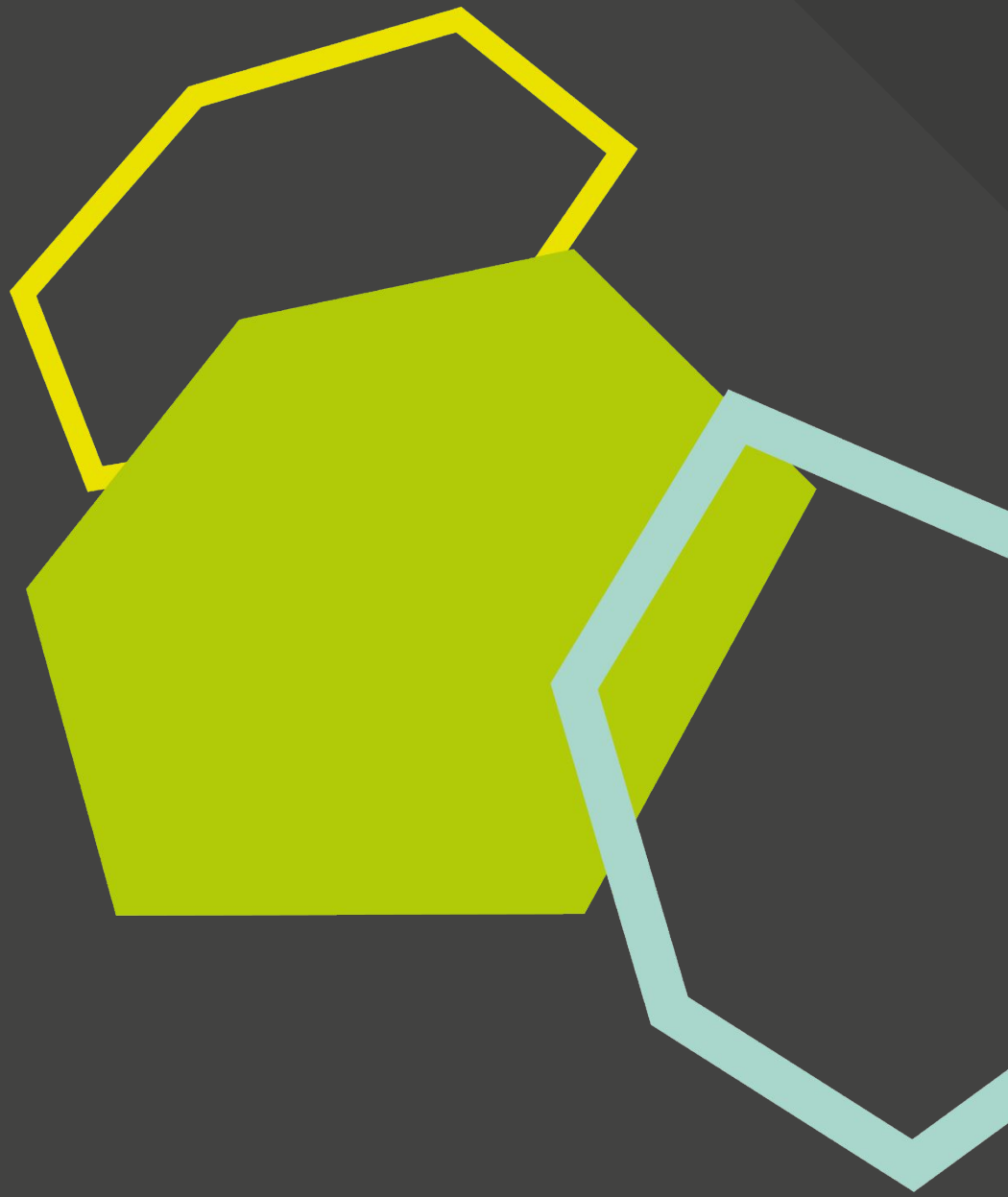
Changing perspectives

in cholestatic liver disease and PBC



This event has been organised and funded by Intercept Pharma Europe Ltd.

Intercept

EU-NP-PB-0141 April 2017

A panoramic view of cholestatic liver disease

Gideon Hirschfield

University of Birmingham, UK

NHS National Institute for Health Research

UK-PBC

UK-PSC

Note to Gideon: Please could you provide the correct values? If you are taking these from references, would you mind letting us know which they are? We are happy to sort out the ‘red herring’ answers if this is useful to you

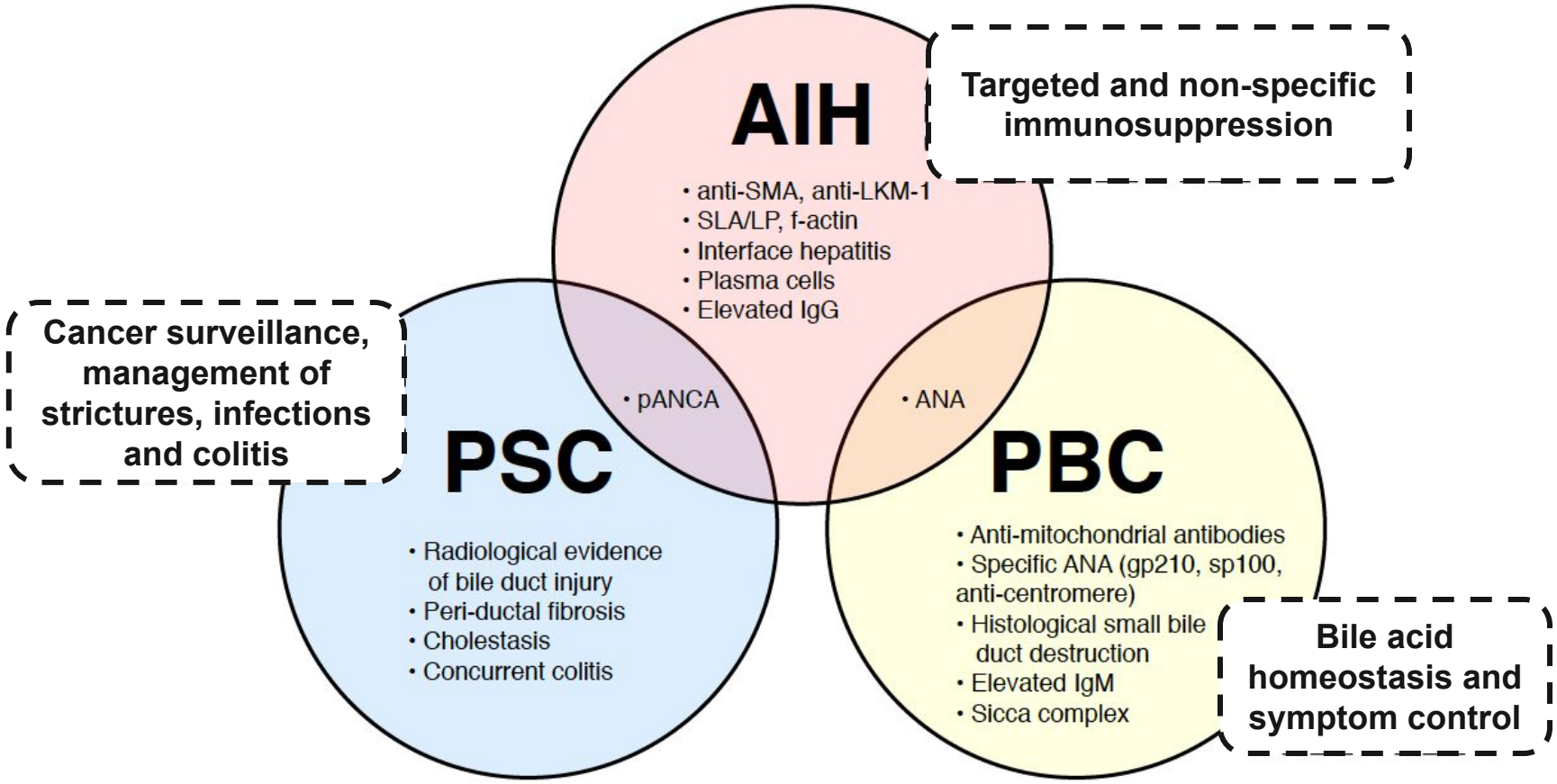
Placeholder for multiple choice voting question

What is the incidence/prevalence of PBC, PSC and AIH?

AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Note to Gideon: Could you please advise which of your publications this is from? We cannot find it in the Webb/Hirschfield paper we have in our reference library

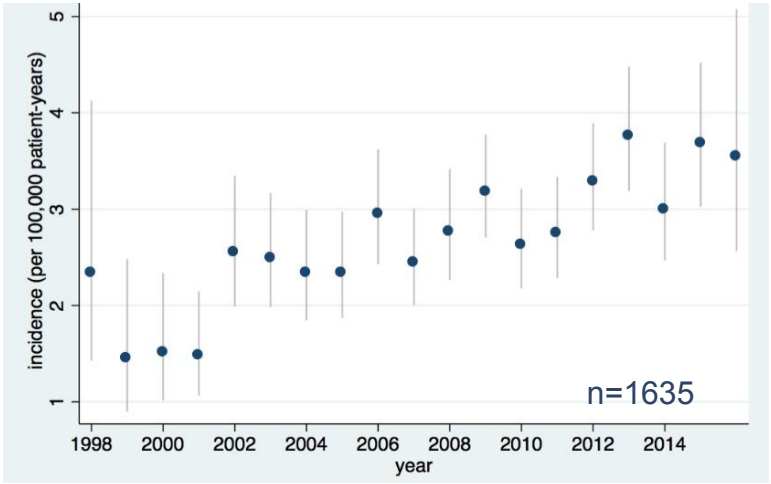
The three autoimmune liver diseases



AIH, autoimmune hepatitis; ANA, anti-nuclear antibody; IgG/M, immunoglobulin G/M; LKM-1, liver kidney microsomal antigen type-1; pANCA, peri-nuclear anti-neutrophil cytoplasmic antibodies; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLA/LP, soluble liver antigen/liver-pancreas; SMA, smooth muscle antibody.
Webb and Hirschfield.

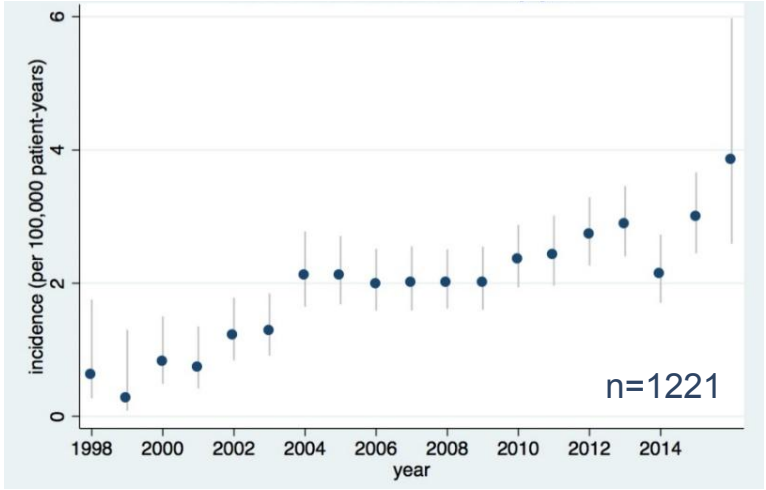
Incidence of cholestatic liver disease is increasing

Crude incidence of PBC by year



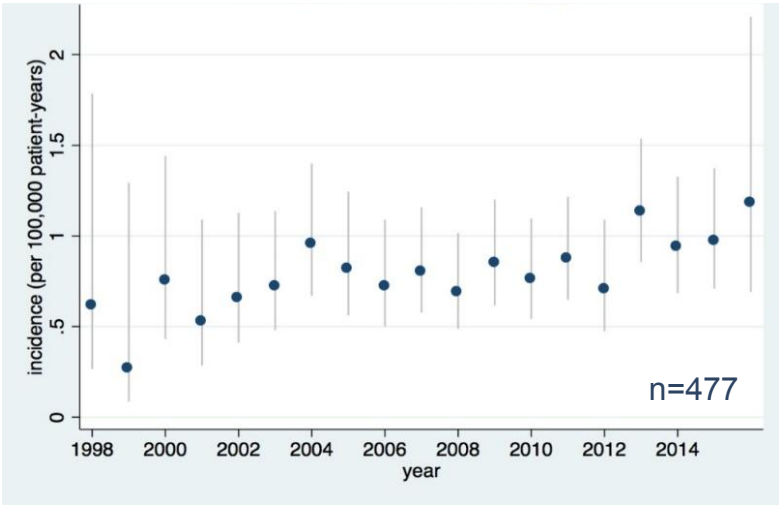
c.f. Boonstra K, *et al*. *J Hepatol* 2012;56:1181–8.
"PBC incidence rates range from 0.33 to 5.8 per 100,000 inhabitants/year".

