10th International Congress
OF INTERNAL MEDICINE
March 22-24, 2018 Royal Olympic Hotel Athens - Greece

IgG4-related Disease:

An underrecognized entity

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MEDICAL UNIVERSITY OF VIENNA

Die menschliche Größe

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An *increasingly recognized* entity

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Disclosures

- Speakers bureau
  - Falk Foundation, Gilead, MSD, Roche
- Advisor
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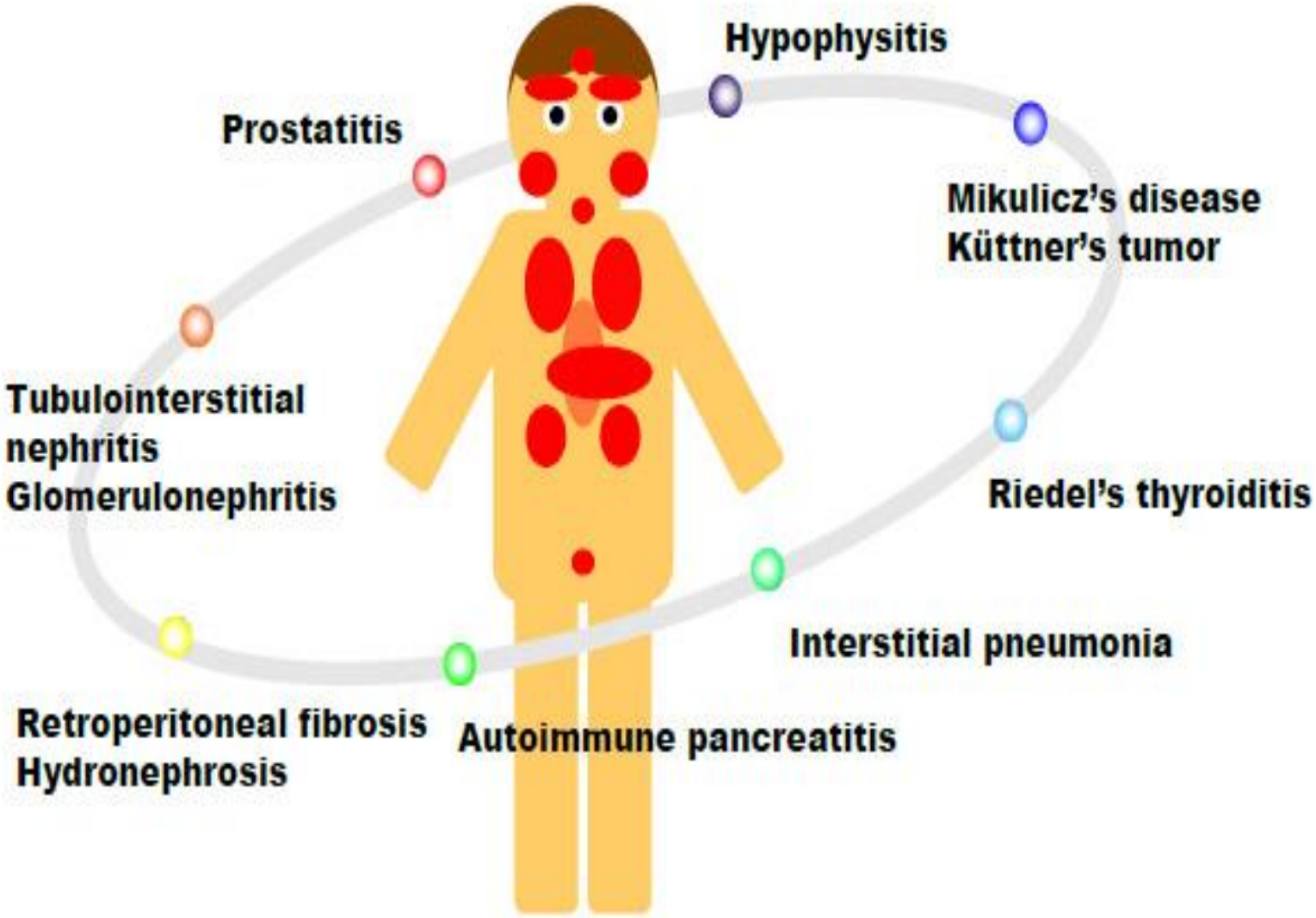
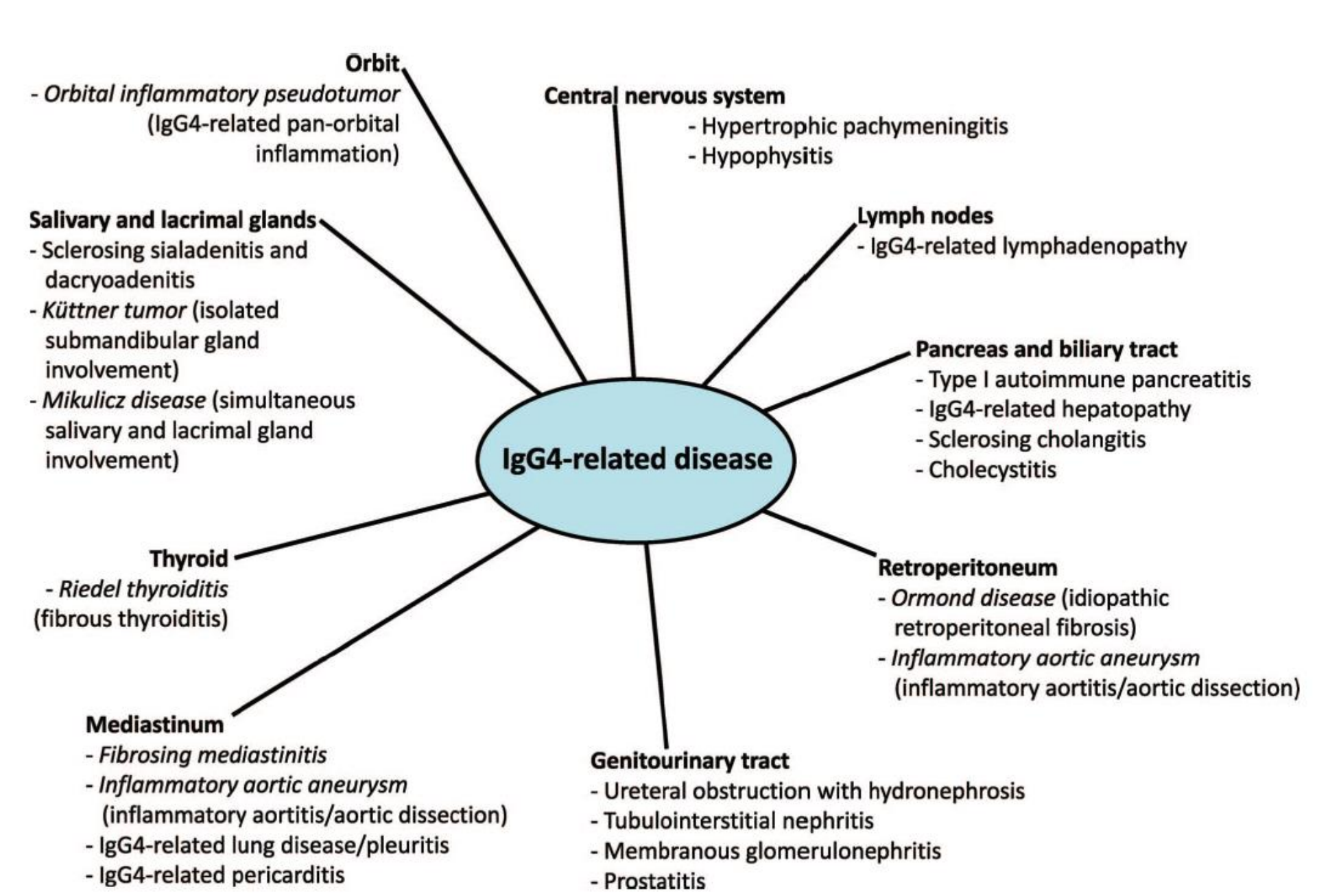
- Travel grants
  - Falk Foundation, Gilead, Roche
- Unrestricted research grants
  - Albireo, Falk Pharma, Gilead, Intercept, MSD, Takeda
- Property rights
  - The Medical University of Graz has filed patents on the medical use of *nor*UDCA and I am listed as co-inventor

