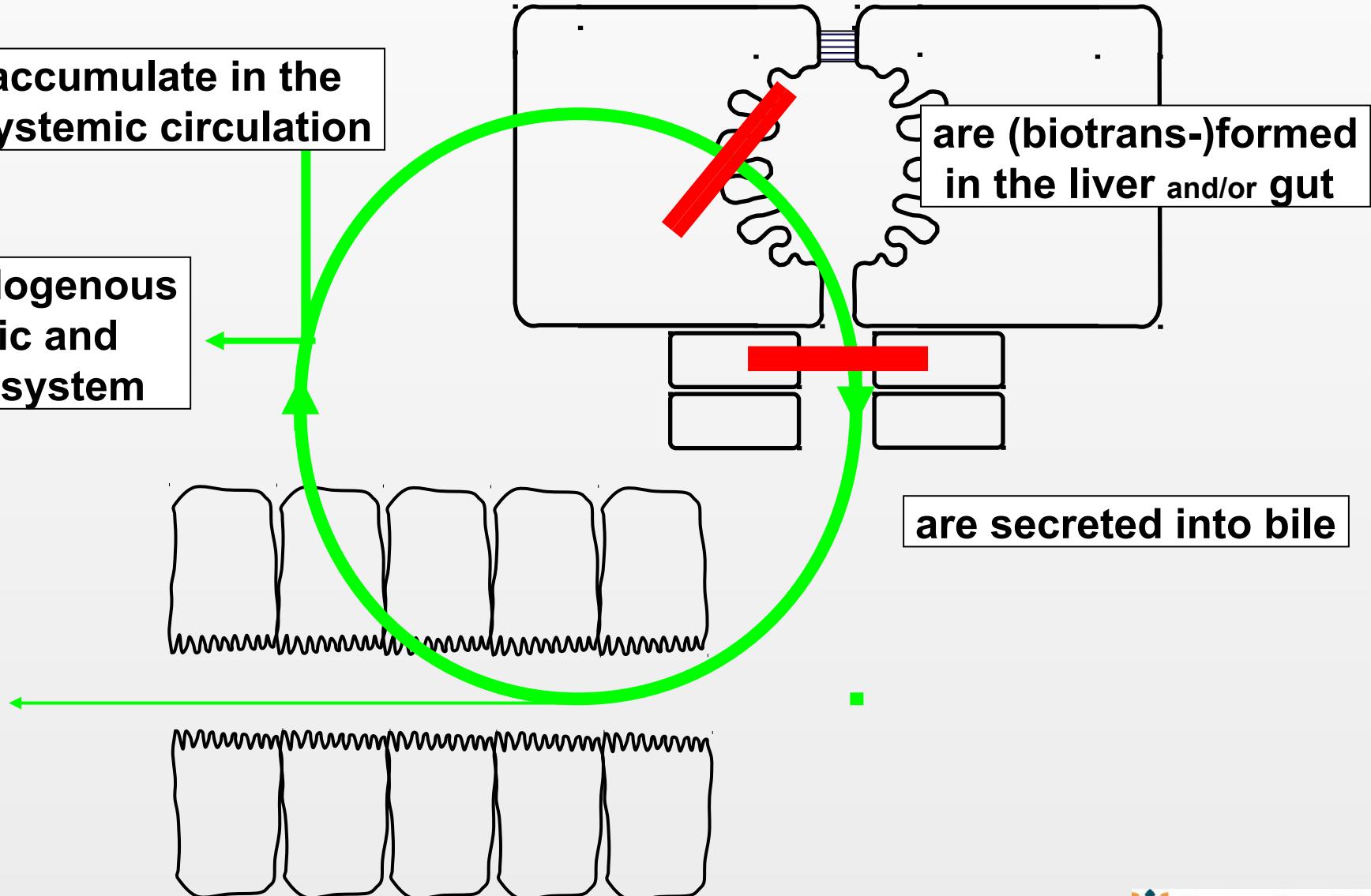
Pruritogens...

accumulate in the systemic circulation

affect the endogenous serotonergic and opioidergic system

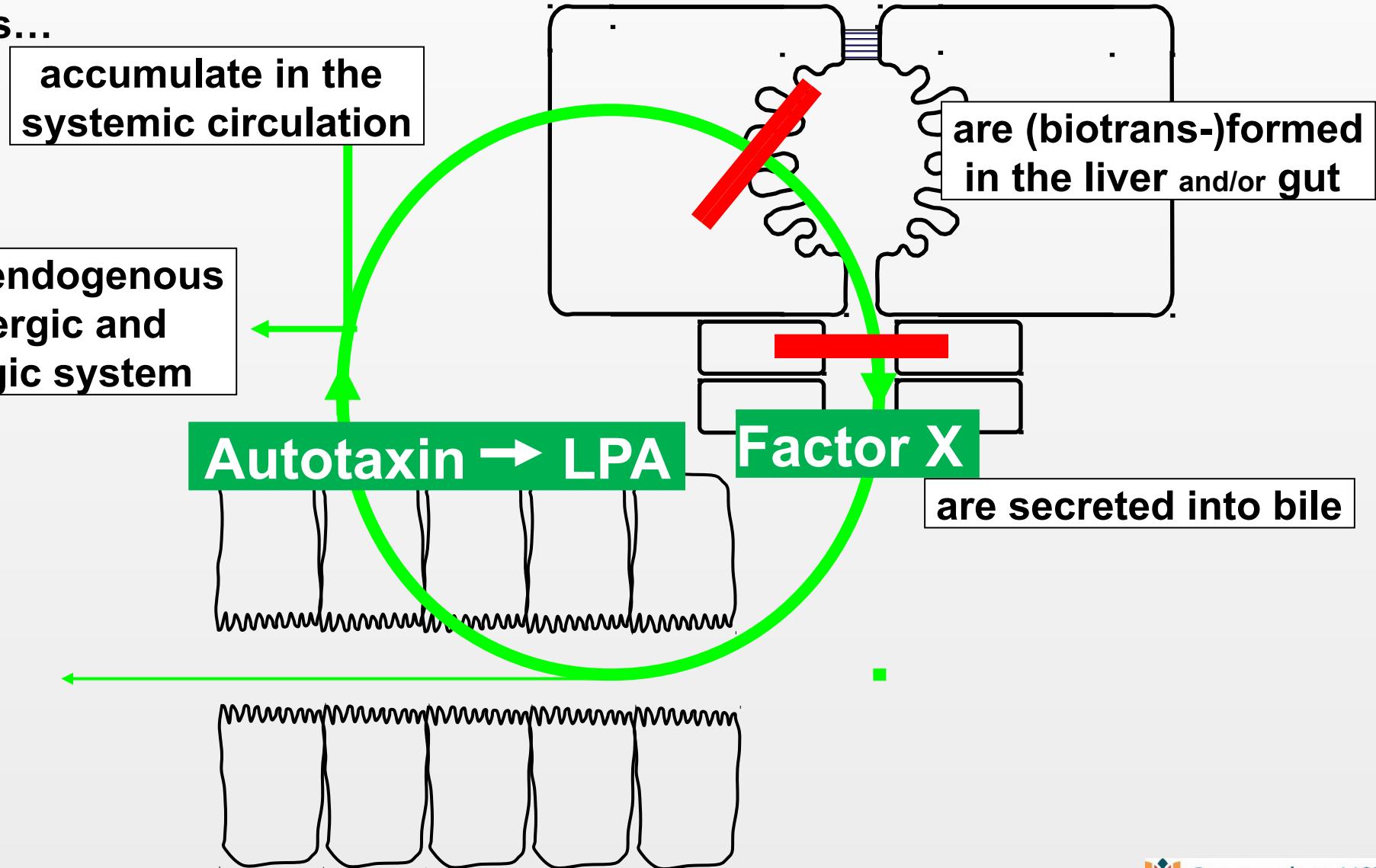
are (biotrans-)formed in the liver and/or gut

are secreted into bile



# Therapeutic Targets in Pruritus of Cholestasis

Pruritogens...



# Therapeutic Targets in Pruritus of Cholestasis

Pruritogens...

accumulate in the systemic circulation

Albumin dialysis etc.