Crude incidence of AIH by year



van Gerven NM, *et al. Scand J Gastroenterol* 2014;49:1245–54.
Dutch annual incidence of 1.1 (95% CI: 0.5–2) in adults.

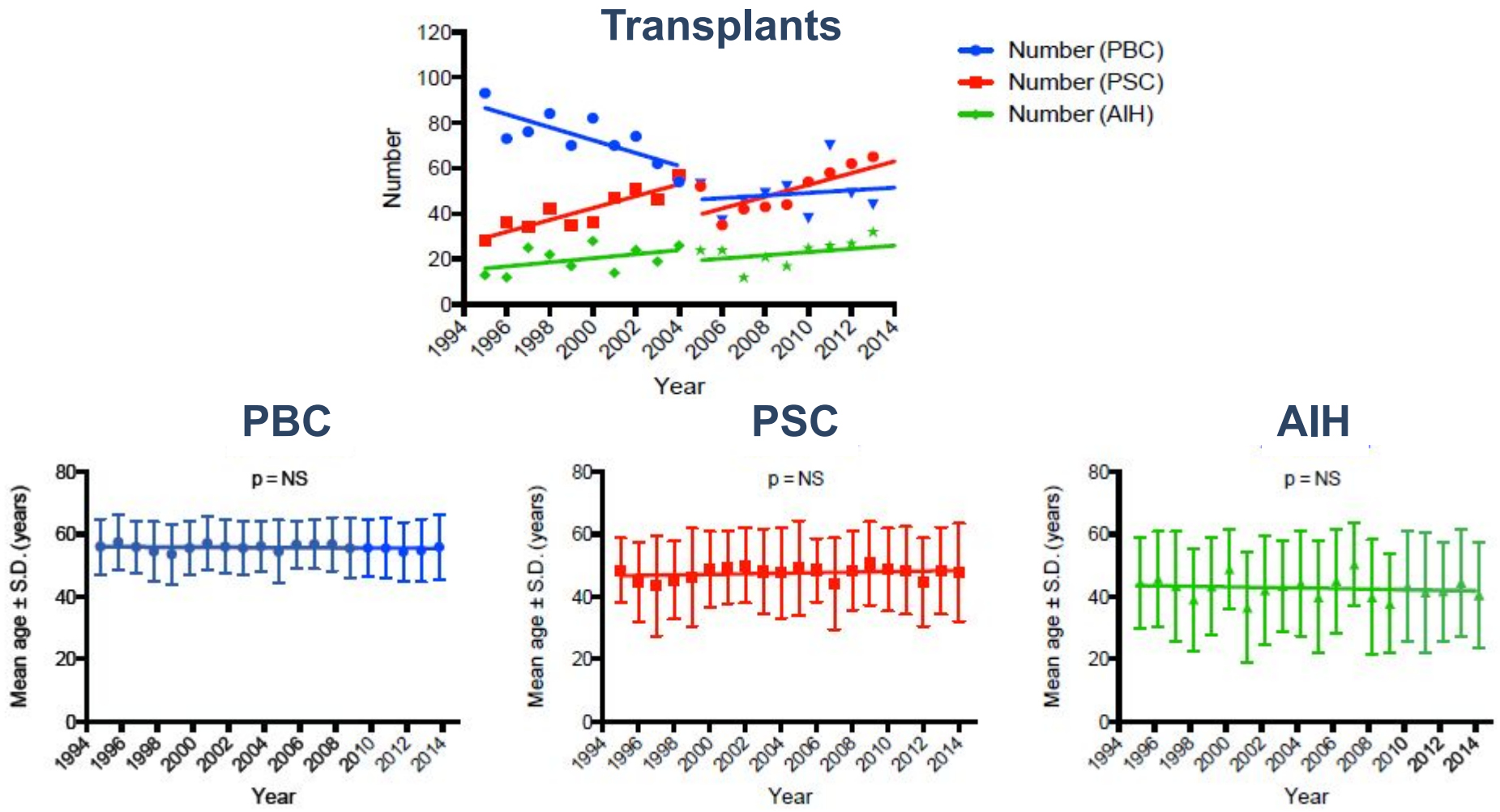
Crude incidence of PSC by year



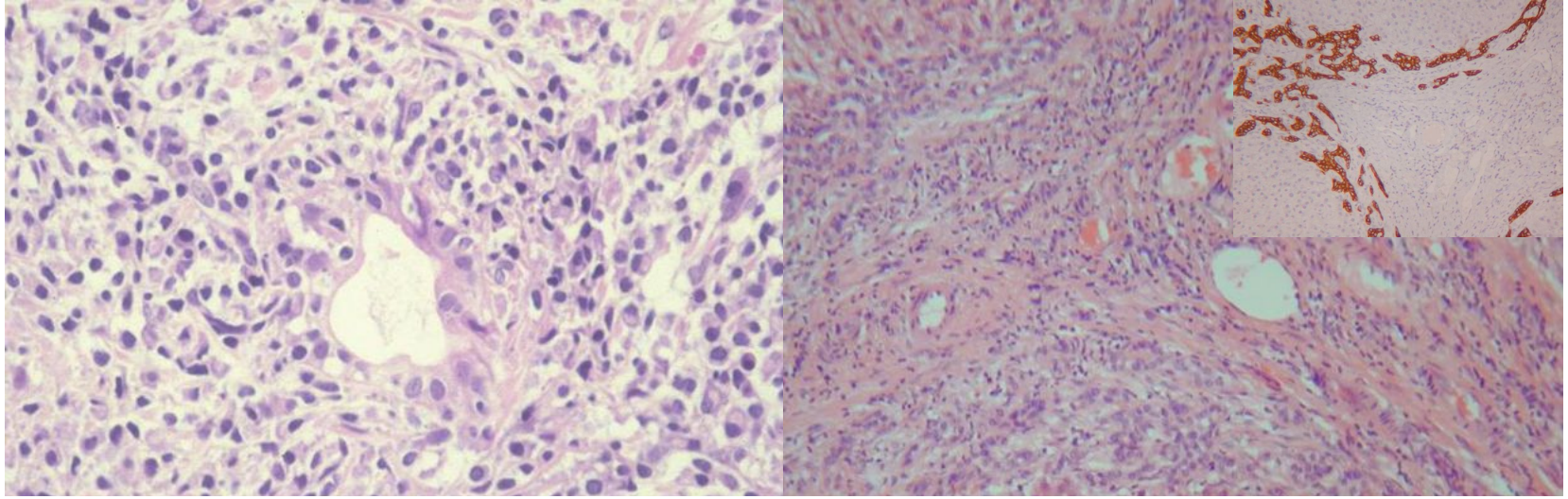
c.f. Boonstra K, *et al*. *J Hepatol* 2012;56:1181–8.
"PSC incidence rates range from 0 to 1.3 per 100,000 inhabitants/year".

AIH, autoimmune hepatitis; CI, confidence interval; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
Webb G, *et al*. In preparation.

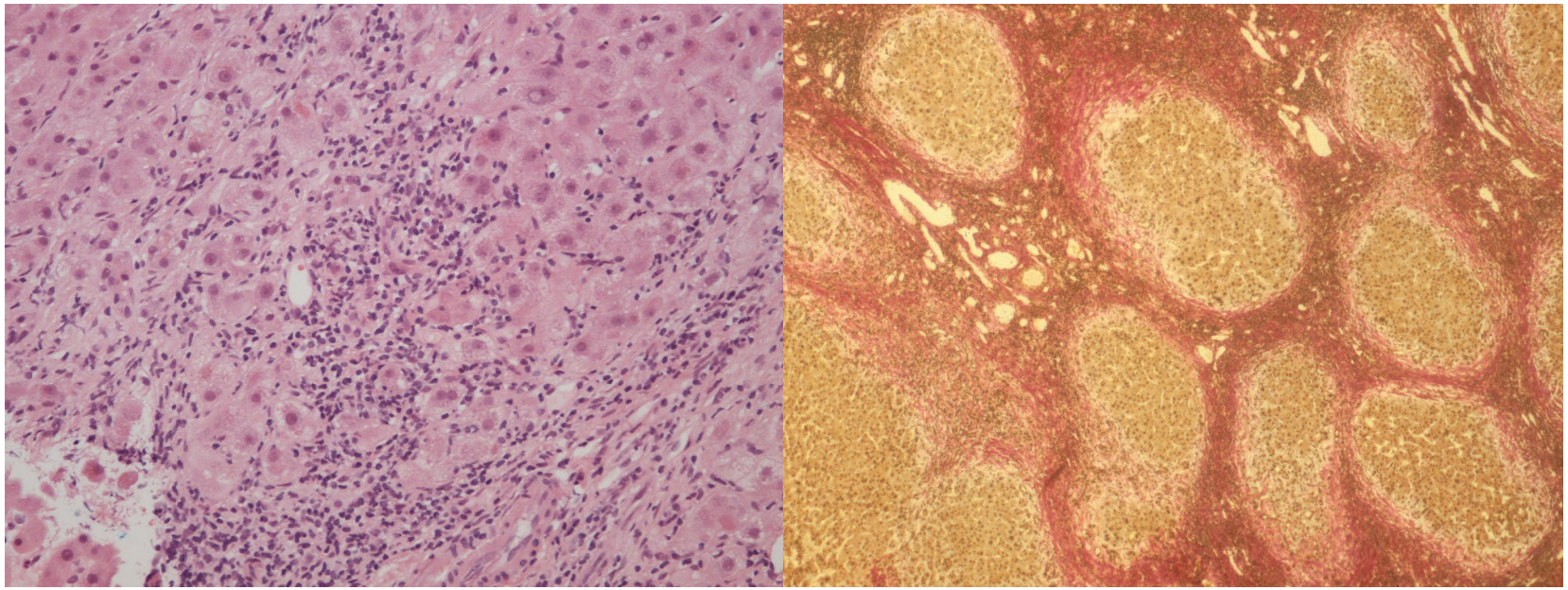
Increasing numbers of transplants for PSC and AIH and no change in age at listing for any indication



AIH, autoimmune hepatitis; NS, not significant; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SD, standard deviation.
Webb G, *et al*. *Hepatology* 2015;62(1 suppl):523A.