IgG4-related Disease (IgG4-RD)



Multisystemic disease - frequently misdiagnosed (chameleon)

De Buy Wenninger … Beuers, *Endoscopy* 2012: 44: 66-73



Weindorf & Fredriksen, *Arch Pathol Lab Med* 2017; 141: 1476-83

IgG4-related disease of the bile ducts and pancreas

Background

1961	Sarles et al.	**Chronic inflammatory sclerosis of pancreas**	Am J Dig Dis 6:688
1963	Bartholomew et al.	**Sclerosing cholangitis, Riedel ‘s struma, fibrous retroperitonitis**	N Engl J Med 269:8
1984	Montefusco et al.	**Sclerosing cholangitis, chronic pancreatitis, sialadenitis: a symptom complex?**	Am J Surg 147:822
1995	Yoshida et al.	**Autoimmune pancreatitis (AIP)**	Dig Dis Sci 40:1561
1999	Erkelens et al.	**Sclerosing pancreato-cholangitis responsive to steroid therapy**	Lancet 354:43
2001	Hamano et al.	**IgG4 as marker of AIP**	N Engl J Med 344:732
2003	Kamisawa et al.	**IgG4-related systemic disease**	J Gastroenterol 38:982
2007	Björnsson et al.	**“IgG4-associated cholangitis“ (IAC)**	Hepatology 45:1547

amc

Slide Courtesy U. Beuers, Amsterdam

Panel 1: Conditions once regarded as individual disorders now recognised to be part of IgG4-related disease

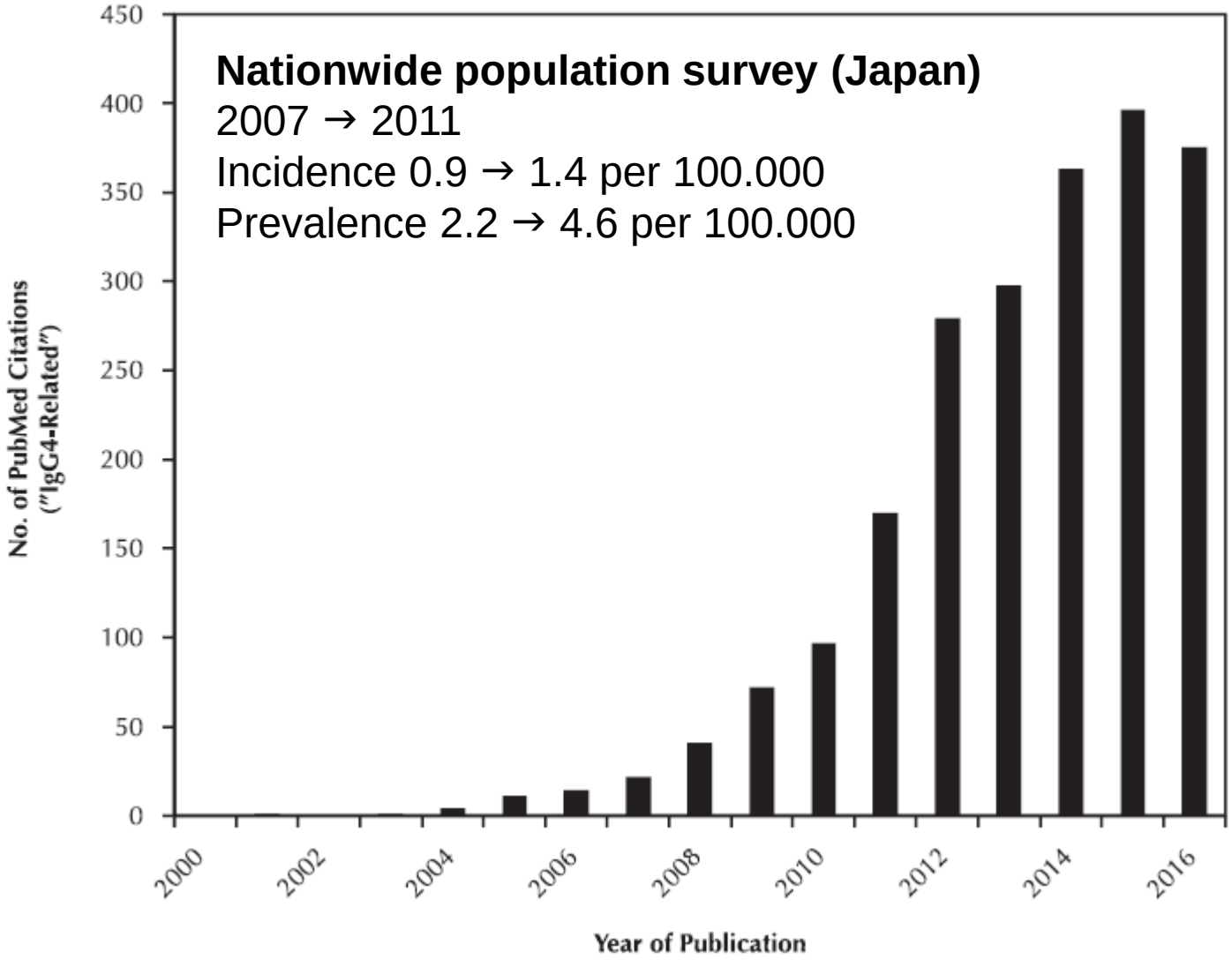
- Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
- Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
- Fibrosing mediastinitis
- Hypertrophic pachymeningitis
- Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
- Küttner's tumour (affecting the submandibular glands)
- Mikulicz's disease (affecting the salivary and lacrimal glands)
- Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
- Periaortitis and periarteritis
- Inflammatory aortic aneurysm
- Retroperitoneal fibrosis (Ormond's disease)
- Riedel's thyroiditis
- Sclerosing mesenteritis