affect the endogenous serotonergic and opioidergic system

Naltrexone  
Sertraline

Rifampicin

are (biotrans-)formed in the liver and/or gut

Factor X

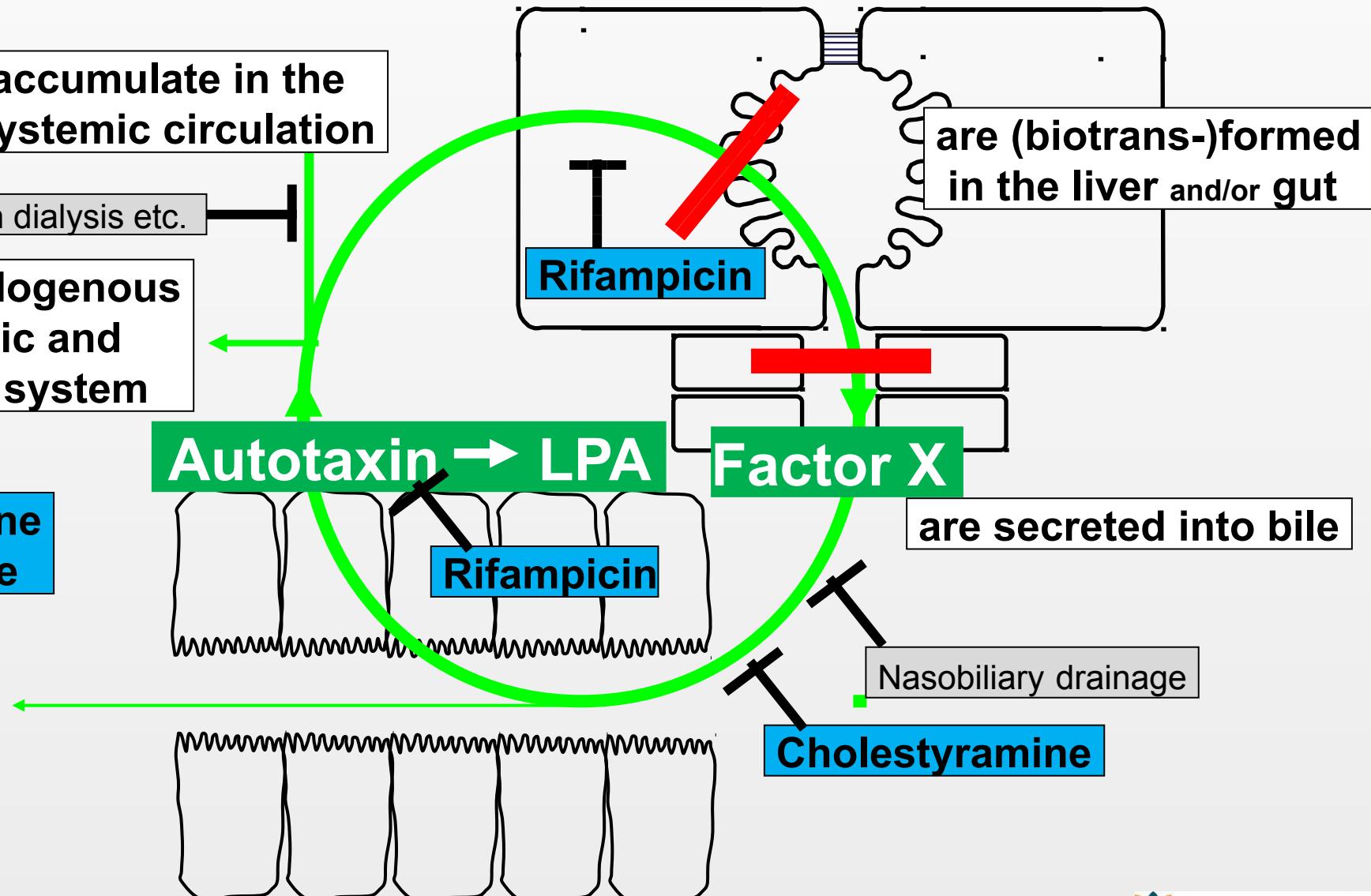
Autotaxin → LPA

Rifampicin

are secreted into bile

Nasobiliary drainage

Cholestyramine



# Therapeutic Targets in Pruritus of Cholestasis

Present and future

Pruritogens...

accumulate in the systemic circulation

Albumin dialysis etc.

affect the endogenous serotonergic and opioidergic system

Naltrexone  
Sertraline

Rifampicin

are (biotrans-)formed in the liver and/or gut

Autotaxin → LPA

Factor X

Rifampicin

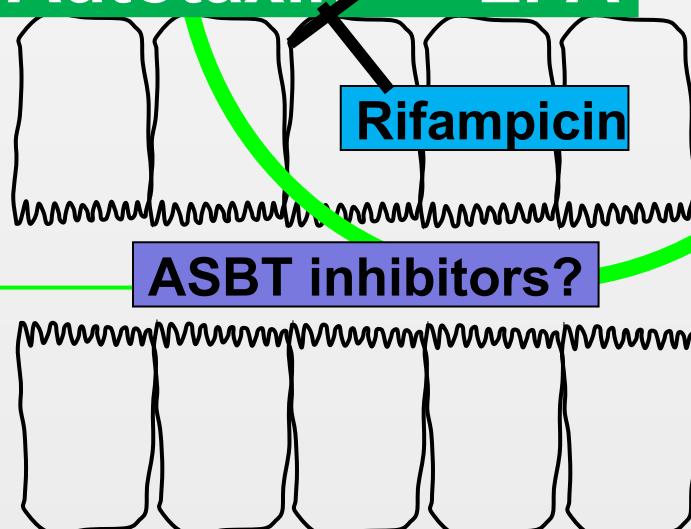
ASBT inhibitors?

Fibrates?  
(FITCH trial)

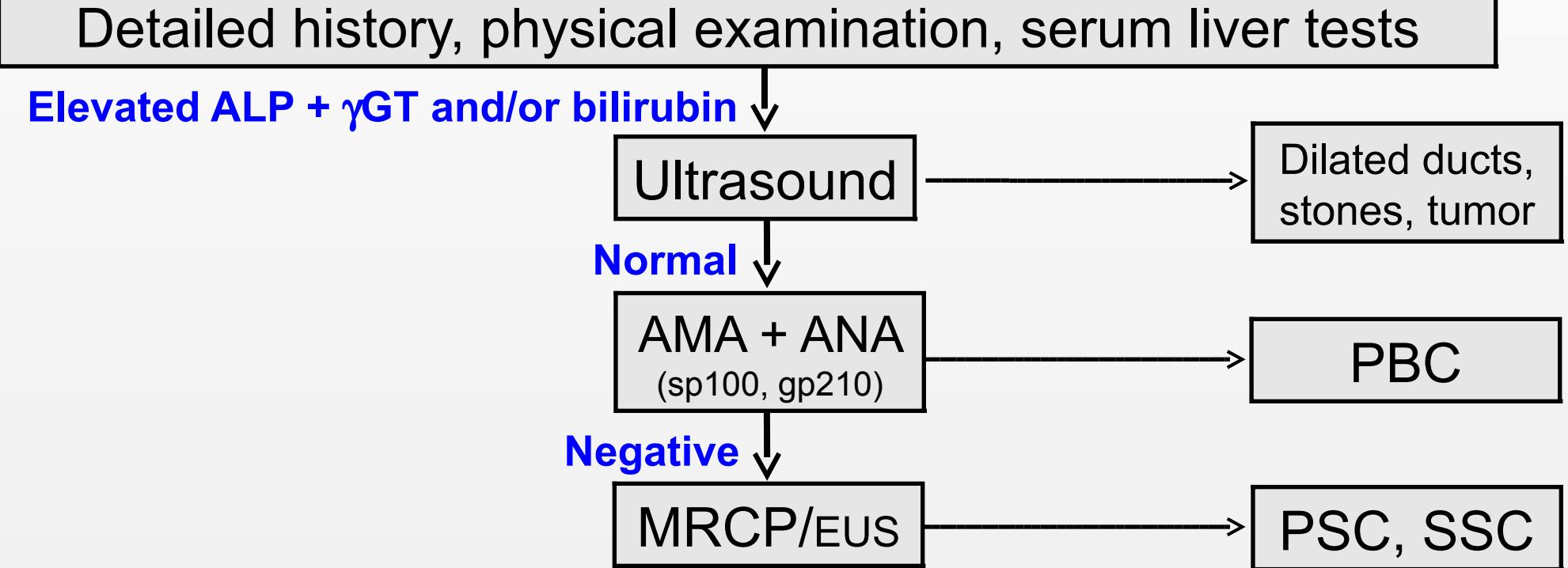
are secreted into bile

Nasobiliary drainage

Cholestyramine



# Diagnostic approach to cholestasis



# 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%

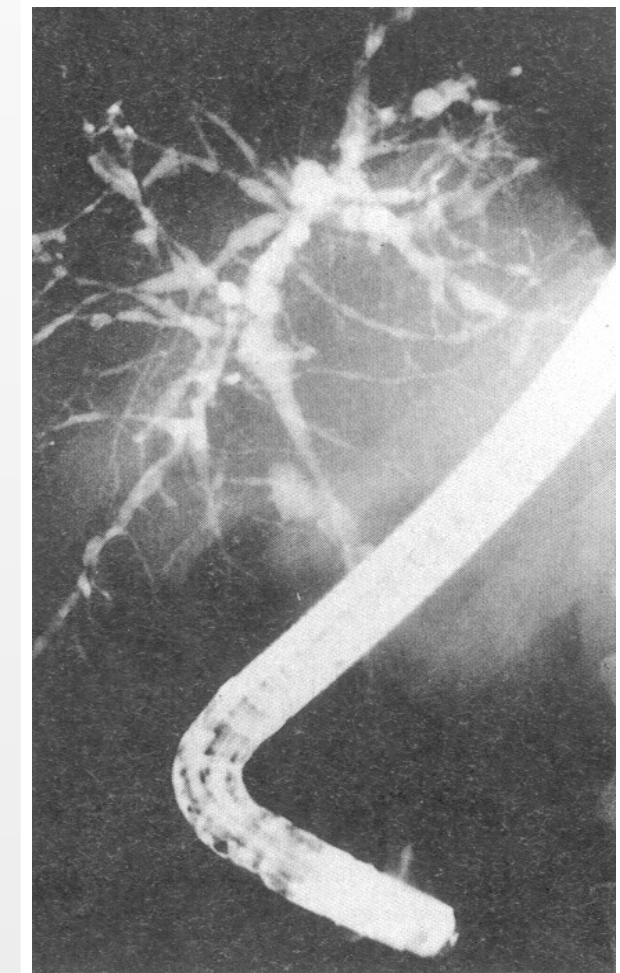
UDCA treatment 92%

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

***Pathogenetic model***

**Immunologic bile duct injury  
(Cytokine-mediated)**



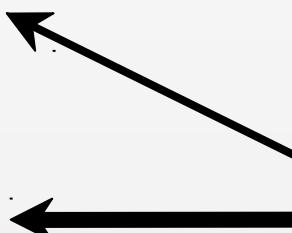
**Bile duct stenoses  
Aggravation of injury by BA**



**Cholestasis with retention of  
hydrophobic bile acids in liver**

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

?