Chronic non-suppurative destructive cholangitis

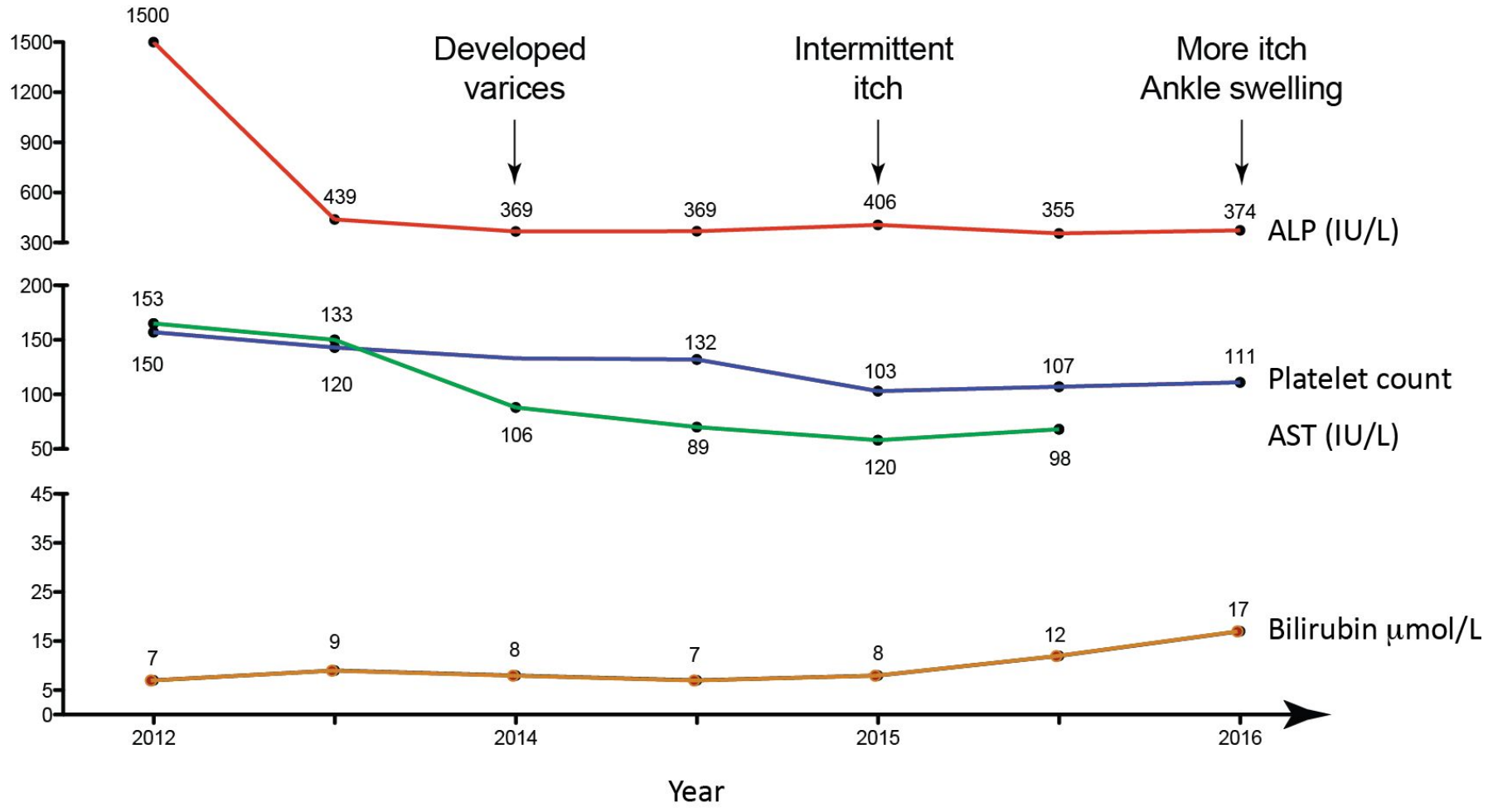


1 in 1000 women over the age of 40 are estimated to have PBC[1]

PBC, primary biliary cholangitis.

1. Hohenester S, *et al. Semin Immunopathol* 2009;31:283–307.

Mrs. P: Clinical course, **high risk**

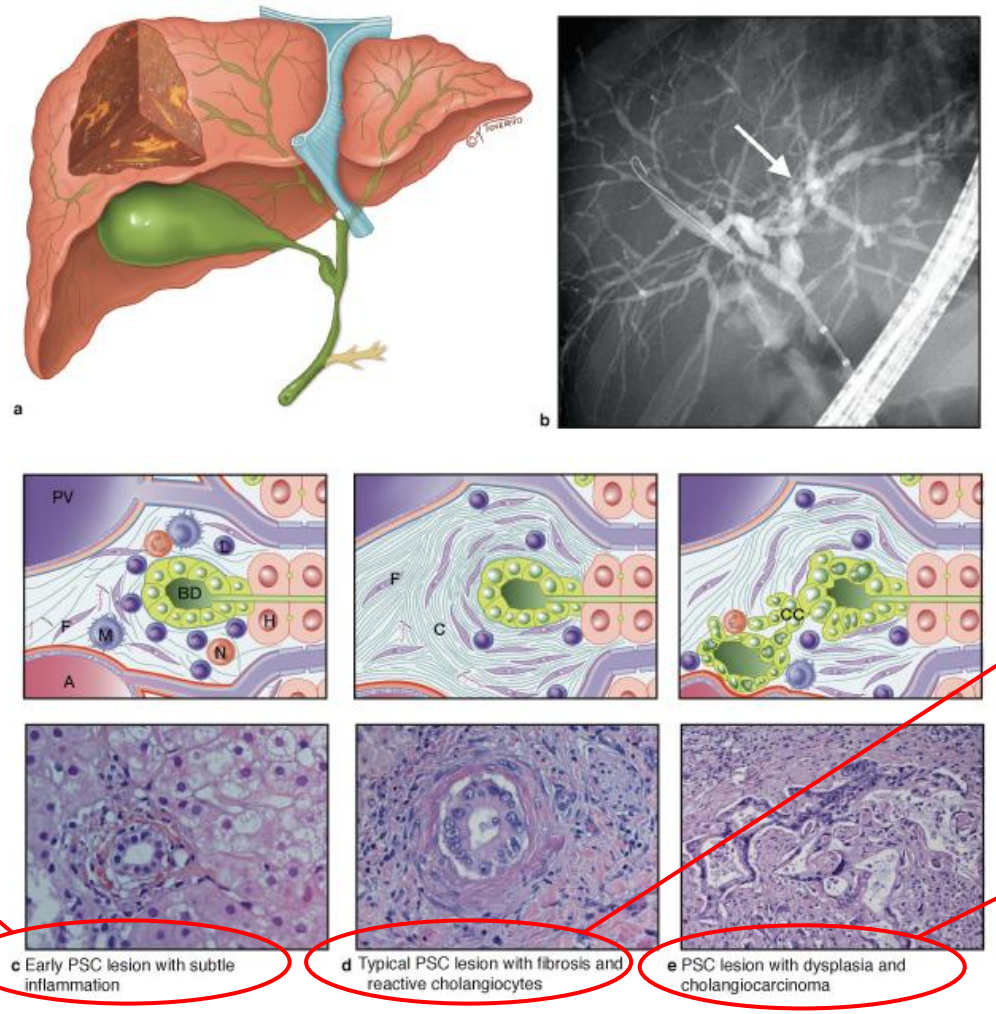


ALP, alkaline phosphatase; AST, aspartate aminotransferase.

Patchy disease characterised by strictures, inflammation and malignancy risk

Primary sclerosing cholangitis

Gideon M Hirschfield, Tom H Karlsen, Keith D Lindor, David H Adams



Early PSC lesion with subtle inflammation

Typical PSC lesion with fibrosis and reactive cholangiocytes

PSC lesion with dysplasia and cholangiocarcinoma

PSC, primary sclerosing cholangitis.
Hirschfield GM, *et al. Lancet* 2013;382:1587–99.

Vision statement

- Better treatment targeted in better ways encompassing quantity and quality of life
    - Recognise and act upon individual RISK and STAGE

Key attributes of safe, tolerable and effective therapy:

1. Targeted for patients with unmet need through appropriate risk stratification, and based on precision medicine
2. Proof of benefit in studies of appropriate patient cohorts
3. Manageable and tolerable side effects

Chronic Cholangitides: Aetiology, Diagnosis, and Treatment*

SHEILA SHERLOCK,† M.D., F.R.C.P., F.R.C.P.ED., F.A.C.P.(HON.)