IgG4-related disease

Lancet 2015; 385: 1460–71

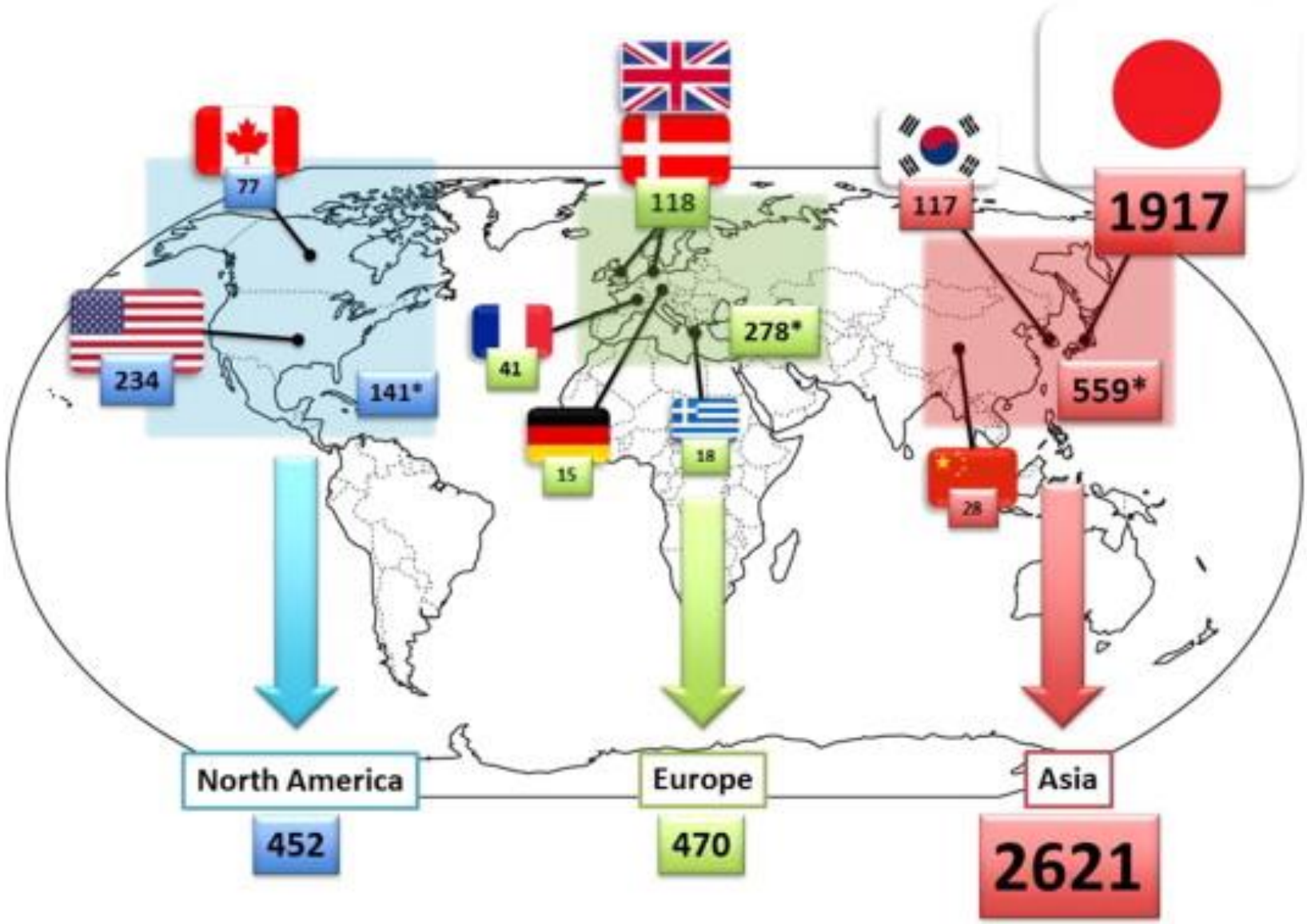
Terumi Kamisawa, Yoh Zen, Shiv Pillai, John H Stone

IgG4-related Disease - Pubmed



Weindorf & Fredriksen, *Arch Pathol Lab Med* 2017; 141: 1476-83

IgG4-related Disease - Worldwide



Slide Courtesy B. Eksteen, Alberta

IgG4-related Disease (IgG4-RD)

Abdominal and pelvic IRD localisation	Extra-abdominal IRD localisation
Bile ducts (IAC), gallbladder and liver	Hypophysis
Pancreas (AIP)	Eye, retro-orbital tumor
Stomach, intestine, ileal pouch	**Salivary** and lacrimal **glands**
Retroperitoneum	Thyroid gland
Kidney	Lungs
Pseudotumor	Lymphatic system (lung hilus !)
Prostate Testis	Vascular system (aortitis)

Stone et al. *N Engl J Med* 2012;366:539

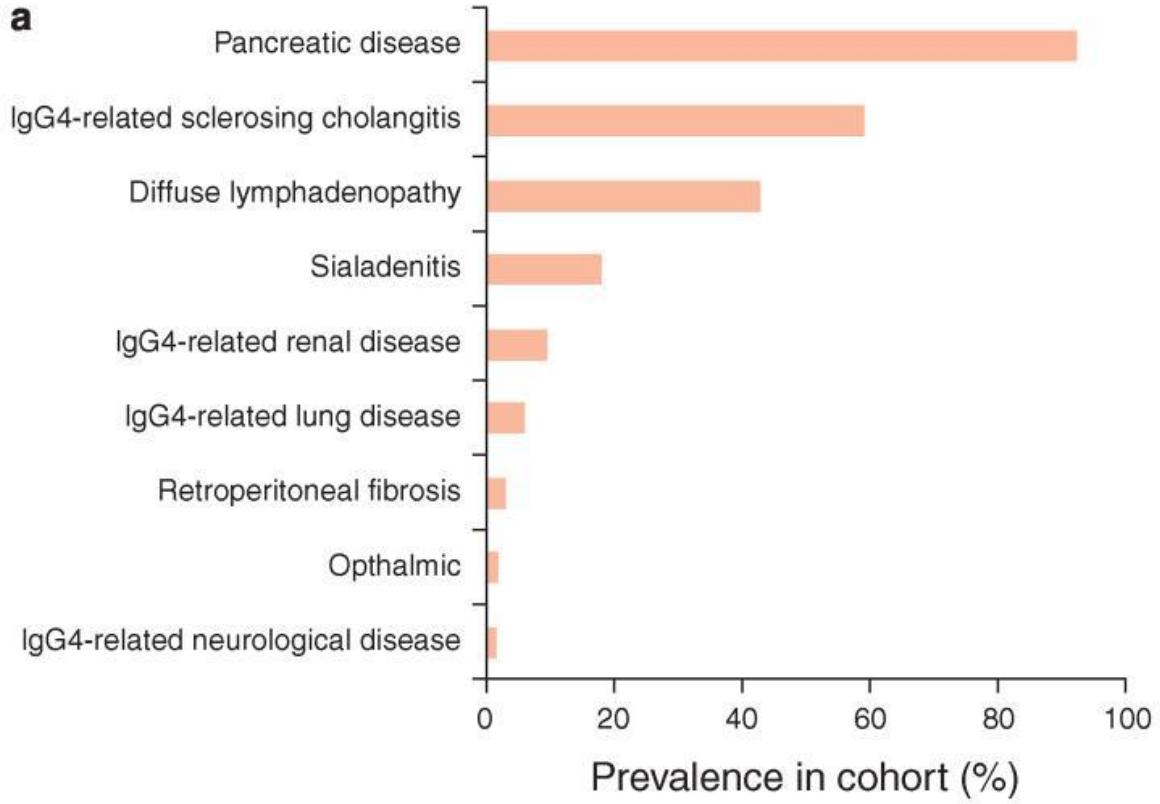
Hubers et al. *Clin Rev Allerg Immuno*l 2015;48:198