**Fibrosis, cirrhosis**



**Liver failure**

**Liver transplantation**

*Pathogenetic model*

**Immunologic bile duct injury  
(Cytokine- mediated)**



**Bile duct stenoses**  
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**Cholestasis with retention of  
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**Fibrosis, cirrhosis**



**Liver failure**



**Endoscopic balloon dilatation**

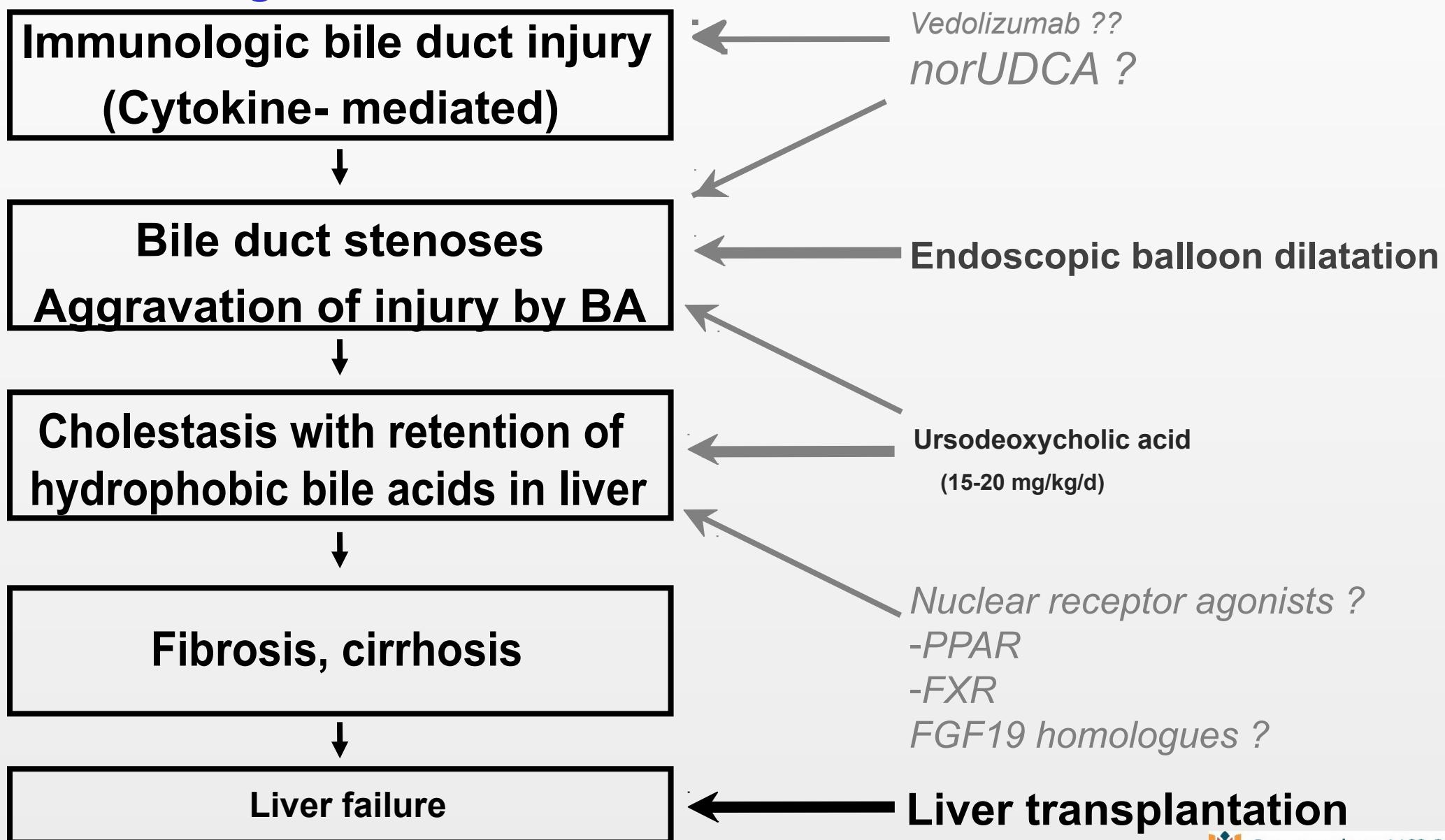
Ponsioen et al., Gastroenterology 2018;155:752

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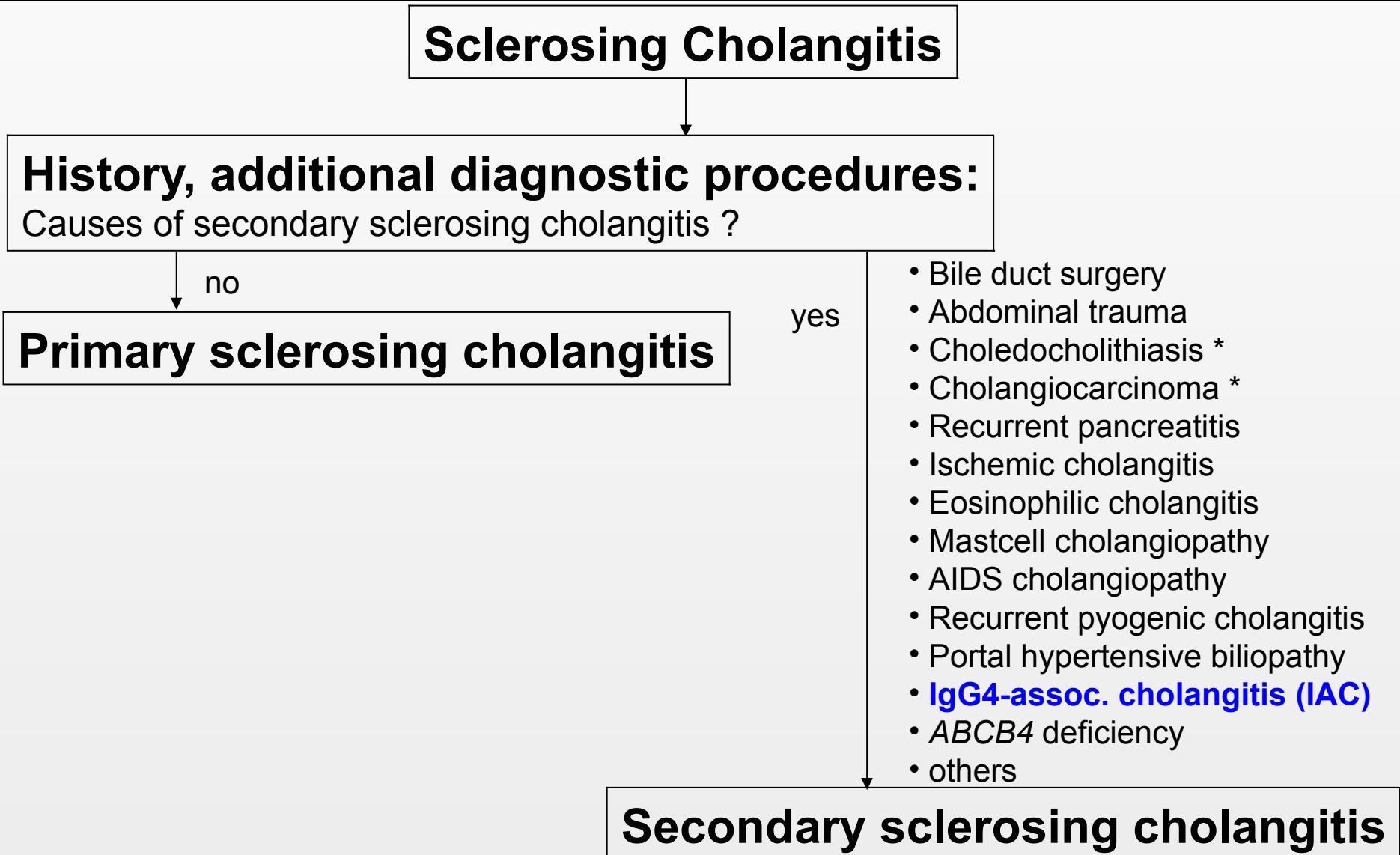
?