Brit. med. J., 1968, 3, 515–521

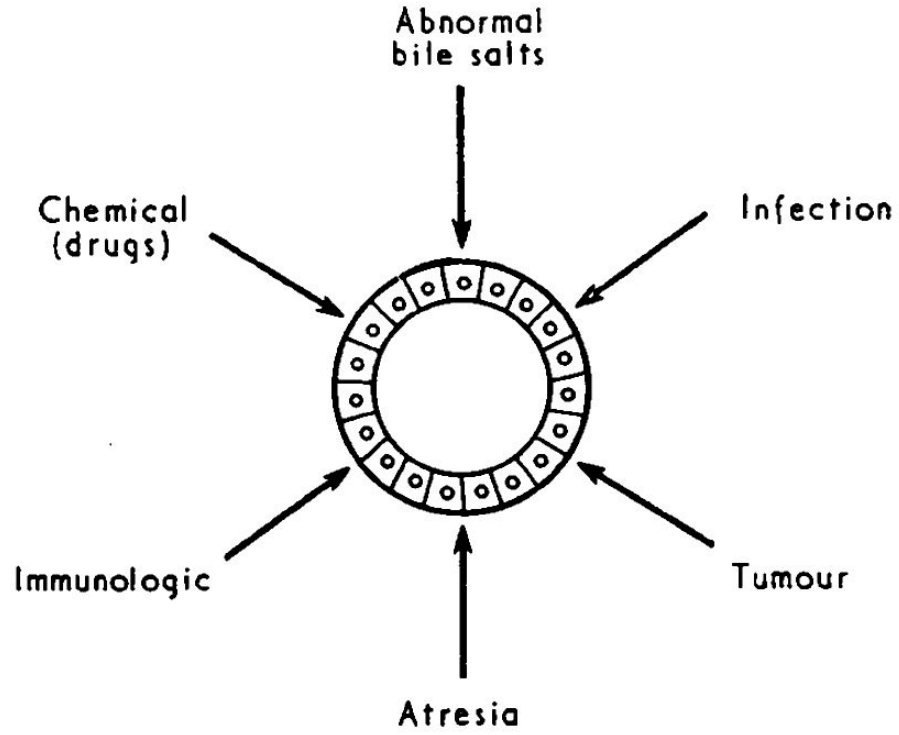


FIG. 1

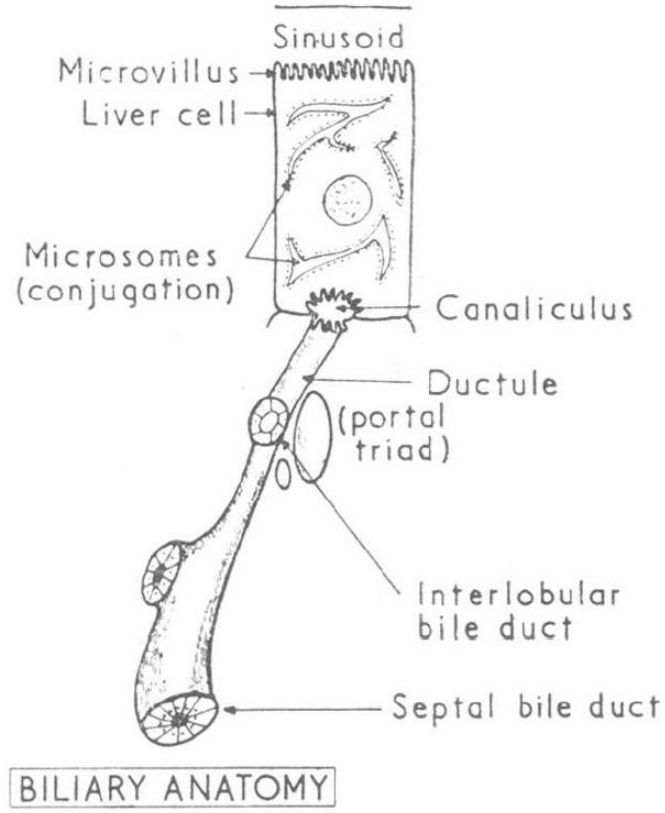
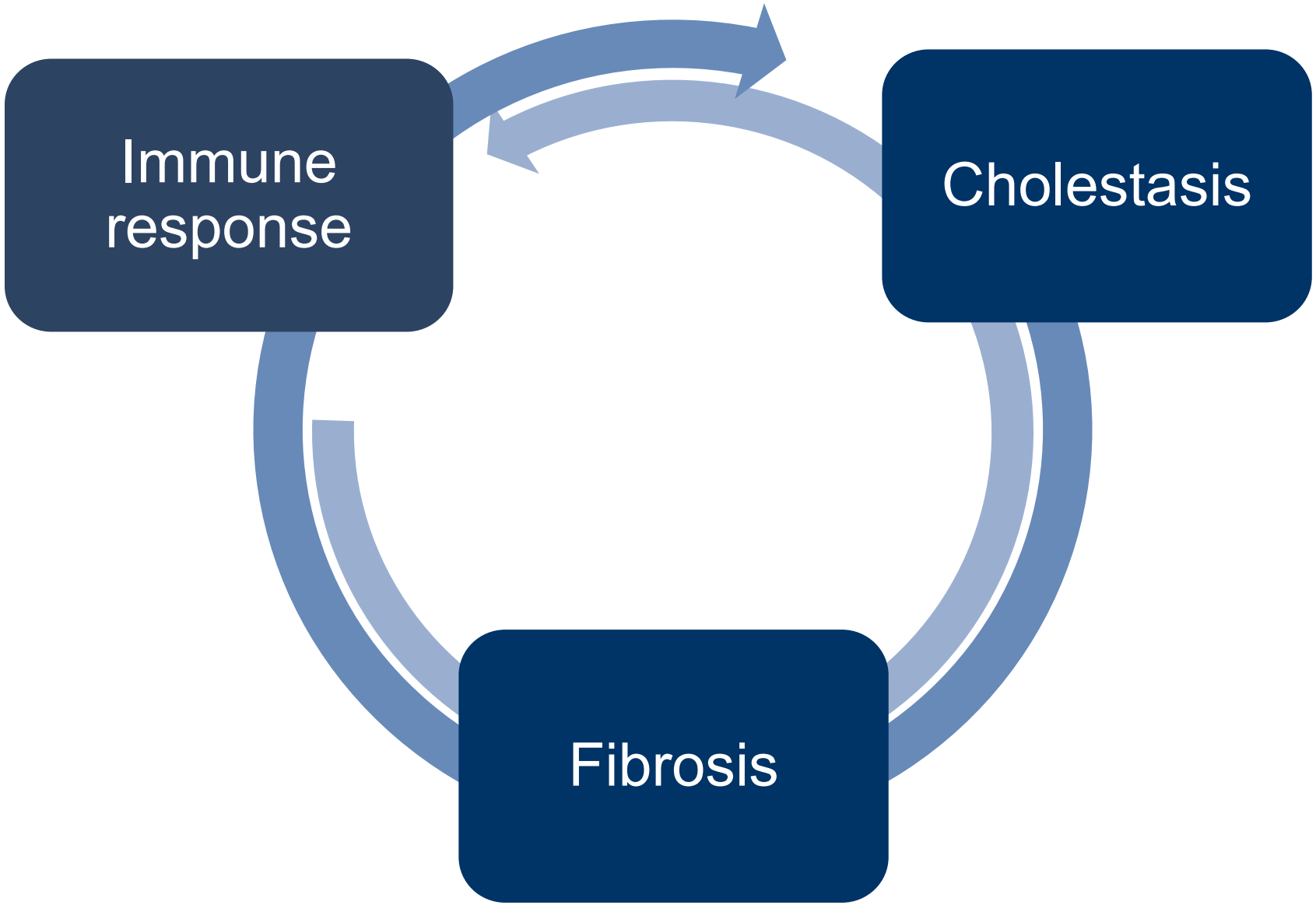


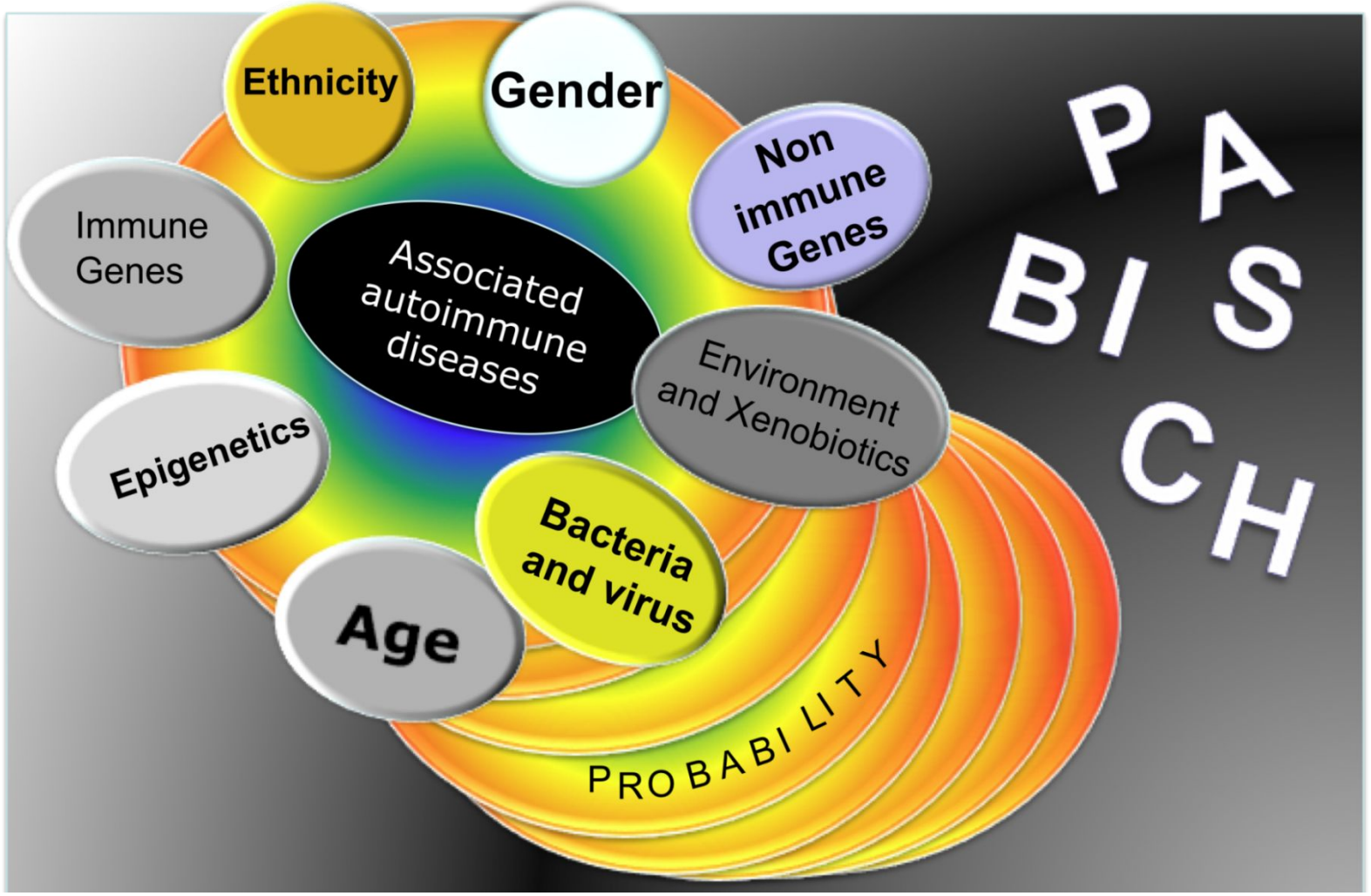
FIG. 2

FIG. 1.—Aetiological factors concerned in disease of the cholangiole include infection, atresia, carcinoma, and immunological. FIG. 2.—Anatomy of the cholangiole. This extends from the canaliculus to the septal bile ducts, which join in branches of ever-increasing size until the right and left main bile ducts are formed.



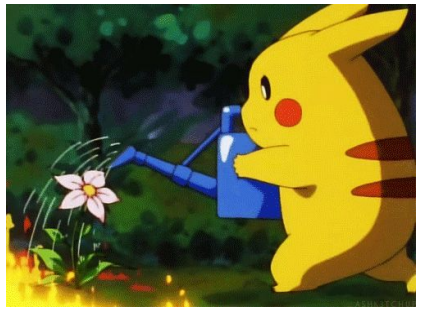
Slide adapted from Parés A.

A potpourri of risks



Hirschfield GM, Gershwin ME. *Ann Rev Pathol* 2013;8:303–30.

We aren’t all equal



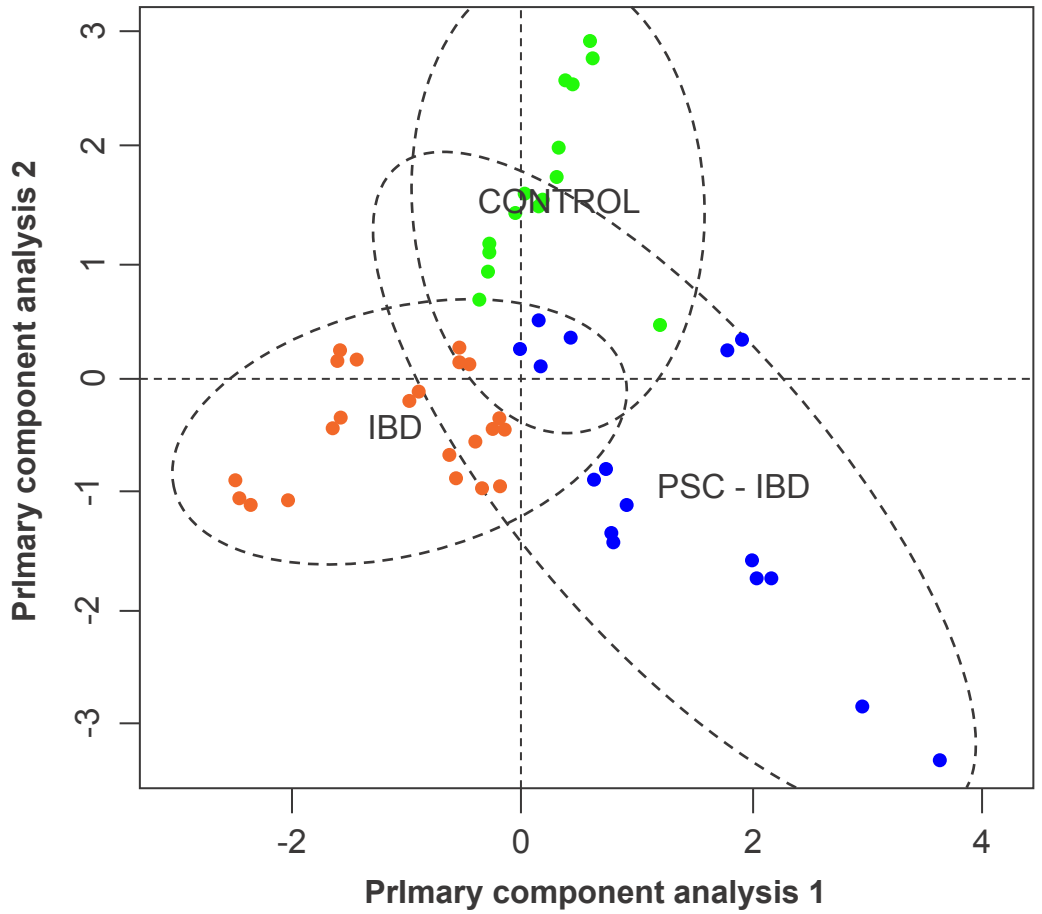
High risk of disease
e.g. multiple autoimmunity, AIRE deficiency, GATA-2

Low risk of disease

AIRE, autoimmune regulator.