IgG4-related Disease (UK Experience)

105 cases, prospective 10 yr follow-up, Oxford
74% jaundice
37% abdominal pain
3% pancreatitis
21% hepato-biliary surgery
59% PSC-biliary changes

Median 3 months FU mortality 10%
97% initial steroid response
but 50% relapse rate
Malignancy 11% (any cancer)

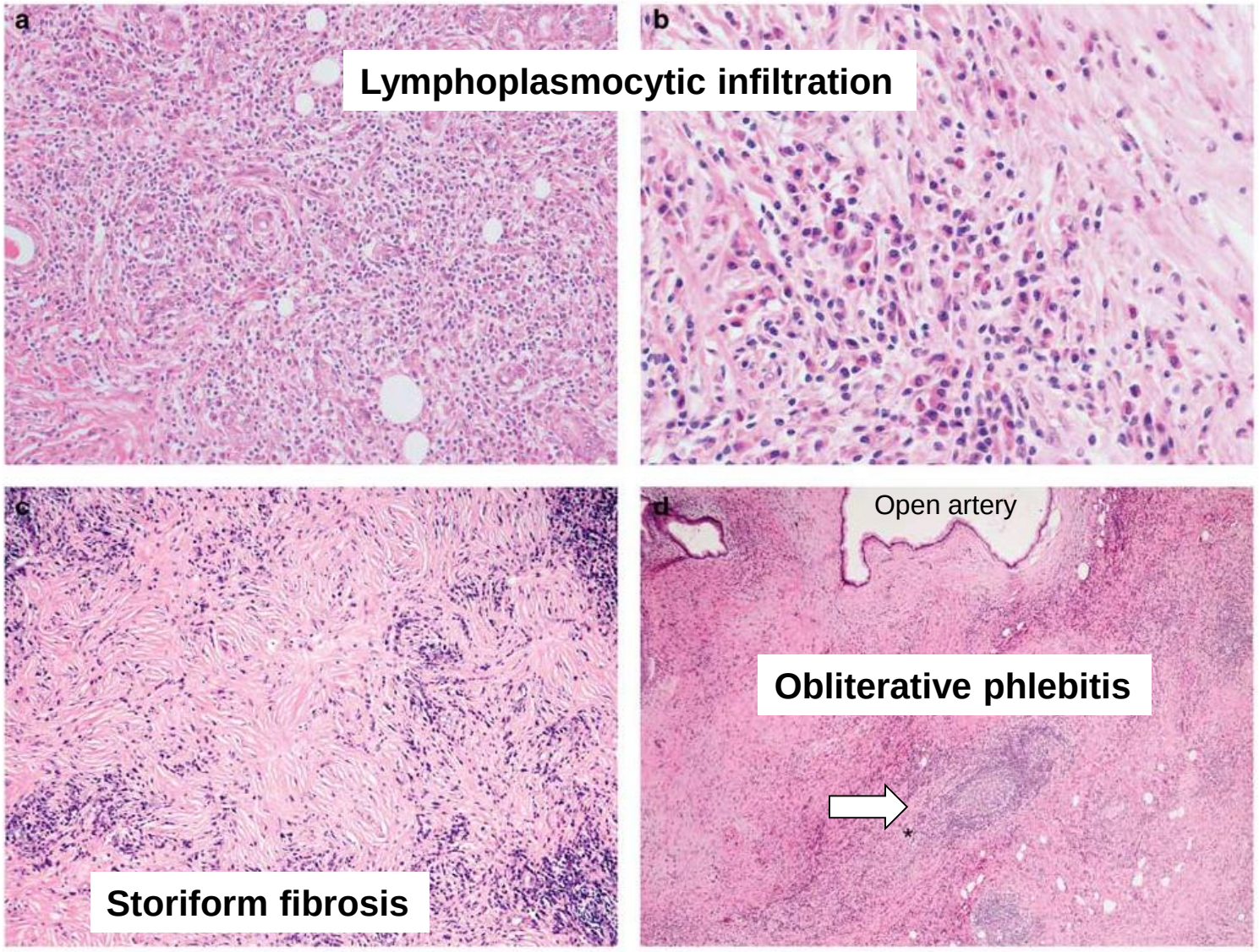
10% of PSC cases are IgG4 disease



Hugget et al., *Am J Gastroenterol* 2014: 109: 1675-1683

Consensus statement on the pathology of IgG4-related disease

Modern Pathology (2012) 25, 1181–1192



Deshpande et al., *Modern Pathology* 2012; 25: 1181-92

Consensus statement on the pathology of IgG4-related disease

MODERN PATHOLOGY (2012) 25, 1181–1192

Characteristic histological features
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform in character
3. Obliterative phlebitis

Cases with ≥ 2 pathology features

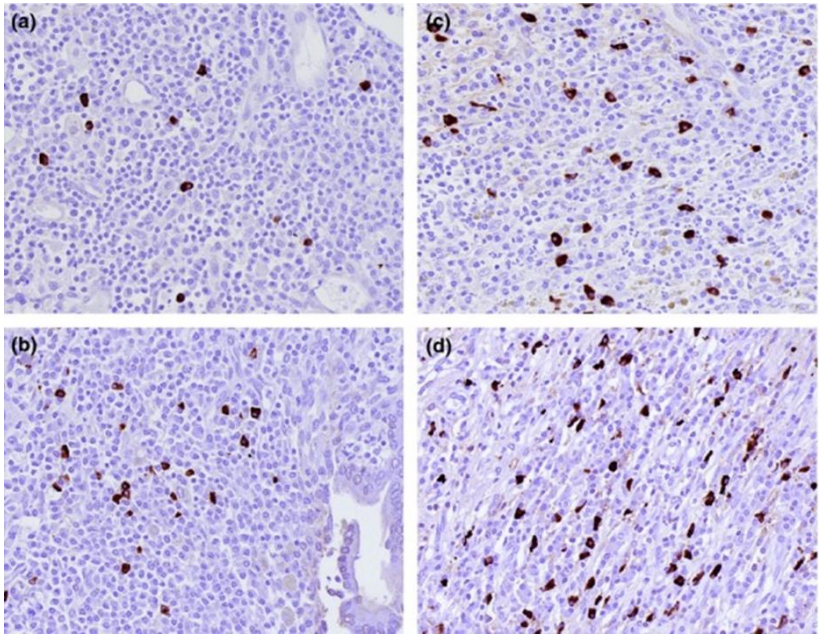
Cases with 1 pathology feature

	Numbers of IgG4+ plasma cells (/hpf)		Ref
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	6
Pancreas (surgical specimen)	>50	>50	30,32
Pancreas (biopsy)	>10	>10	56,57
Bile duct (surgical specimen)	>50	>50	49
Bile duct (biopsy)	>10	>10	58,59
Liver (surgical specimen)	>50	>50	49
Liver (biopsy)	>10	>10	12,60
Kidney (surgical specimen)	>30	>30	15
Kidney (biopsy)	>10	>10	61
Aorta	>50	>50	16,51,52
Retroperitoneum	>30	>30	8
Skin	>200	>200	62,63

IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD

:al features of IgG4-RD



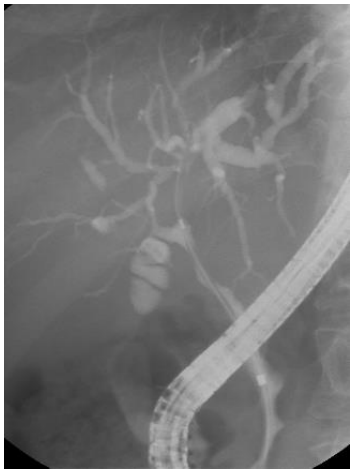
IgG4+ plasma cells

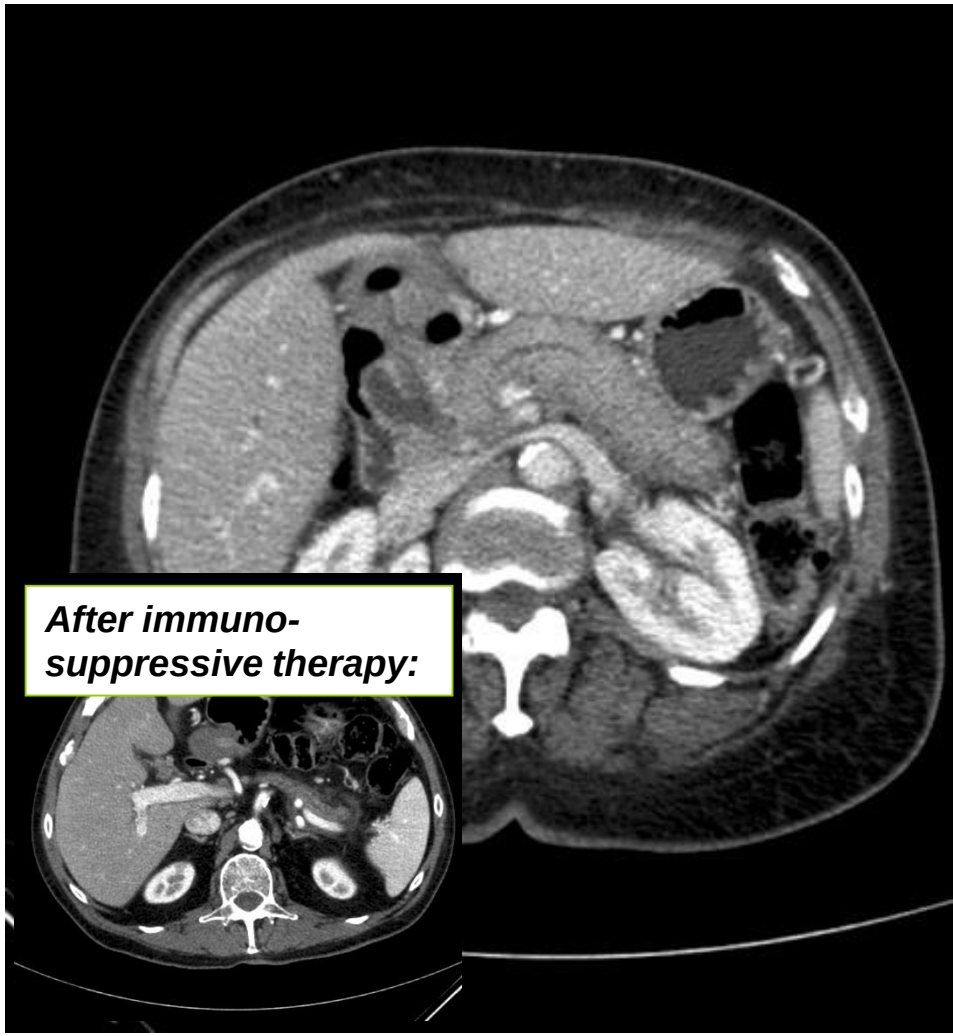
Deshpande et al., *Modern Pathology* 2012; 25: 1181-92

IgG4-related disease (IgG4-RD)

The typical patient in Gastroenterology & Hepatology

- Male (>80%)
- Middle aged / elderly (> 50 yrs)
- Localized organ swelling / tumor
- Elevated serum / tissue IgG4
- Other organ manifestations of IgG4-related disease (IRD)





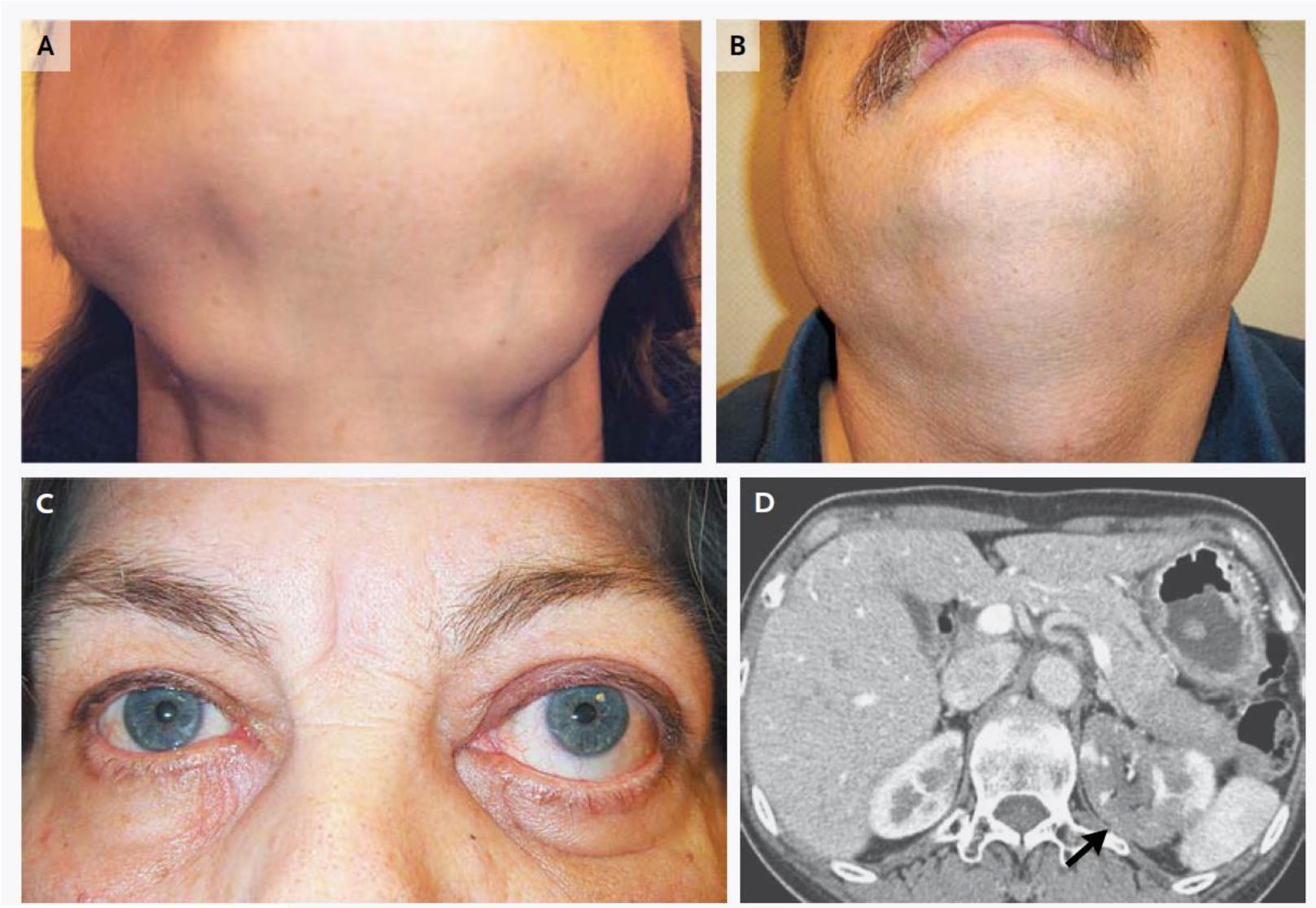
71 yrs, m; IgG4 11.9 g/L (n < 1.4)