**Liver transplantation**

***Pathogenetic model***

# The Patient with Sclerosing Cholangitis

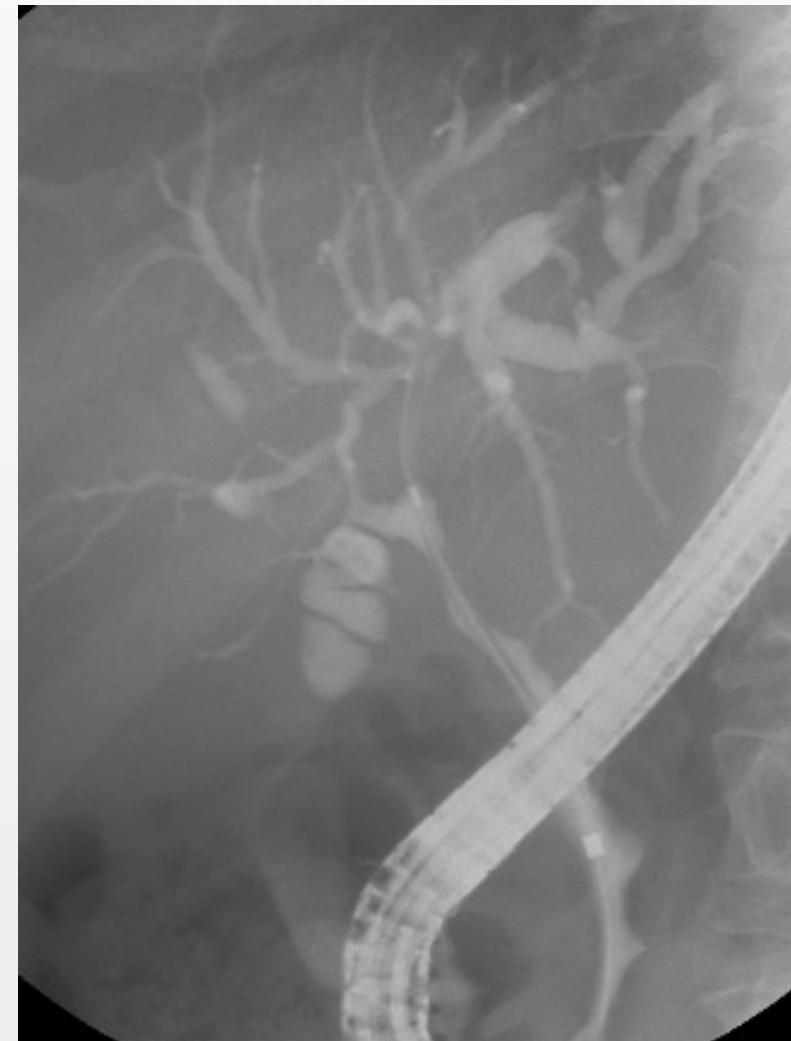
## Diagnostic Algorithm



\* may be consequence of PSC

# IgG4-associated cholangitis (IAC)

- Male (>80%)
- Middle aged / elderly (> 50 yrs)
- **Jaundice**, weight loss, abdominal pain
- Localized organ swelling / tumor
- Elevated serum / tissue IgG4
- Other organ manifestations of IgG4-RD

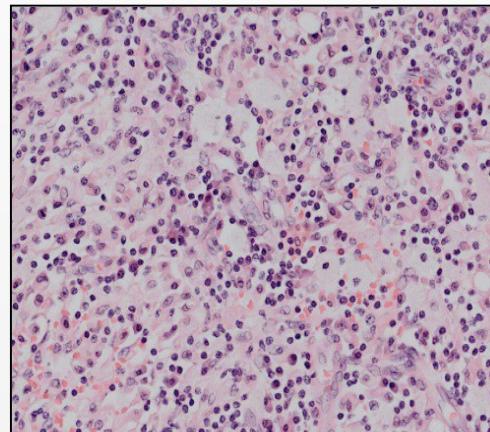


# Consensus criteria: Histology of IgG4-related disease

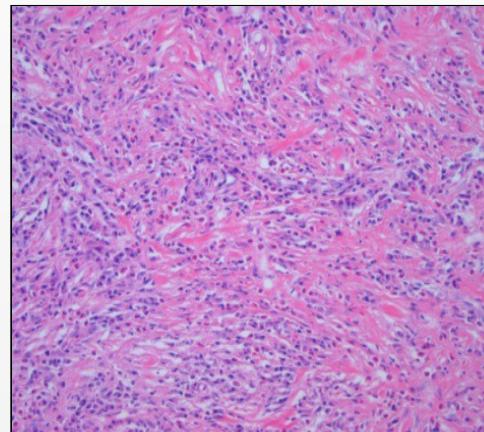
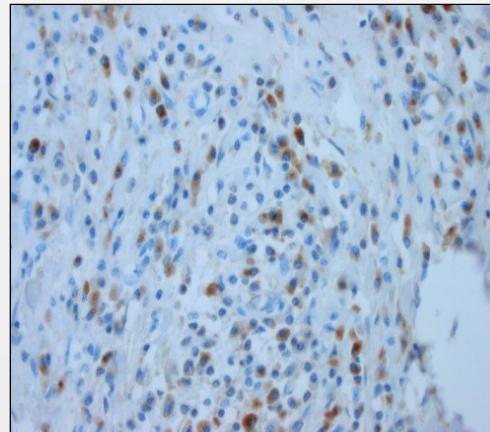
2 of 3 major histological features



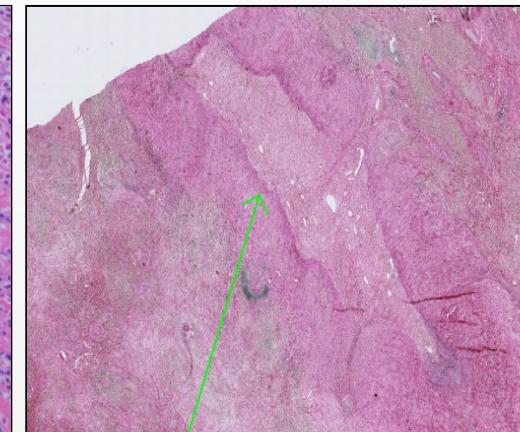
>50 IgG4+ plasma cells  
(resection specimen)