The gut-adherent microbiota of PSC-IBD is distinct to that of IBD

Quraishi MN, Sergeant M, Kay G, Iqbal T, Chan J, Constantinidou C, Trivedi P, Ferguson J, Adams DH, Pallen M, Hirschfield GM

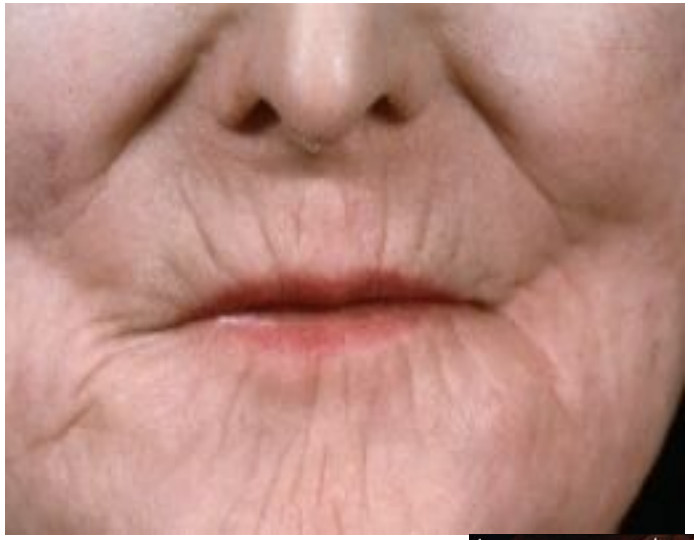


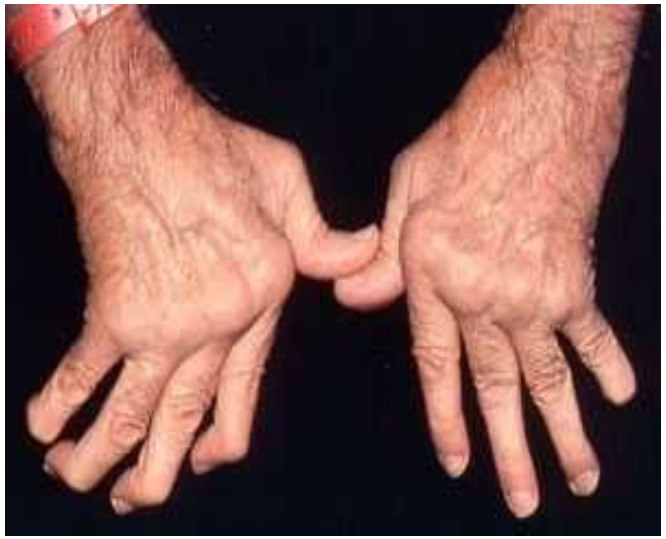
16 s rRNA-based analysis (Illumina MiSeq) of mucosa-associated bacteria in patients with PSC-IBD, PSC and healthy controls undergoing elective colonoscopy was performed. A principal component analysis is shown with visualisation of observed bacterial communities based on the presence and absence of operational taxonomic units identified in PSC-IBD (blue), IBD (orange) and healthy controls (green). Analysis by UPARSE (http://drive5.com/uparse/) and the 'Vegan' statistical computational package demonstrates significant difference between these disease groups (p=0.001).

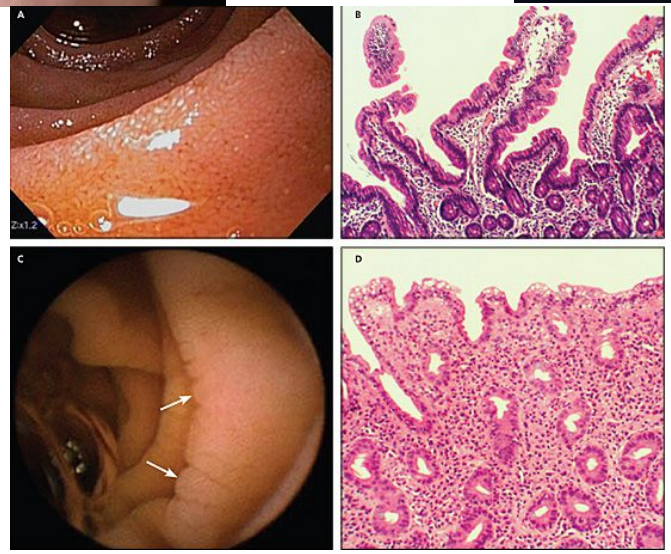
IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; rRNA, ribosomal ribonucleic acid.

Quraishi MN, et al. Gut 2017;66:386–8

Families share risk but the family tree is full of surprises

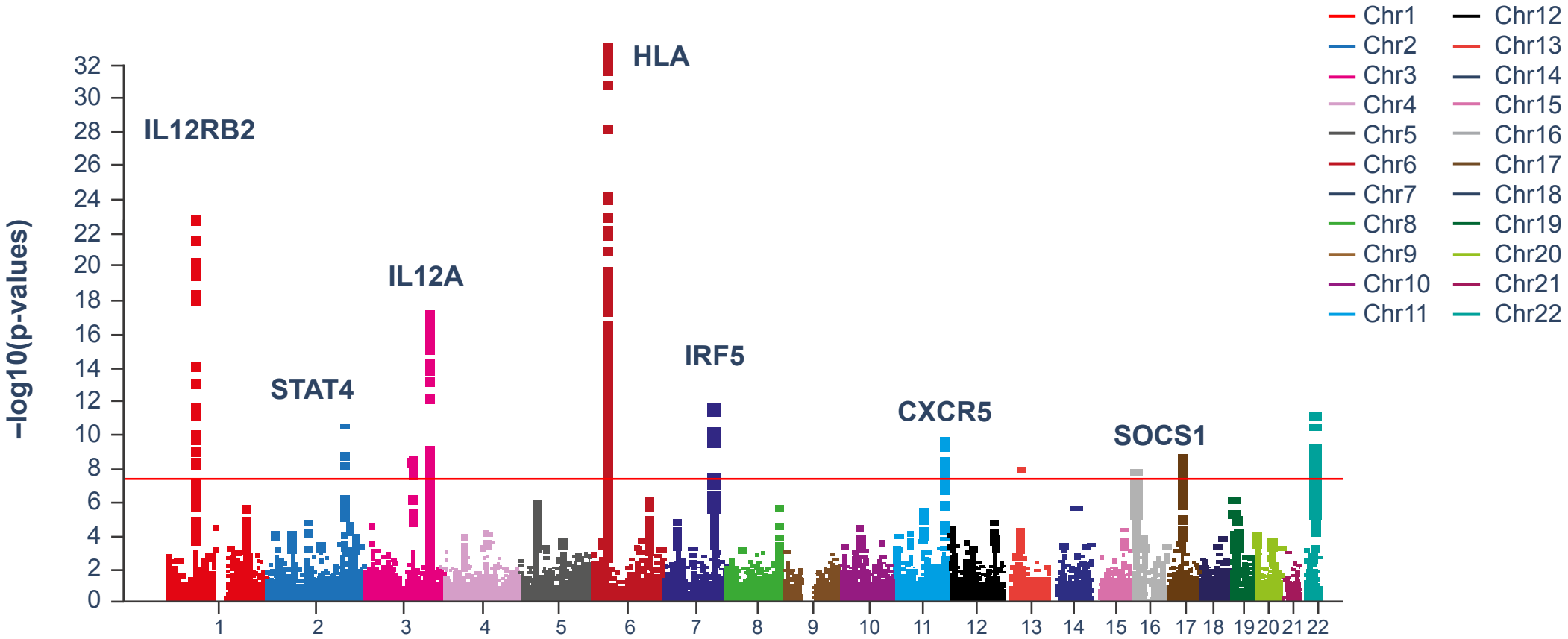






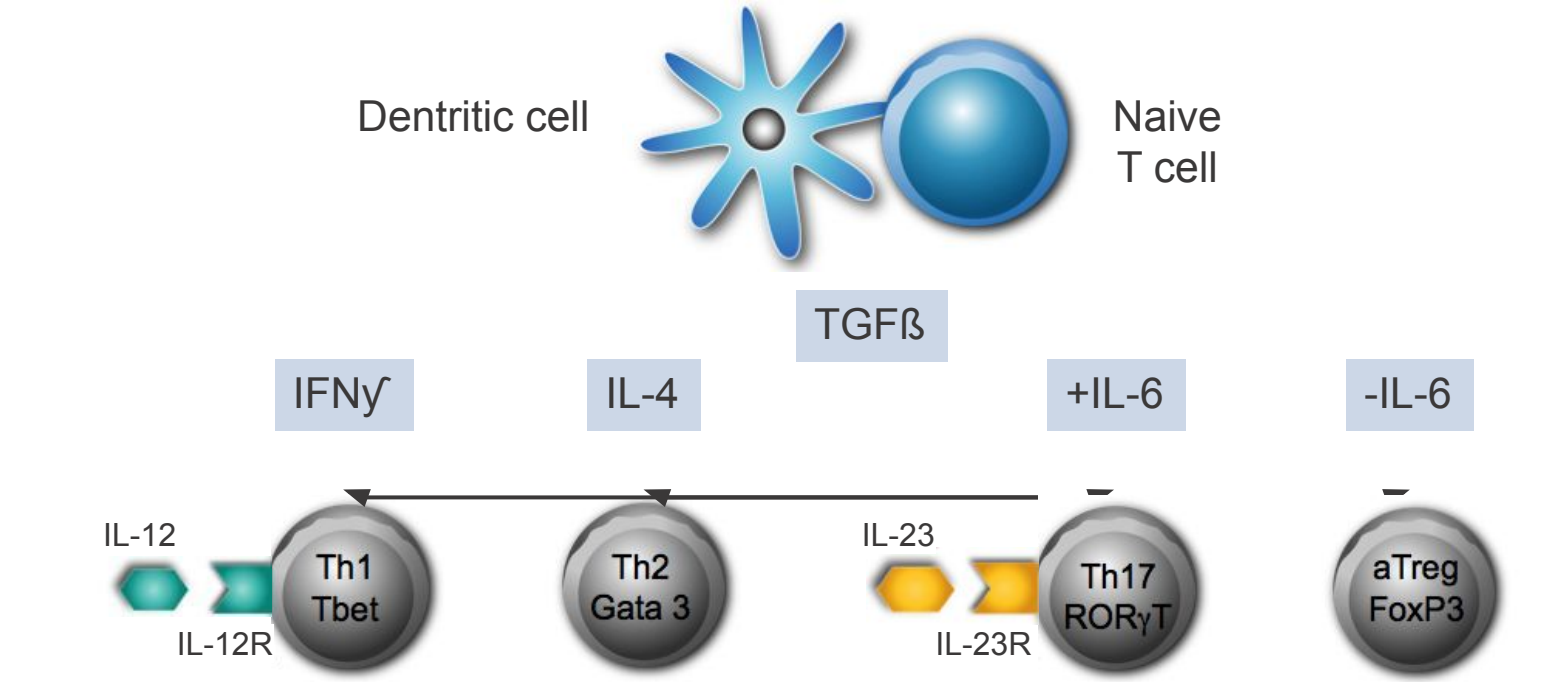
Images sourced from Google.

The immunoregulatory skyline is striking



Chr, chromosome; CXCR, C-X-C receptor; HLA, human leukocyte antigen; IL, interleukin; IRF, interferon regulatory factor; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription.
Juran BD, *et al*. *Hum Mol Genet* 2012;21:5209–21.