De Buy Wenninger et al., Endoscopy 2012: 44: 66-73

Slide Courtesy U. Beuers, Amsterdam

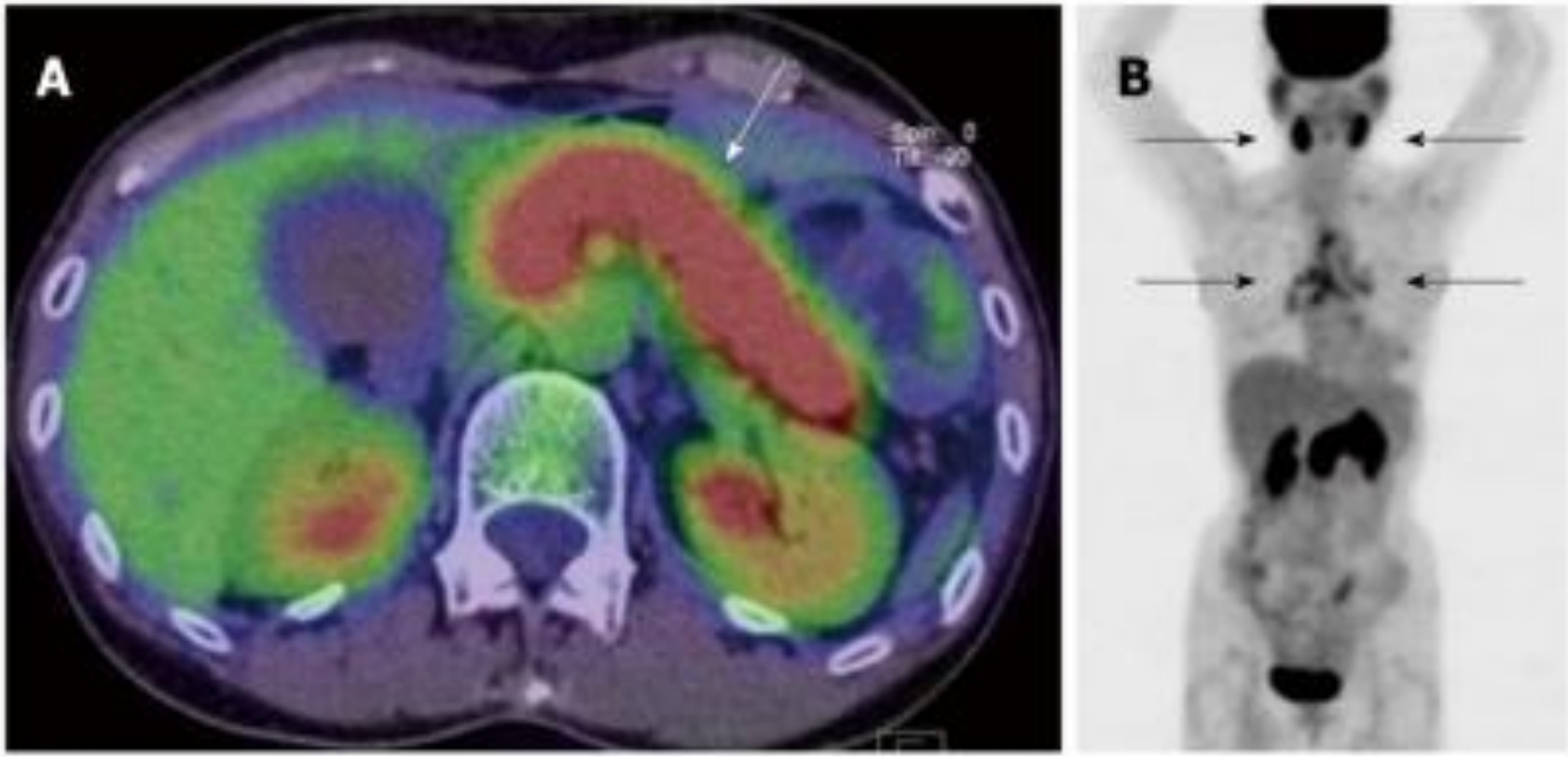
IgG4-related disease (IgG4-RD)