Lymphoplasmacytic infiltrate



Storiform fibrosis

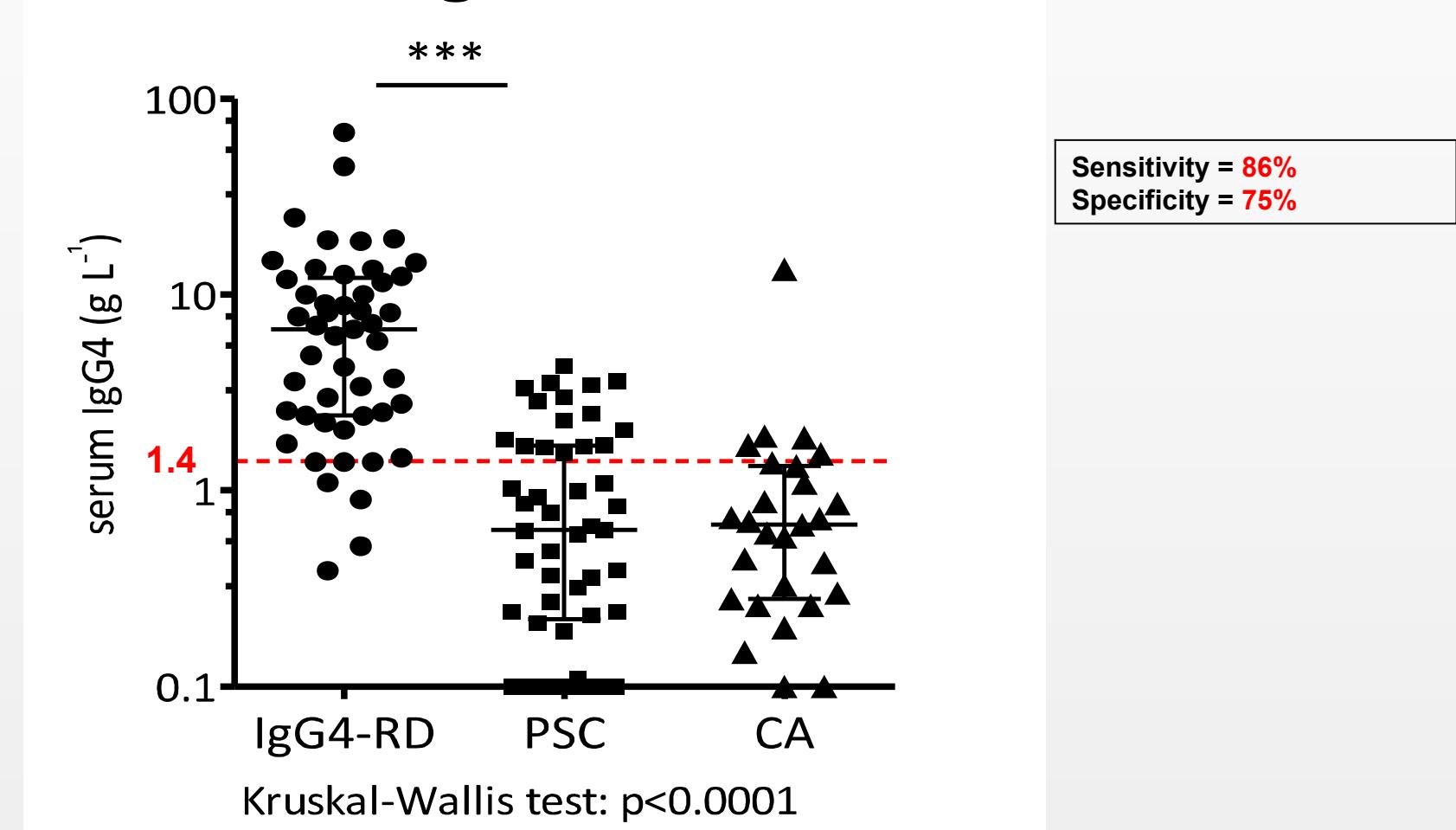


Obliterative phlebitis

Deshpande *et al.* Mod Pathol 2012;25:1181

Courtesy of J. Verheij

# Diagnostic value of serum IgG4 is limited for IgG4-RD

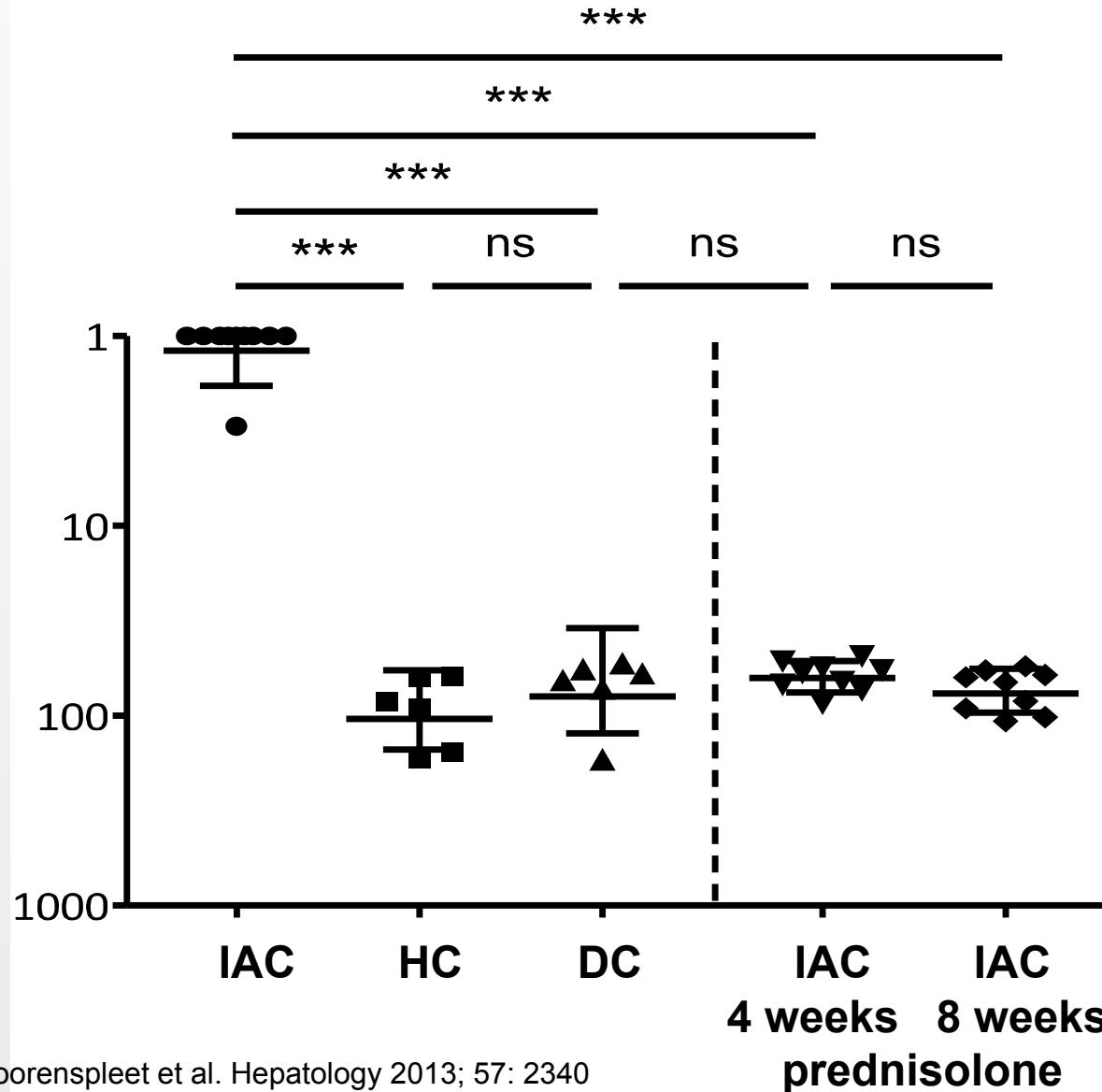


# IgG4-associated cholangitis: B cell receptor sequencing

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

Ranking of the most prominent IgG4+ BCR clone

among all IgG clones



IAC: IgG4 cholangiopathy

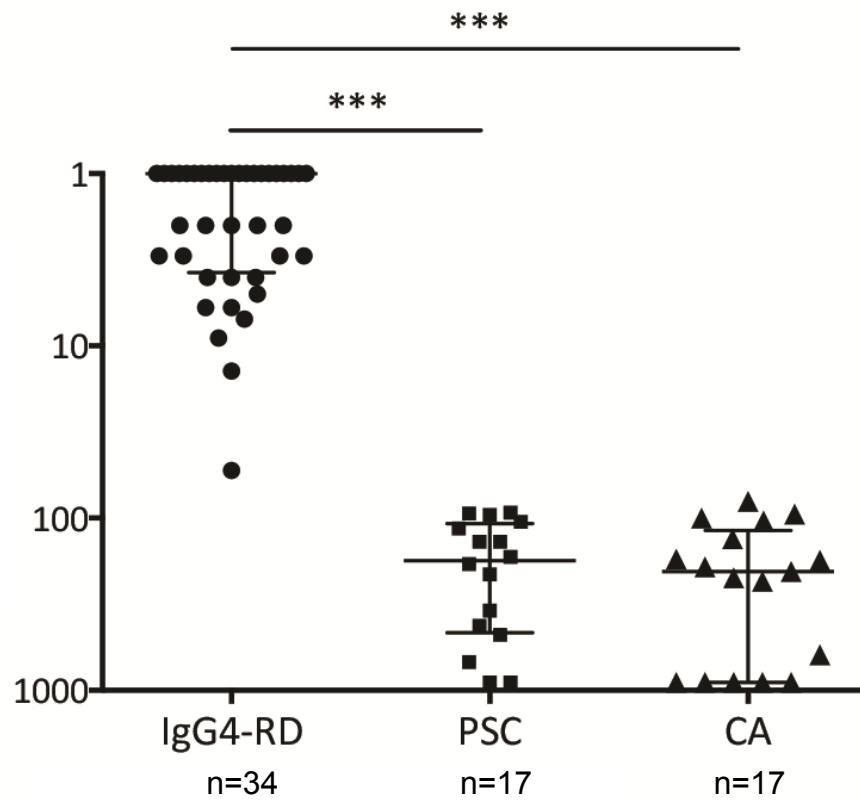
HC: Healthy control

DC: Disease control

# Diagnosis of IgG4-associated cholangitis

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

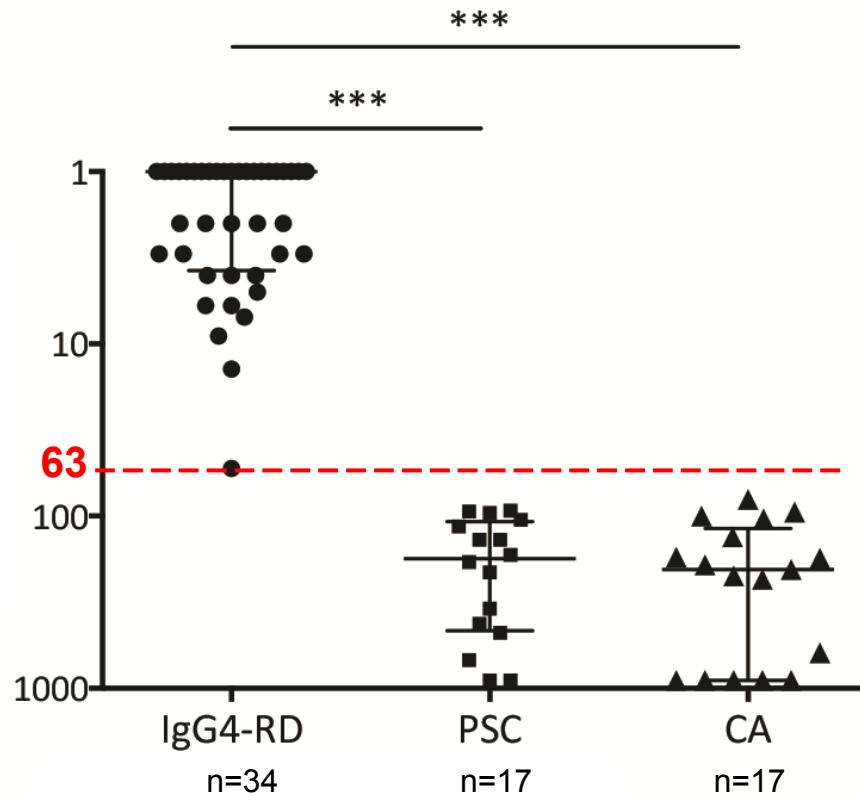
**Rank of the most prominent IgG4+ BCR clone among all IgG clones**



# Diagnosis of IgG4-associated cholangitis

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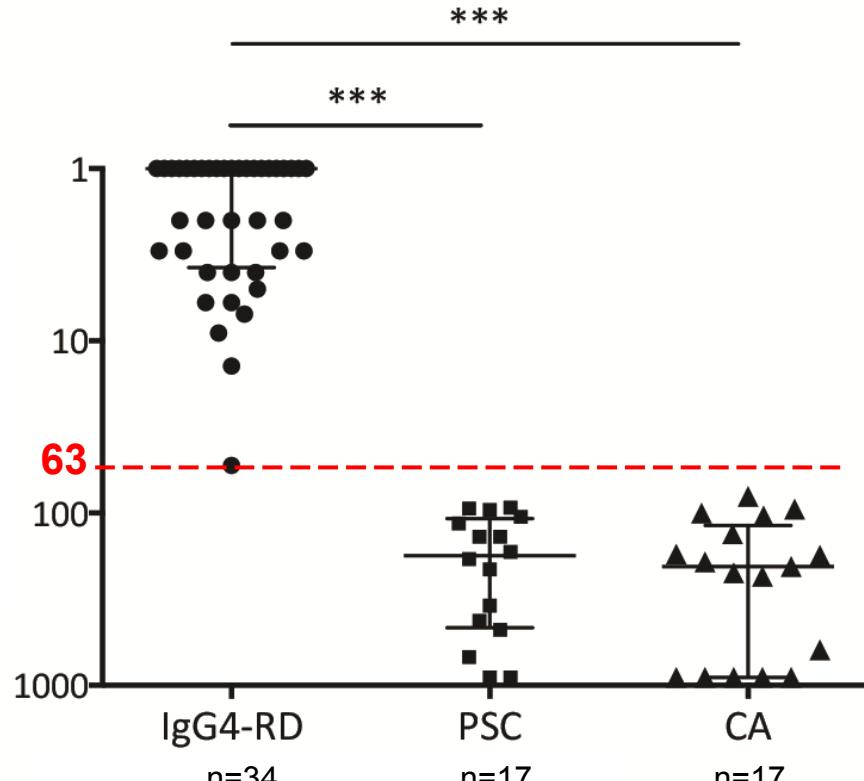
Rank of the most prominent IgG4+ BCR clone among all IgG clones