T cell subpopulations

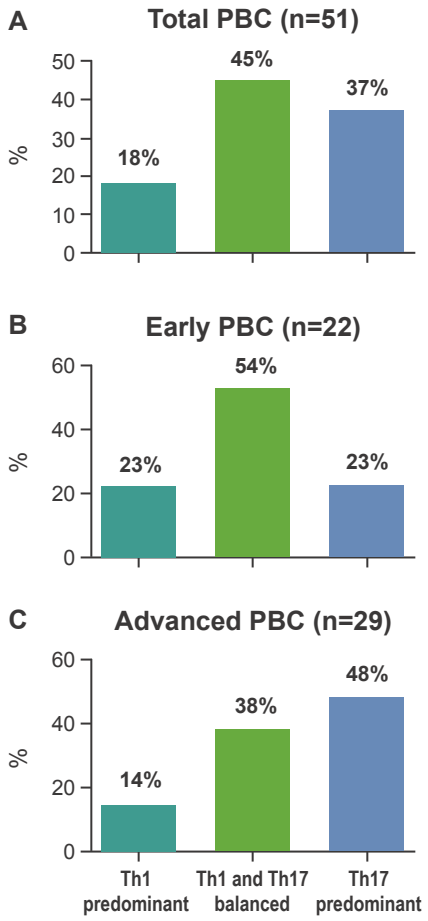


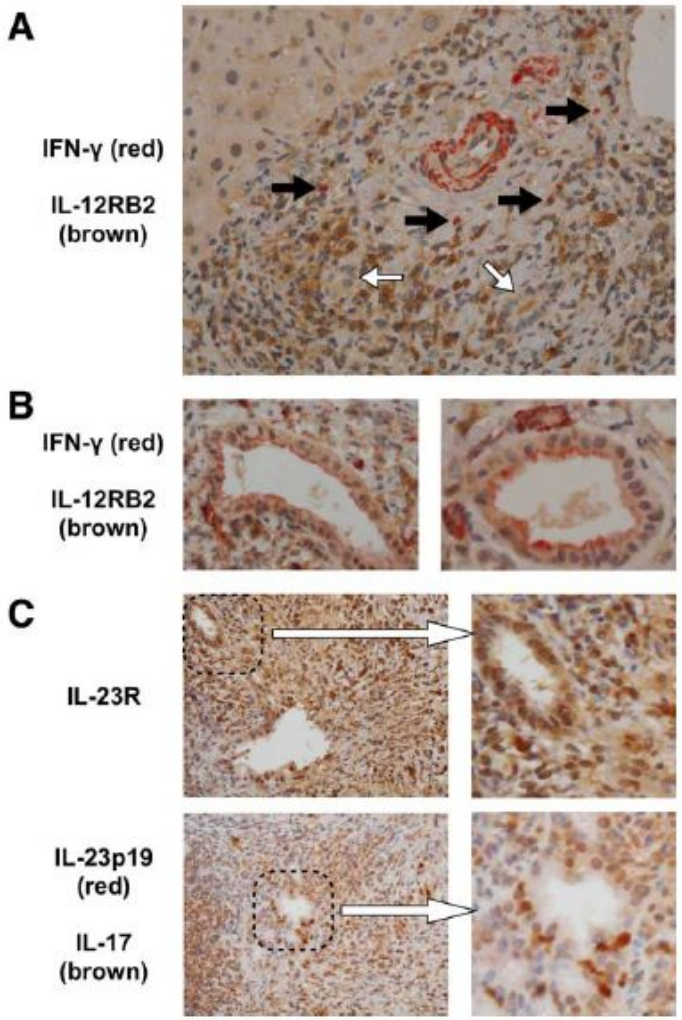
Protective role	Intracellular pathogens	Parasitic worms	Extracellular bacteria	Counter regulation
Harmful role	Systemic pathology	Allergy and asthma	Autoimmunity, inflammation, cancer	

IFN, interferon; IL, interleukin; TGF, transforming growth factor; Th, T helper cell.
Graphic adapted from Reiner SL. *Cell* 2007;129:33–6.

Significance of the IL-23/Th17 pathway in the perpetuation of IL-12/Th1-mediated immunopathology in PBC

The distribution of the Th1/Th17 ratio in (A) total PBC (n=51), (B) early PBC (n=22), and (C) advanced PBC (n=29). The intensity of Th1/Th17 staining in the majority of total and early PBC patients was Th1 and Th17 balanced. However, the intensity skewed from Th1 to Th17 predominantly in advanced PBC. The Th1/Th17 ratio was negatively correlated (Spearman rs=−0.2959) with disease stage in PBC ($p<0.05$).



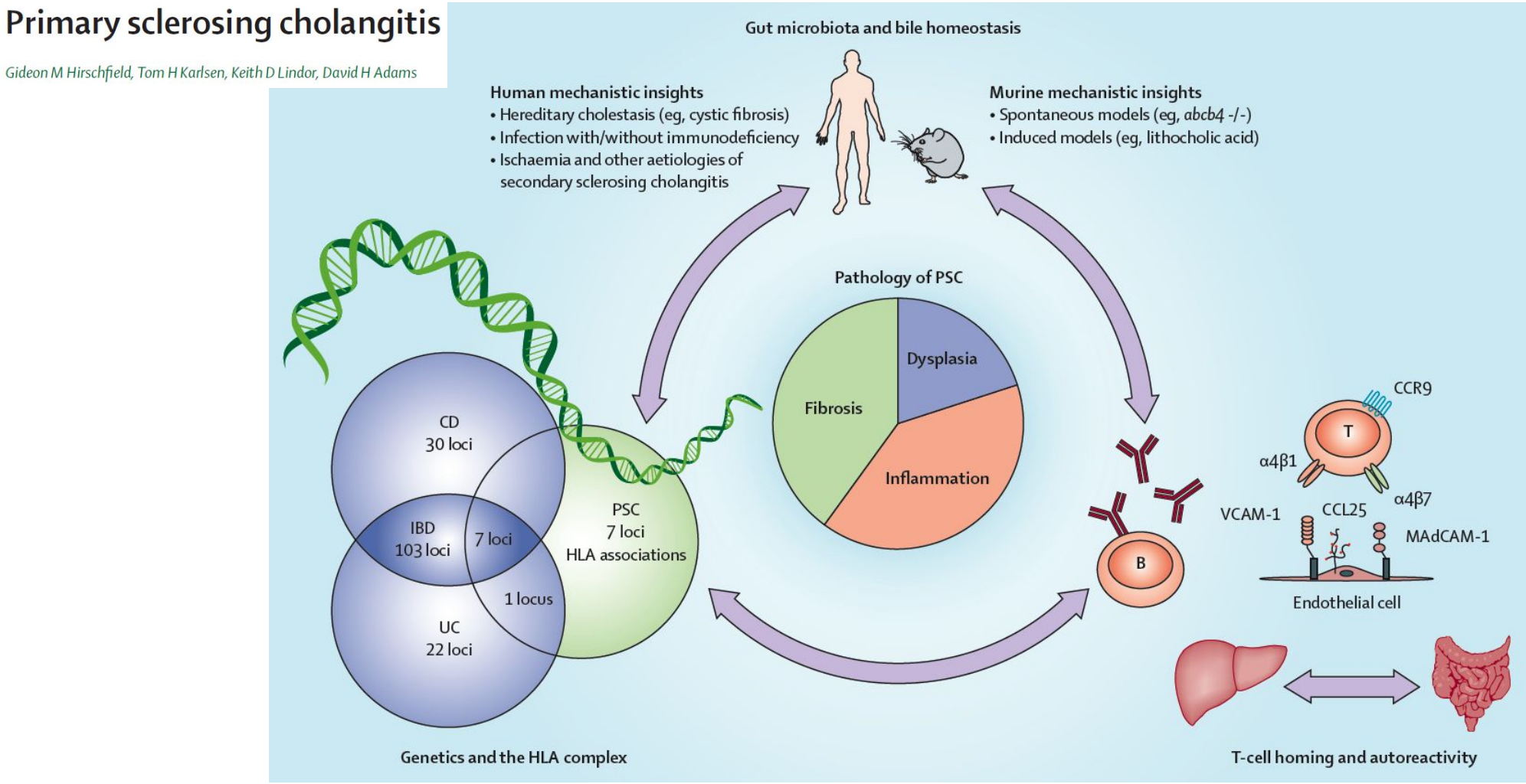


The expression of IL-12RB2 and the presence of IFN-γ-positive mononuclear cells (black arrows) around damaged bile ducts (white arrows) in PBC. (B) The expression of IFN-γ in the biliary lumen of degenerated biliary epithelial cells in PBC. (C) The expression of IL-23R and the infiltration of IL-17-positive cells around damaged biliary epithelial cells in PBC. Liver sections were stained with anti-IL-23R individually, as well as anti-IL-23p19 (red) combined with anti-IL-17 (brown) or IFN-γ (red) combined with IL-12RB2 (brown) concurrently. Representative staining images from patients with PBC (n=51) are shown.

IFN, interferon; IL, interleukin; PBC, primary biliary cholangitis; Th, T helper cell.

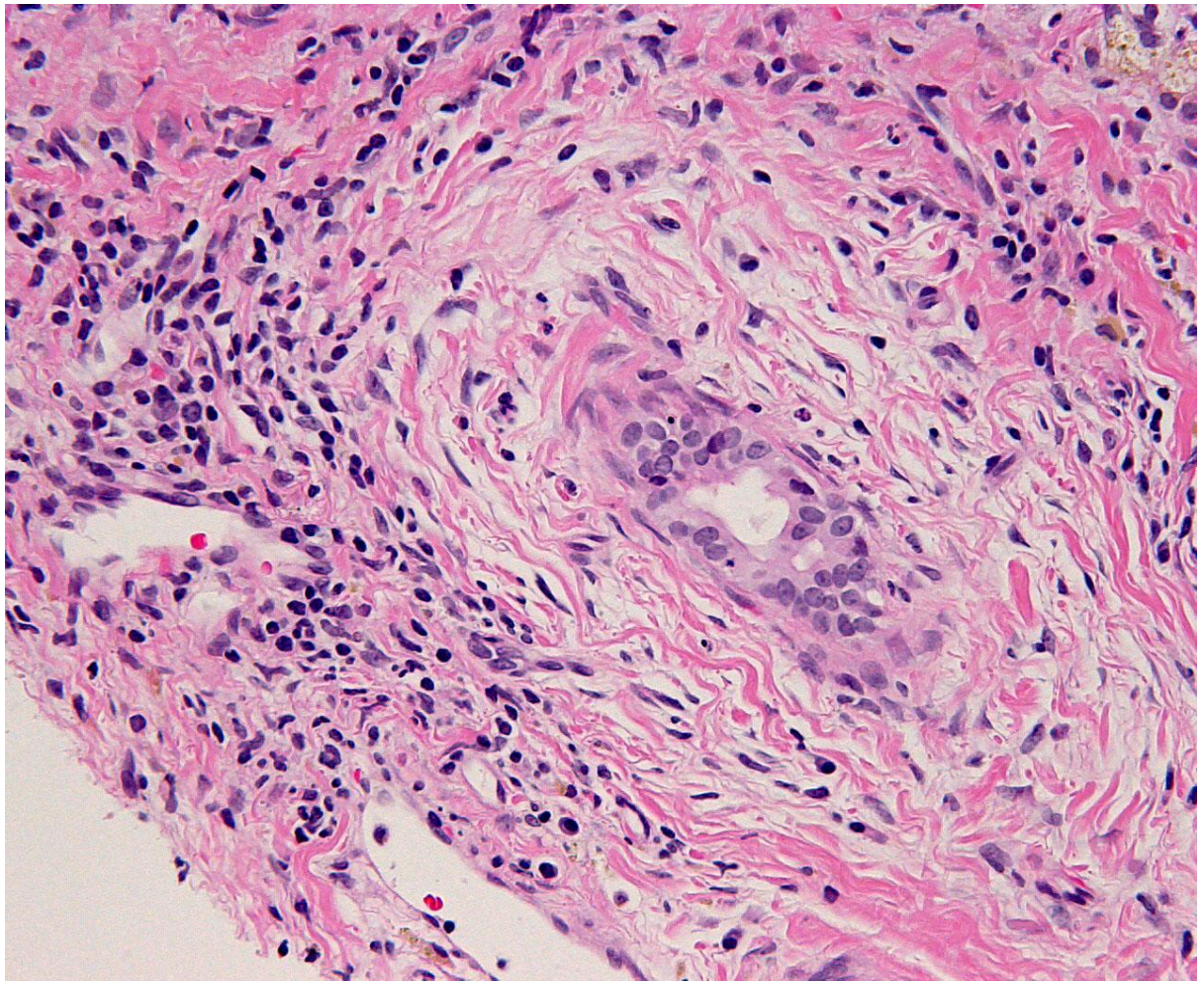
Yang C-Y, *et al. Hepatology* 2014;59:1944–53.