Clinical and radiologial features in a typical patient



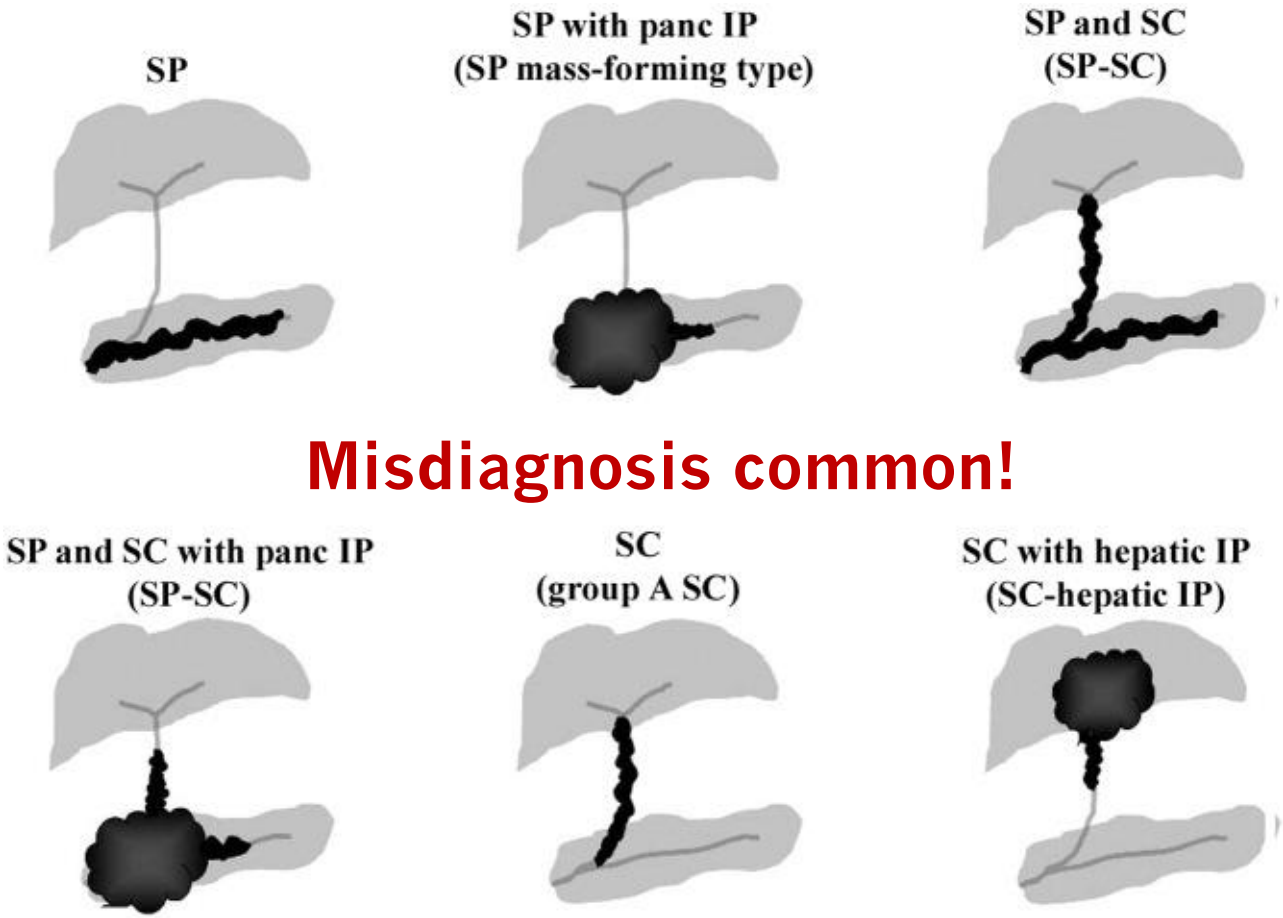
Stone et al., *New Engl J Med* 2012; 366: 539-51

Spectrum of IgG4 organ involvement on FDG-PET/CT imaging



World J Clin Oncol. 2011; 2(5): 229–236

IgG4-associated cholangitis & pancreatitis



Björnsson et al., *Hepatology* 2007; 45: 1547

Diagnostic HISORt criteria for IgG4-RD

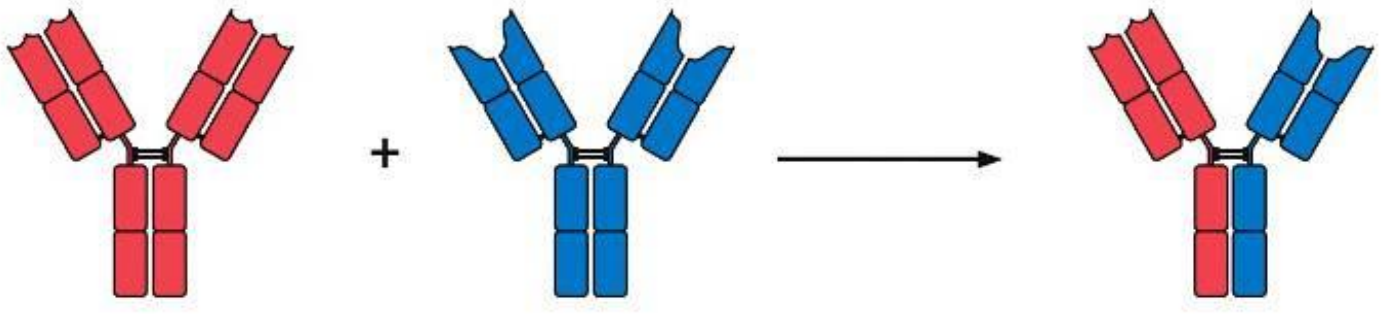
Category	Criteria
Histology	- Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis - Lymphoplasmacytic infiltrate with > 10 IgG4+ plasma cells/HPF
Pancreatic **I**maging	Typical: diffuse gland enlargement; diffuse attenuated pancreatic duct. Others: focal mass/stricture; atrophy; calcification; pancreatitis
Serology	Elevated serum IgG4
Other organs	Biliary strictures; salivary/lacrimal gland enlarged; mediastinal lymphadenopathy; retroperitoneal fibrosis; lung disease; tubulointerstitial nephritis
Response to Steroids	Resolution/marked improvement of pancreatic/extrapancreatic manifestation

Chari ST, et al. Clin Gastro Hepatol, 2006

Slide Courtesy R. Chapman, Oxford

Role of IgG4 in health and disease

- Important diagnostic marker for IgG4-RD (with pitfalls!)
- Smallest fraction of total IgG in serum
- ‘Regulatory’ antibody, unable to bind C1q, low Fc affinity
- Upregulated in chronic immune stimulation (e.g., allergies)
- Can exchange Fab arm



Slide Courtesy U. Beuers, Amsterdam

van der Neut Kolfschoten et al., *Science* 2007; 317: 1554

Role of IgG4 in health and disease

Allergies/hypersensitivities

Advantageous suppression
Beekeepers
Animal laboratory workers
Allergen-specific immunotherapy

Malignancies and Parasitic infections

Disadvantageous suppression
Melanoma and cholangiocarcinoma
Helminthic infections