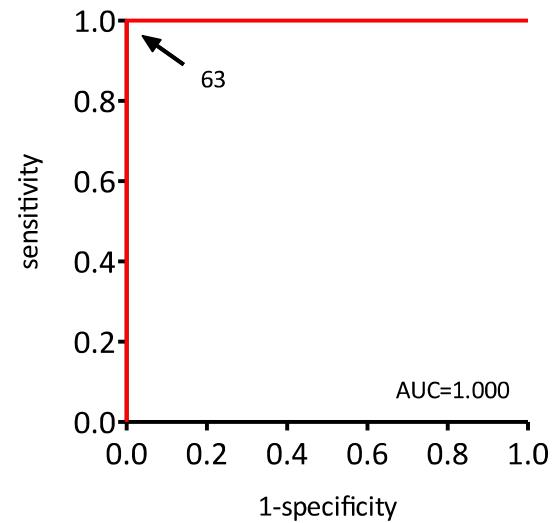
# Diagnosis of IgG4-associated cholangitis

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Rank of the most prominent IgG4+ BCR clone among all IgG clones

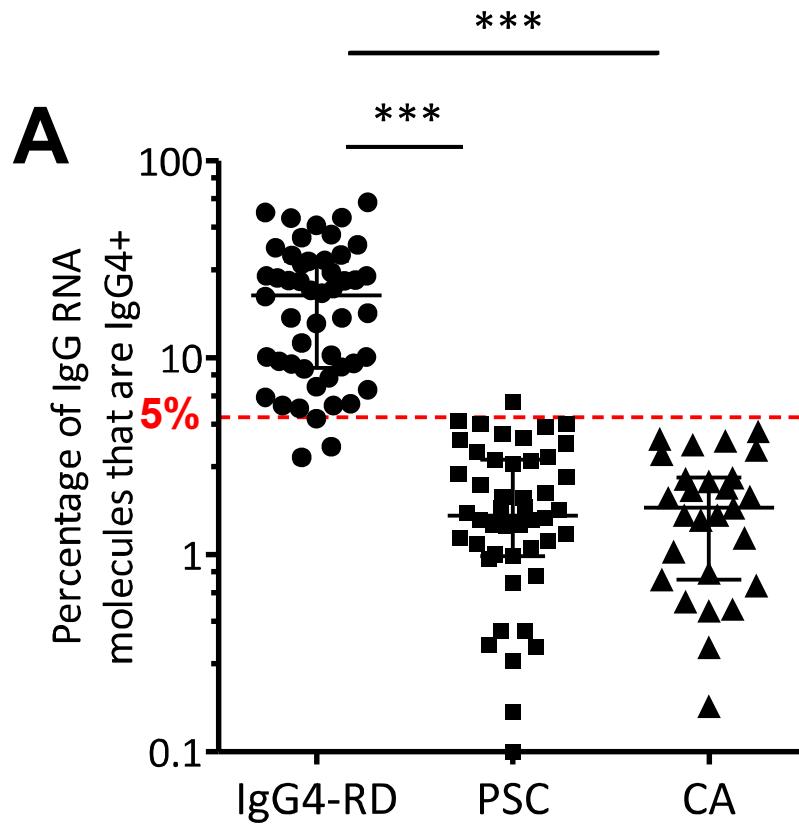


Sensitivity = 100%  
Specificity = 100%



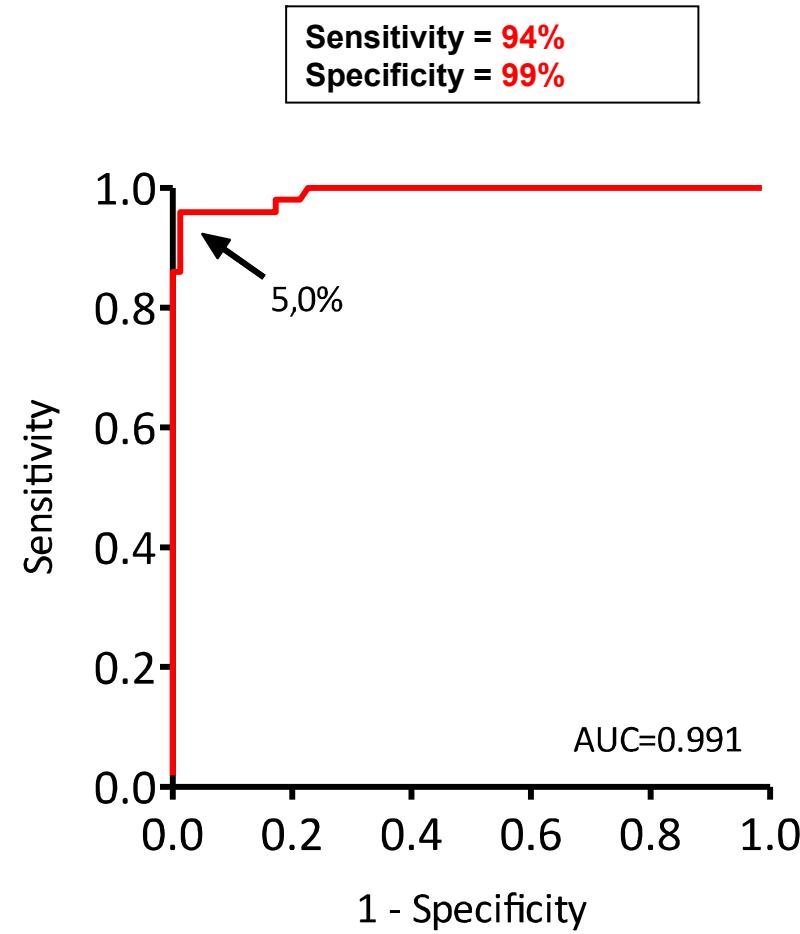
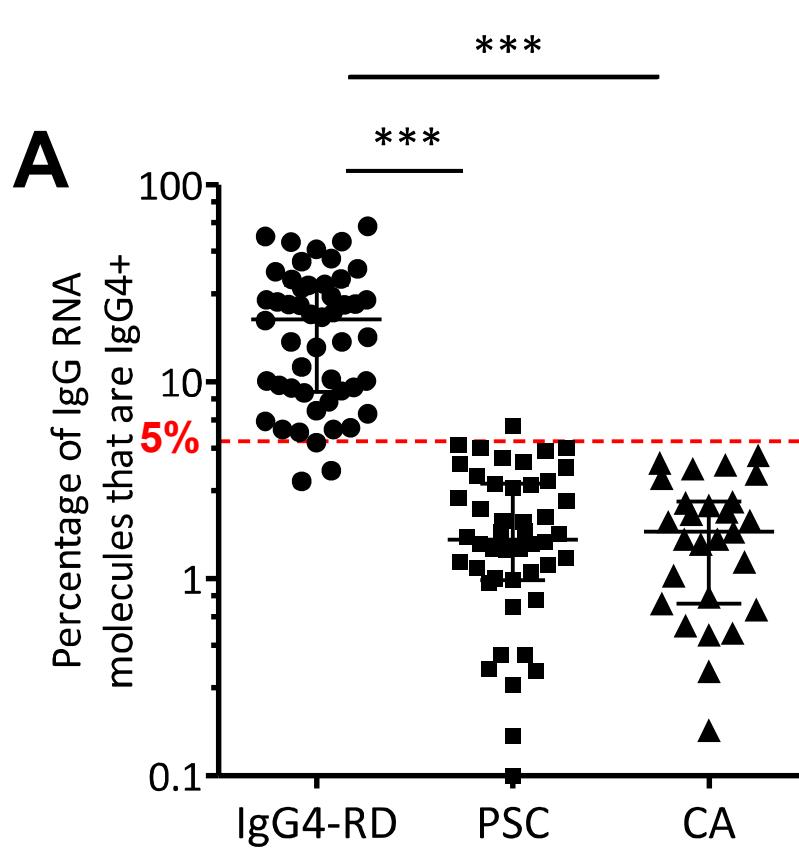
# Diagnosis of IgG4-associated cholangitis

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



# Diagnosis of IgG4-associated cholangitis

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



# 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)

**IAC/AIP** (n=25 and 44, resp.)

**PSC** (n=21 and 22, resp.)

Amsterdam

**88 %**

**16 %**

Oxford

**61 %**

**22 %**

# Treatment of IgG4-associated cholangitis

## 1. Initial treatment:

- 40 mg\* predniso(lo)ne / day for 4 weeks
- Tapering of daily predniso(lo)ne: 5 mg/week
- Total treatment duration: 11 weeks