Unravelling disease mechanisms



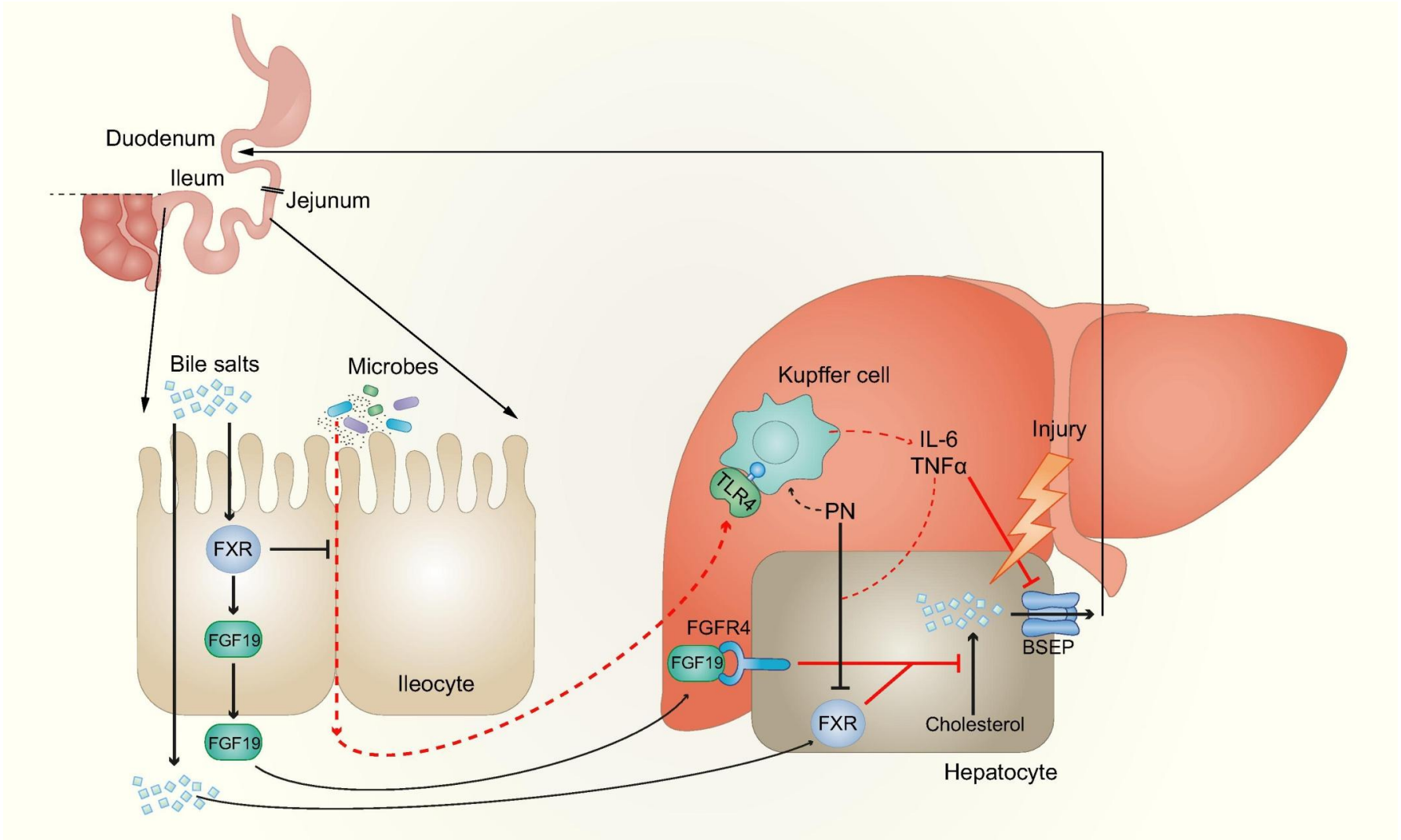
CCL, chemokine ligand; CCR, chemokine receptor; CD, Crohn's disease; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; PSC, primary sclerosing cholangitis; UC, ulcerative colitis; VCAM, vascular cell adhesion molecule.
Hirschfield GM, *et al. Lancet* 2013;382:1587–99.

Fibrotic end point



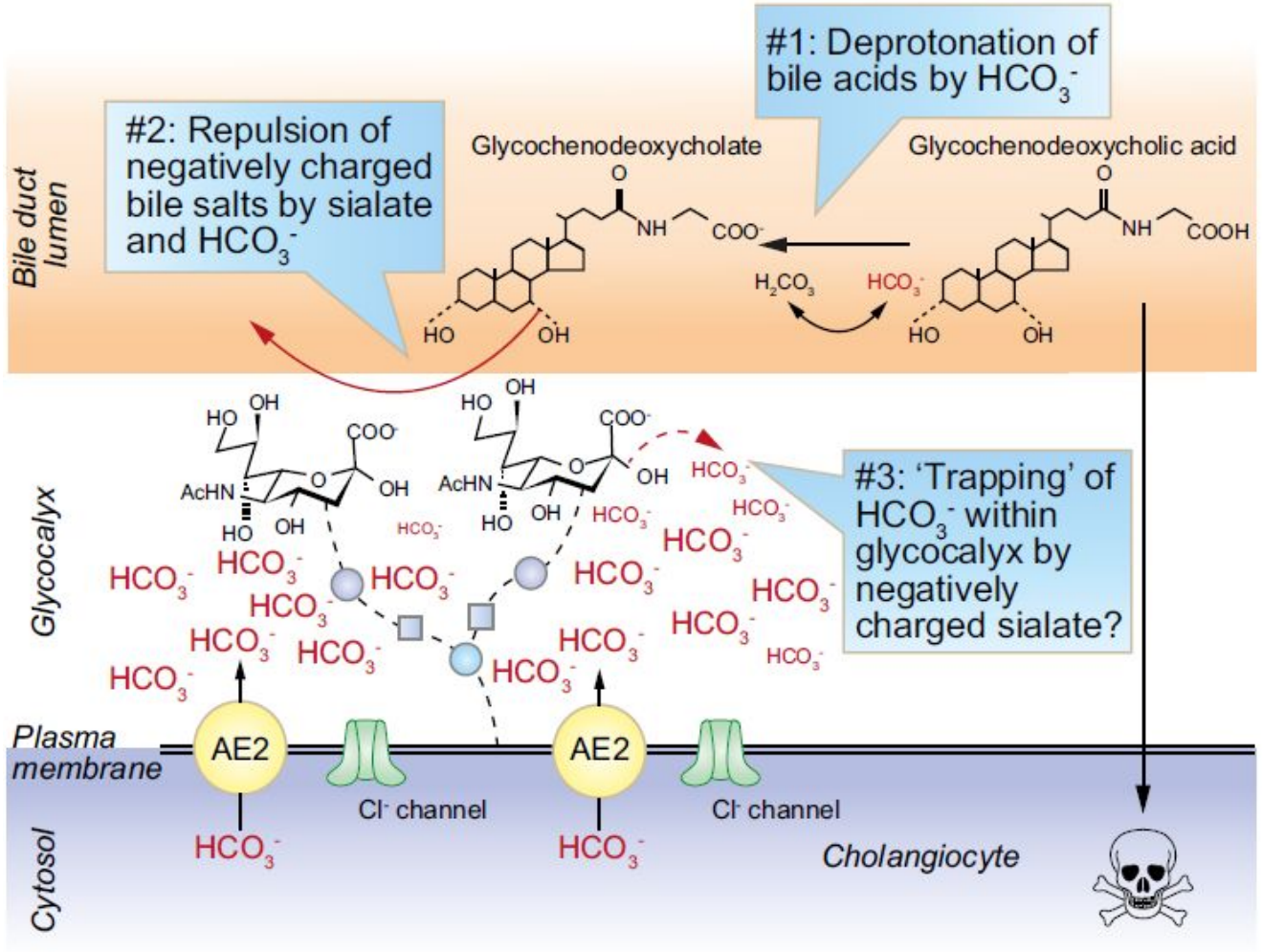
Chronic bile duct disease leading to fibrotic strictures and saccular dilatations of the intra- and extrahepatic bile ducts

Bile: GI/liver communicator



BSEP, bile salt export pump; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FXR, farnesoid X receptor; GI, gastrointestinal; IL, interleukin; PN, parenteral nutrition; TLR, toll-like receptor; TNF, tumour necrosis factor.
van Erpecum KJ, Schaap FG. *J Hepatol* 2015;62:1231–3.

The bile duct lumen is not inert



AE2, anion exchanger 2.
Beuers U, *et al*. *J Hepatol* 2015;62:S25–37.

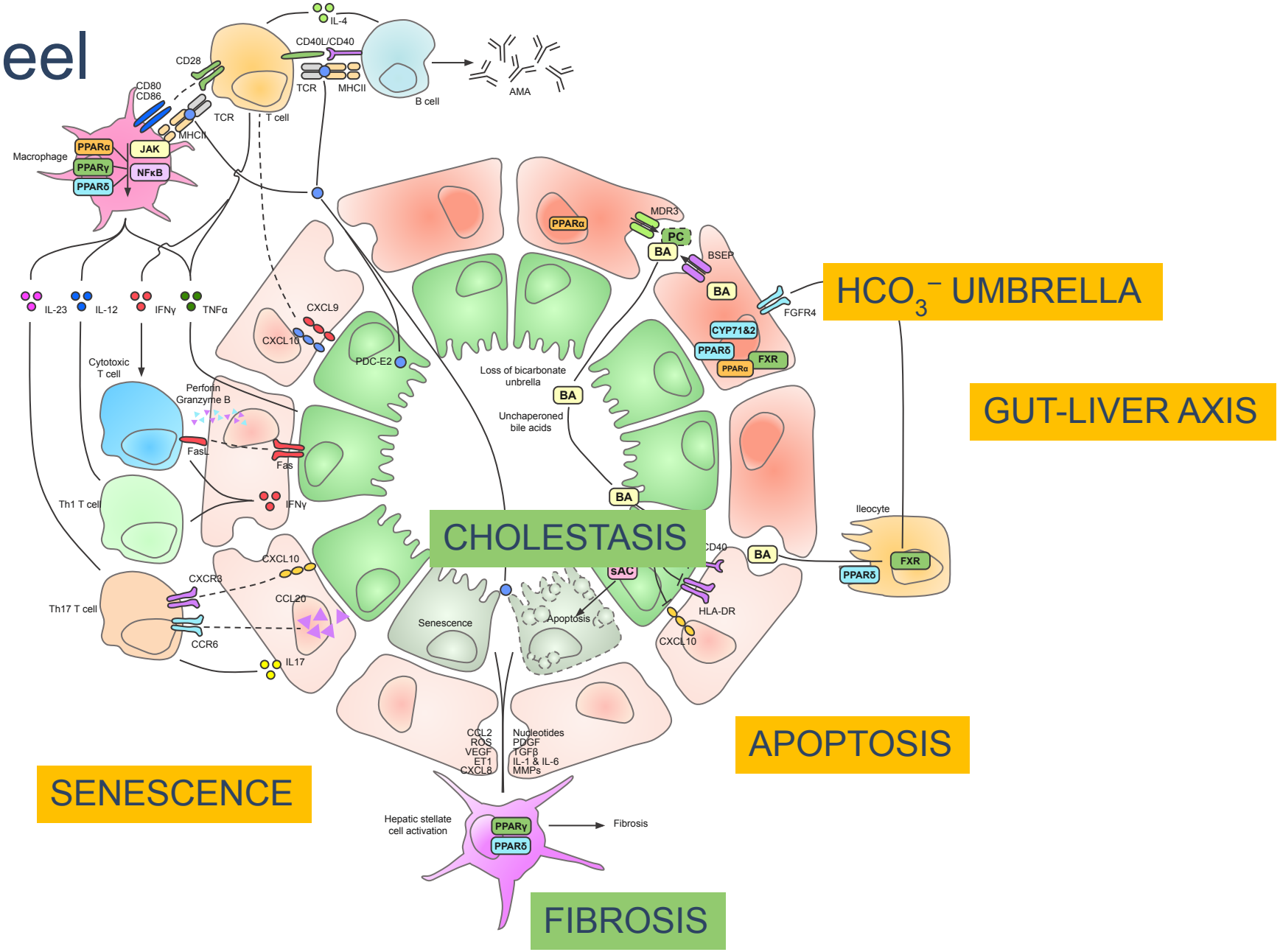
Note to Gideon: Please could you amend the question as you see fit and provide a selection of answers? It is possible to have more than one correct answer on the voting system so please let us know which are the correct answers

Placeholder for multiple choice voting question

Which of the following is/are the most relevant therapeutic target(s) for PBC?