\* (10-)20 mg predniso(lo)n / day may be sufficient

Buijs et al. Pancreas 2014;43:261

## 2. Long-term maintenance treatment (incomplete responders):

- 5(-10) mg/d      Predniso(lo)ne
- $\leq$  2 mg/kg/d      Azathioprine

3. Experimental (corticosteroid-refractory patients):      Rituximab; Tacrolimus

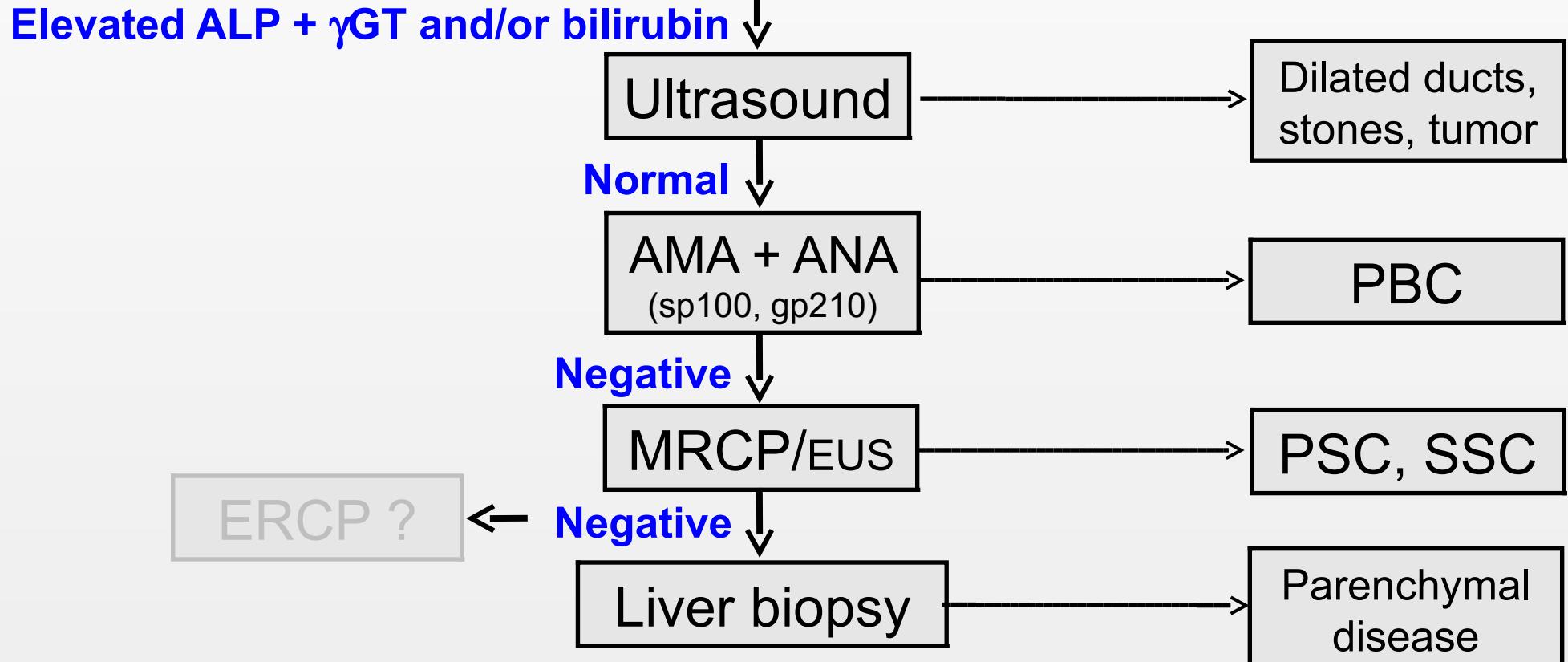
Ghazale et al., Gastroenterology 2008;134:706

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

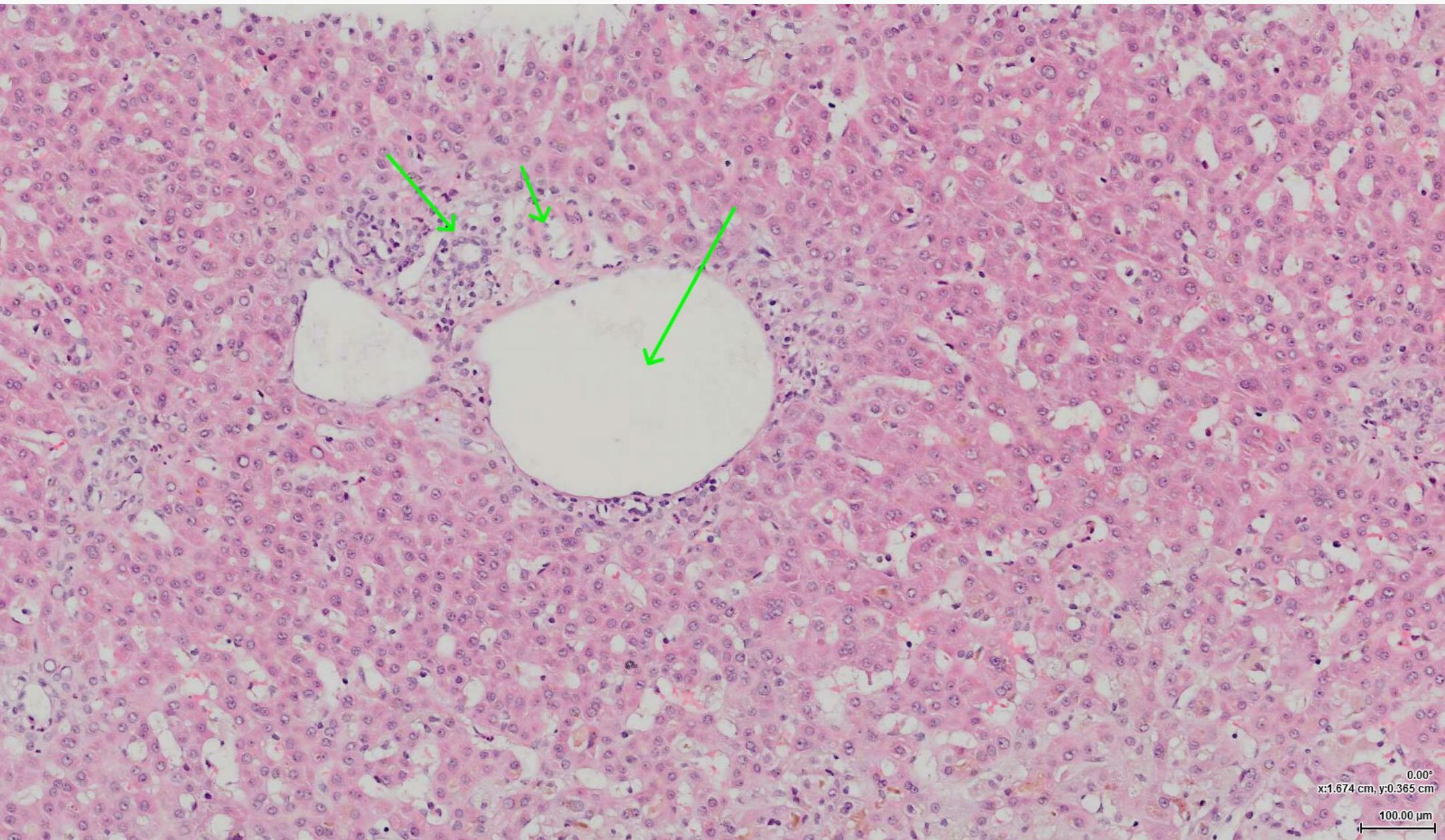
# Diagnostic approach to cholestasis

♀ 34 yrs

Detailed history, physical examination, serum liver tests



# Liver biopsy



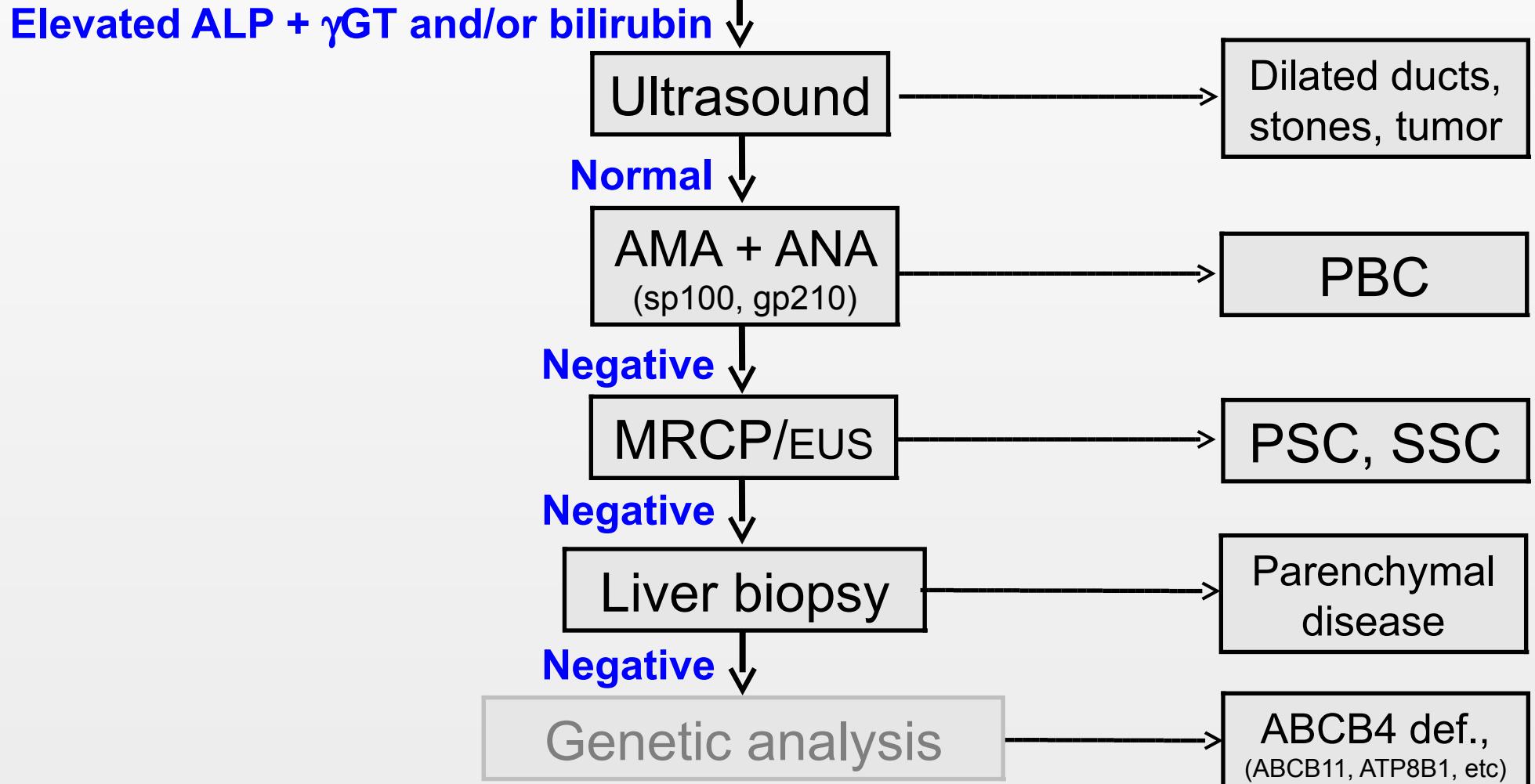
0.00°  
x:1.674 cm, y:0.365 cm

100.00 µm

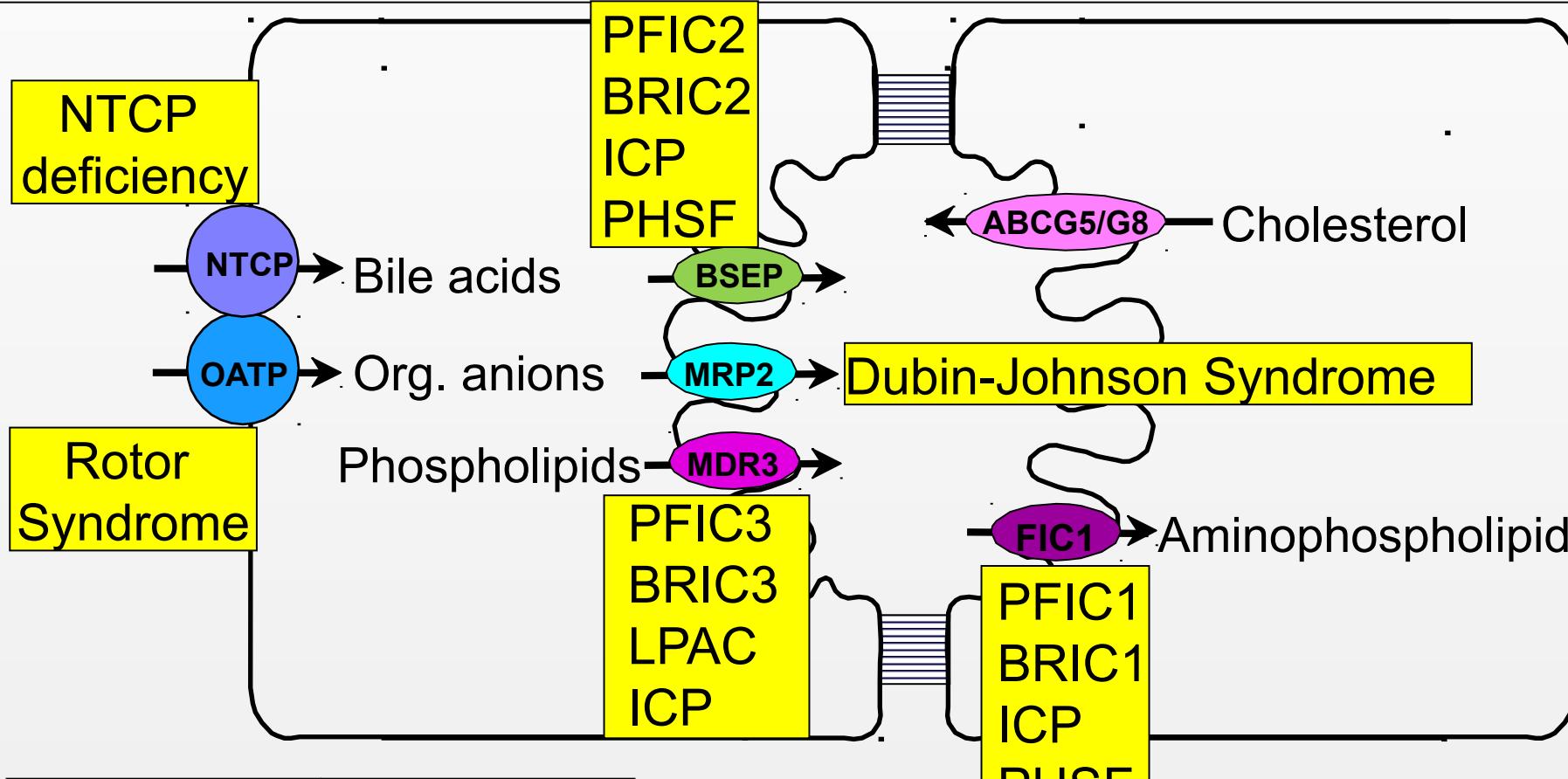
# Diagnostic approach to cholestasis

♀ 34 yrs

Detailed history, physical examination, serum liver tests



# Consequences of transporter defects



Transporter	Gene
FIC1	ATP8B1
BSEP	ABCB11
MDR3	ABCB4

**PFIC:** Progressive familial intrahepatic cholestasis

**LPAC:** Low phospholipid associated cholelithiasis

**BRIC:** Benign recurrent intrahepatic cholestasis

**ICP:** Intrahepatic cholestasis of pregnancy

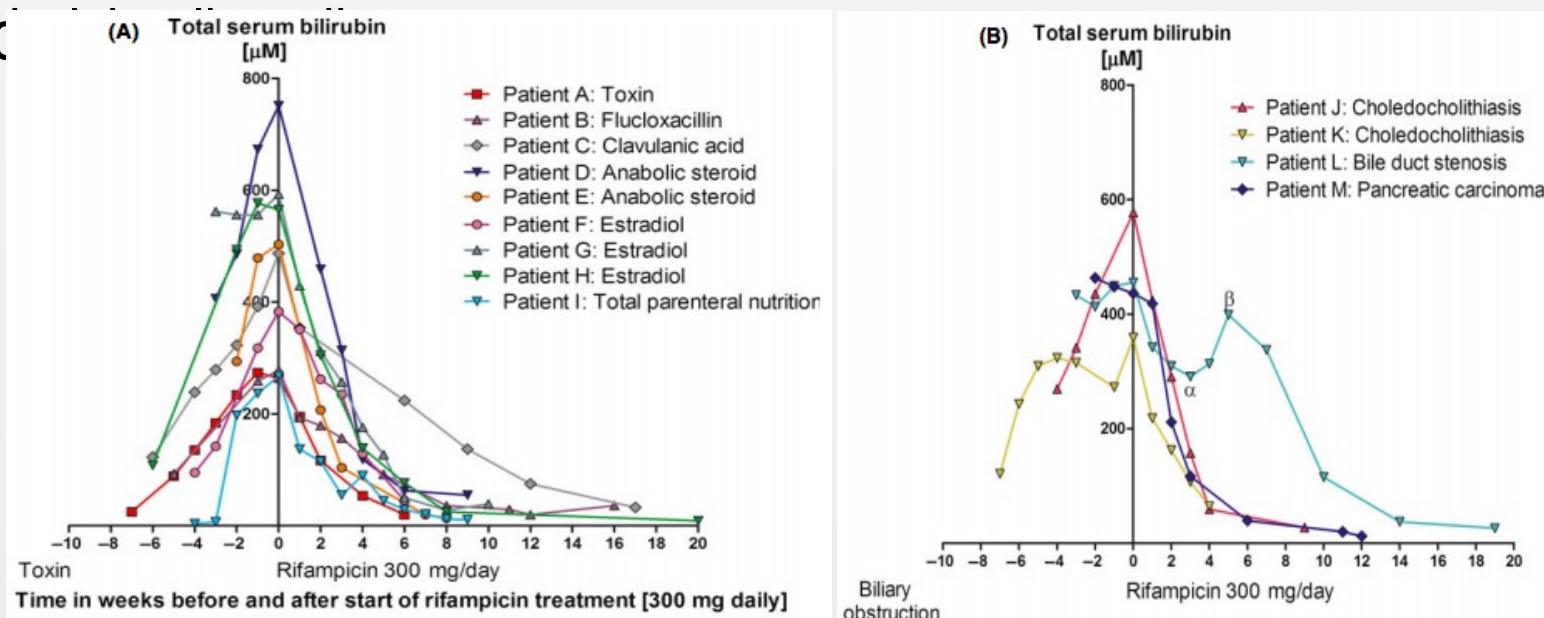
**PHSF:** Persistent hepatocellular secretory failure

# Persistent hepatocellular secretory failure (PHSF)

- Serum bilirubin >255 µmol/L (>15 mg/dL)
- Persistently elevated bilirubin (>1 week) after removal of the underlying cause (medication, toxin, transient mechanical obstruction)
- Exclusion of bile duct obstruction by imaging

• No und

• Rapid



# Management of cholestatic liver diseases 2019