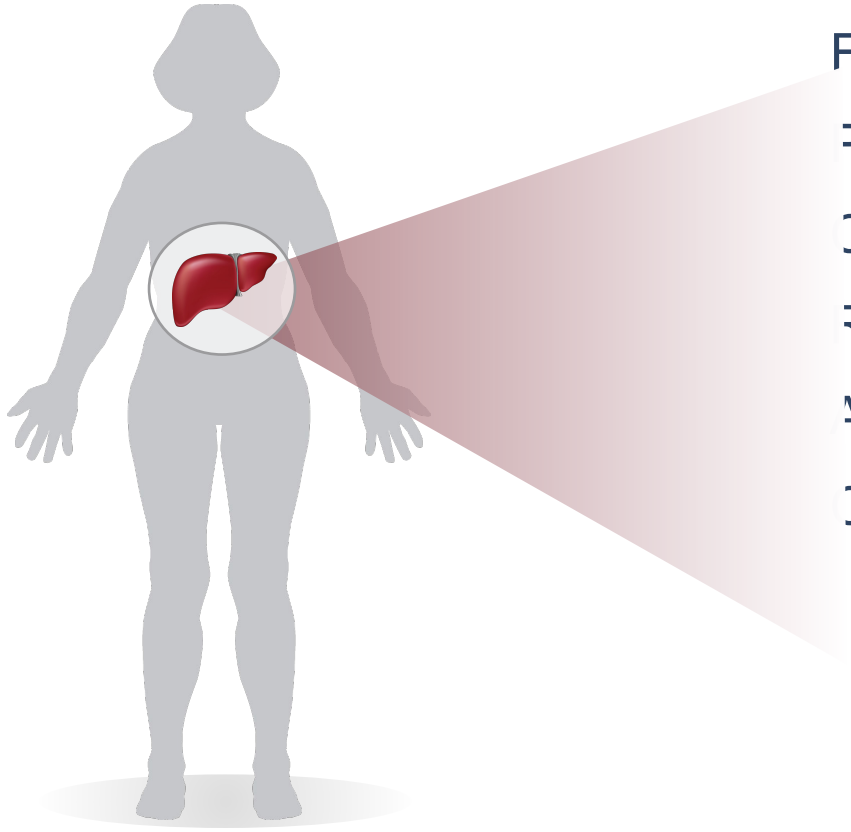
PBC, primary biliary cholangitis.

The PBC wheel



PBC, primary biliary cholangitis.

Beyond the liver

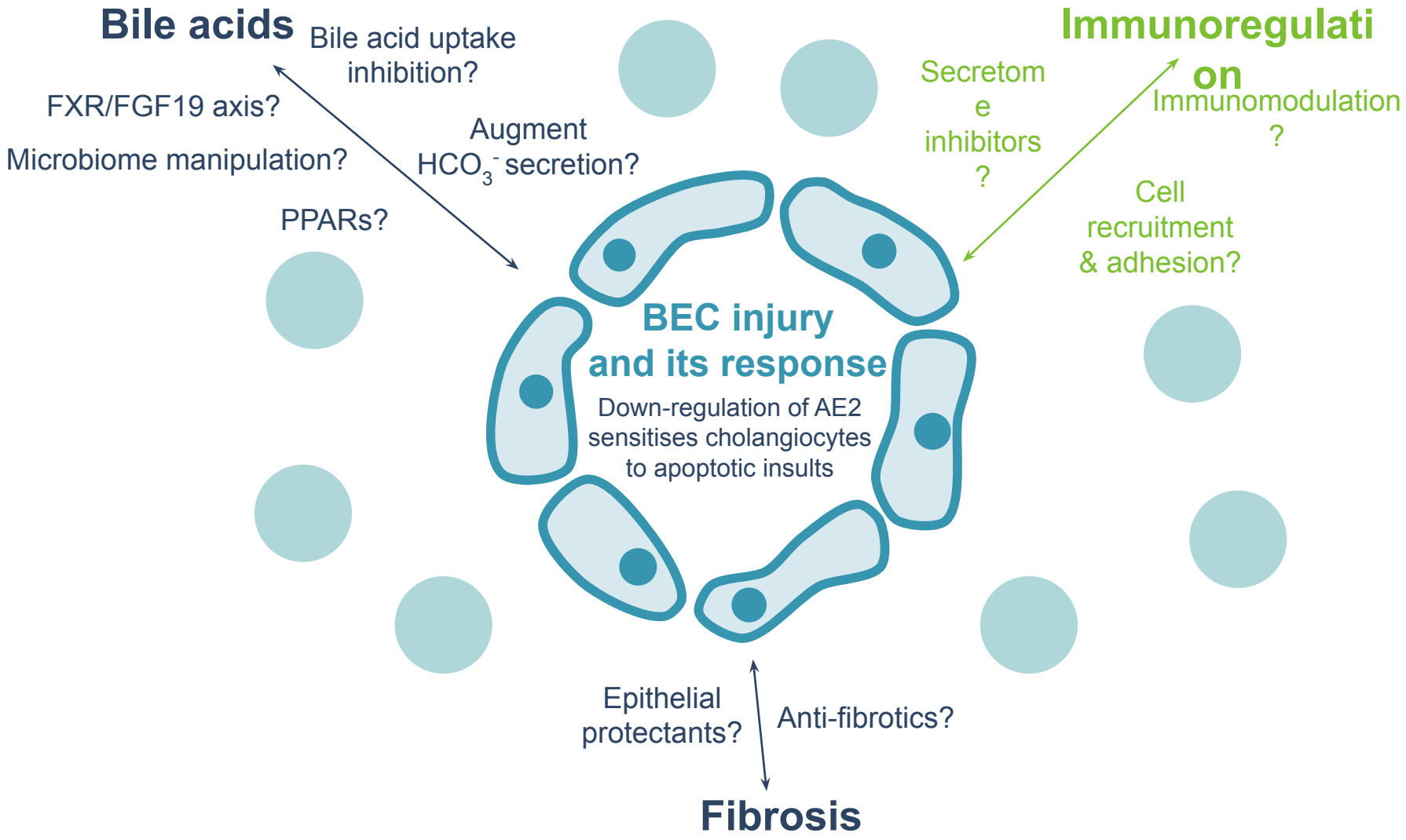


- Fatigue
- Pruritus
- Concurrent autoimmune diseases
- Reduced bone density
- Abdominal pain
- Complications of IBD/Pouch

Cholestatic liver diseases range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.

IBD, inflammatory bowel disease.
Based on original slide by Kris Kowdley.

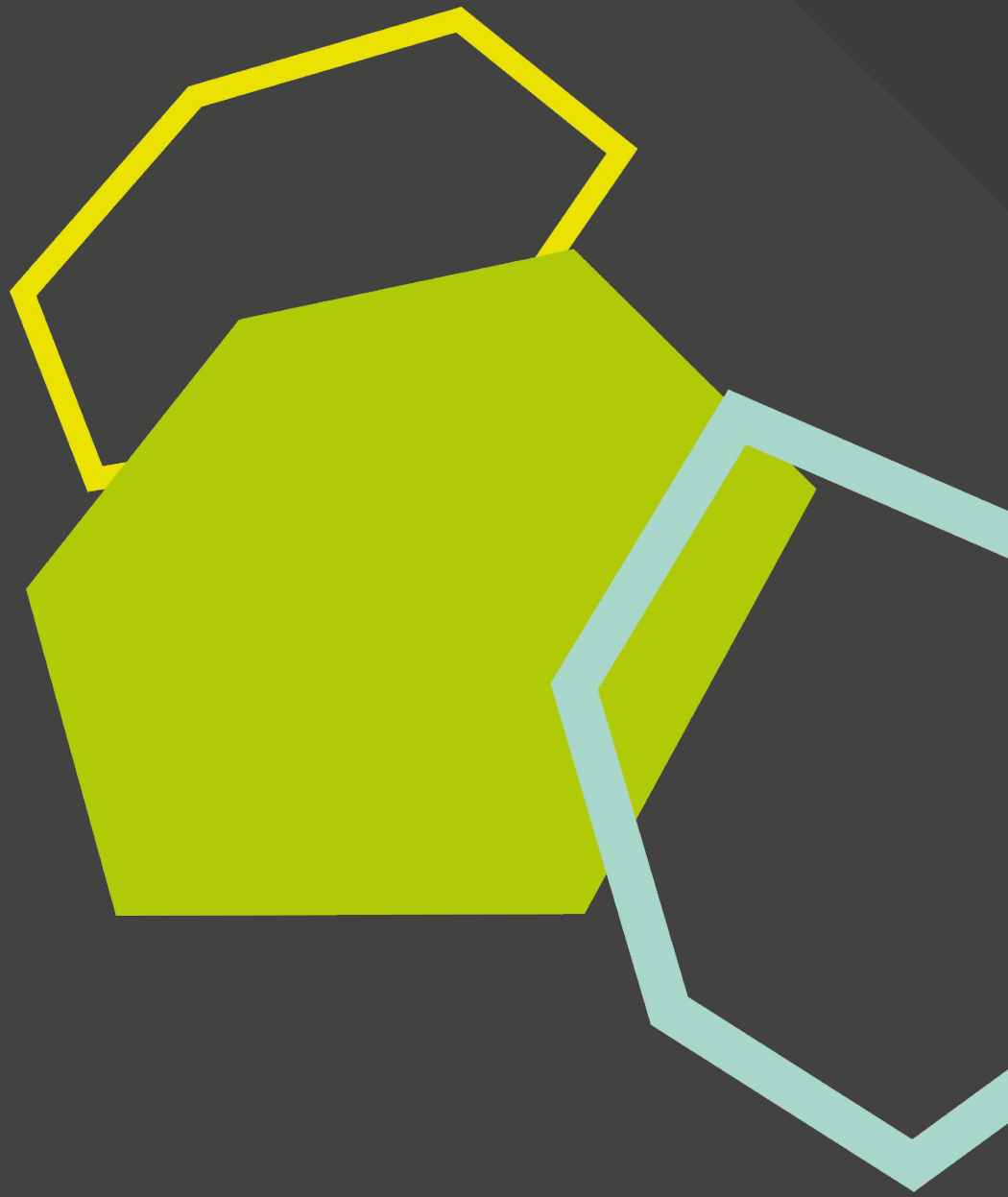
New therapeutic opportunities



AE2, anion exchanger 2; BEC, biliary epithelial cell; FGF, fibroblast growth factor; FXR, farnesoid X receptor; PPAR, peroxisome proliferator-activated receptor.

Changing perspectives

in cholestatic liver disease and PBC



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