Autoimmune/immune-mediated diseases

Pathogenic
Pemphigus vulgaris and foliaceus
MuSK-myasthenia gravis

Slide Courtesy U. Beuers, Amsterdam

Trampert, Hubers, van de Graaf, Beuers. BBA 2018; 1864:1401-1409

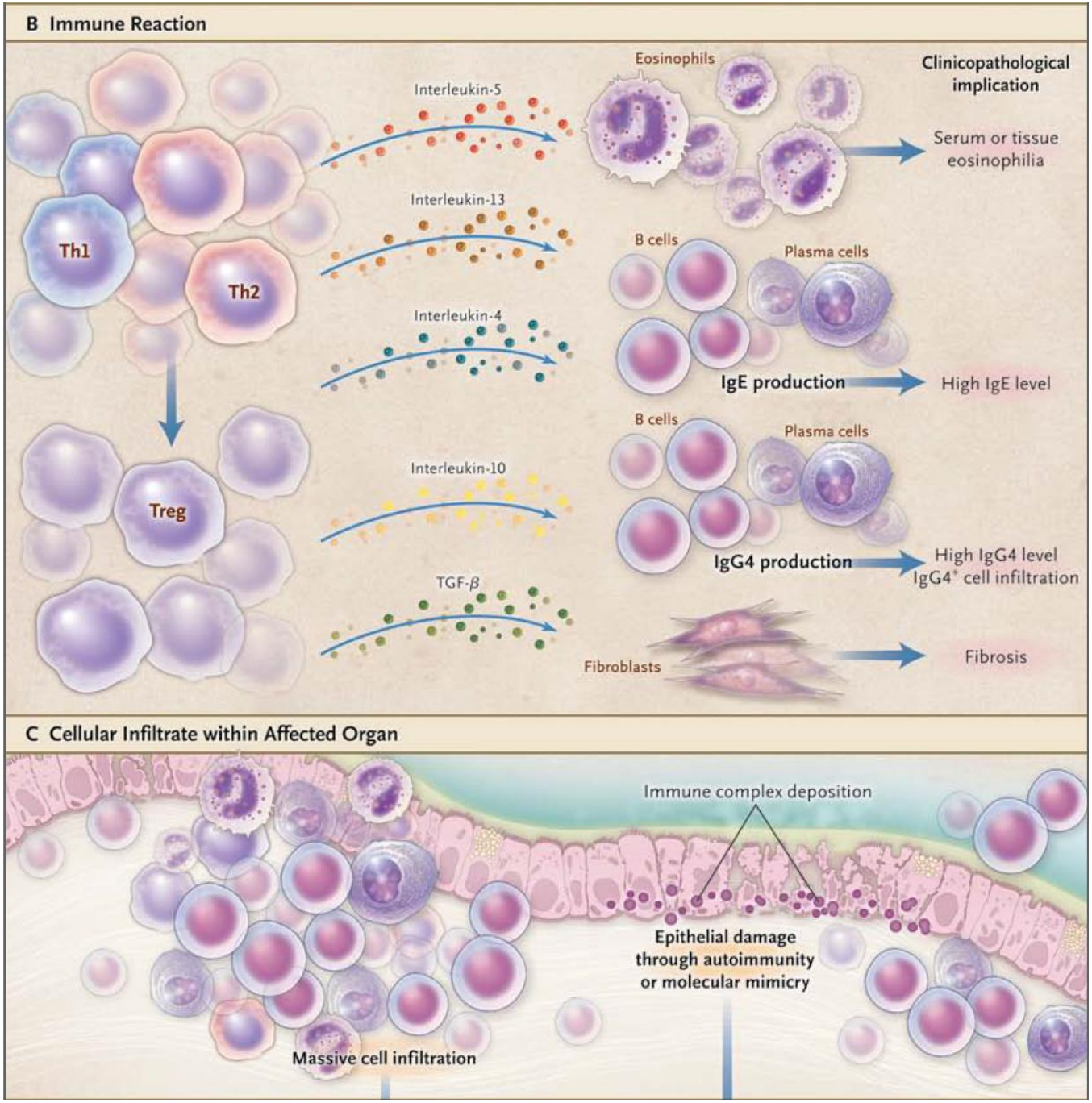
IgG4 – bystander or pathogenic?

- Exact role in disease pathogenesis remains uncertain.
- Th2 and regulatory T cell reactions increased in IGg4 related disease when compared with PSC or PBC. This pattern also observed in allergic disorders such as bronchial asthma and atopic dermatitis.
- Also postulated that IgG4 plays no pathogenic role, but that it is upregulated in response to chronic exposure to microbial or non-microbial antigens (eg H pylori).
- Recruitment of IgG4-committed B cells may result from an excessive production of anti-inflammatory cytokines (eg TGF and IL-10) at the site of inflammation.

Slide Courtesy R. Chapman, Oxford

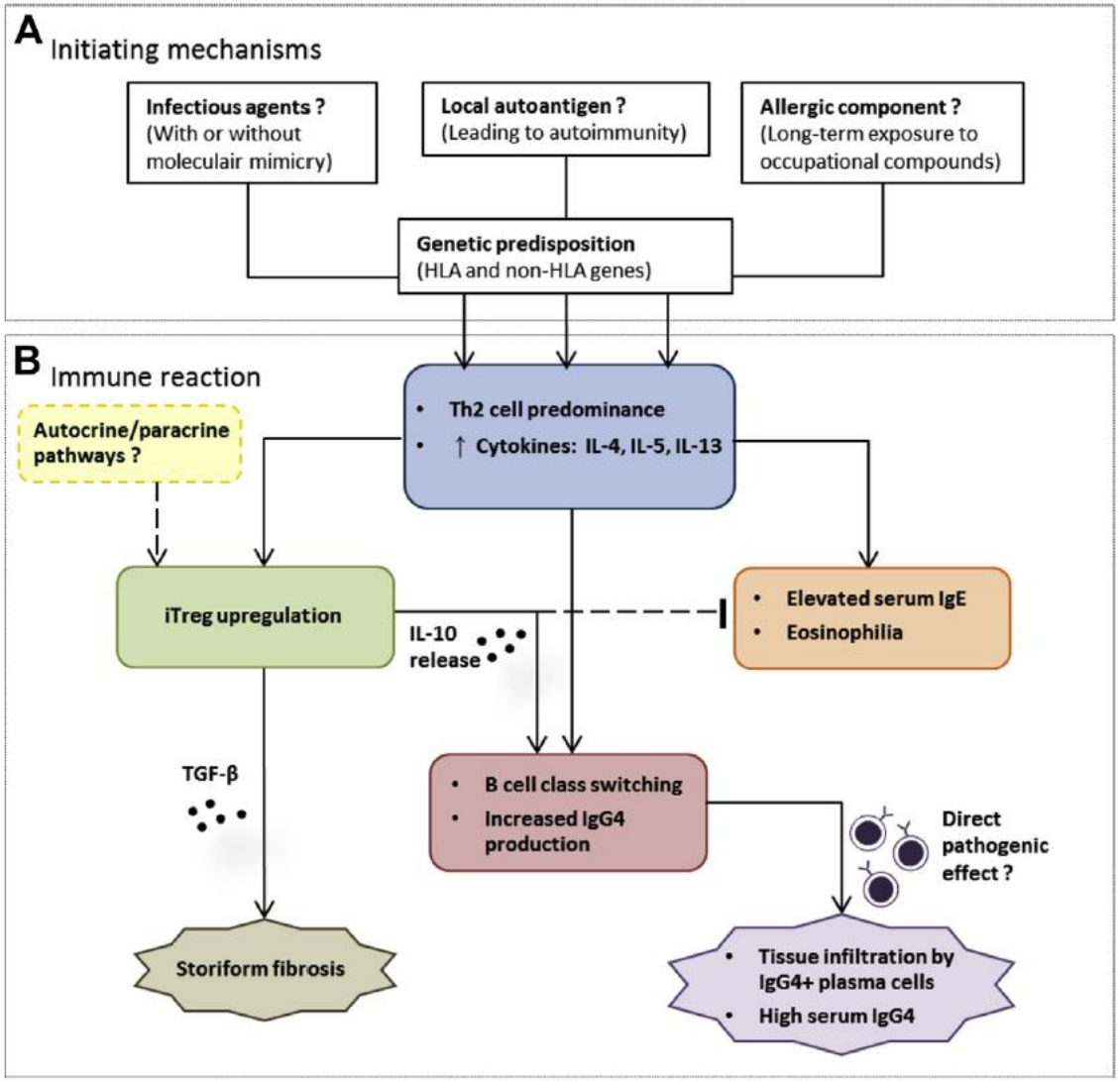
Zen Y et al Hepatology 2007
Park DH et al Gut 2009
Aalberse RC et al Clin Exp Allergy 2009

IgG4-RD



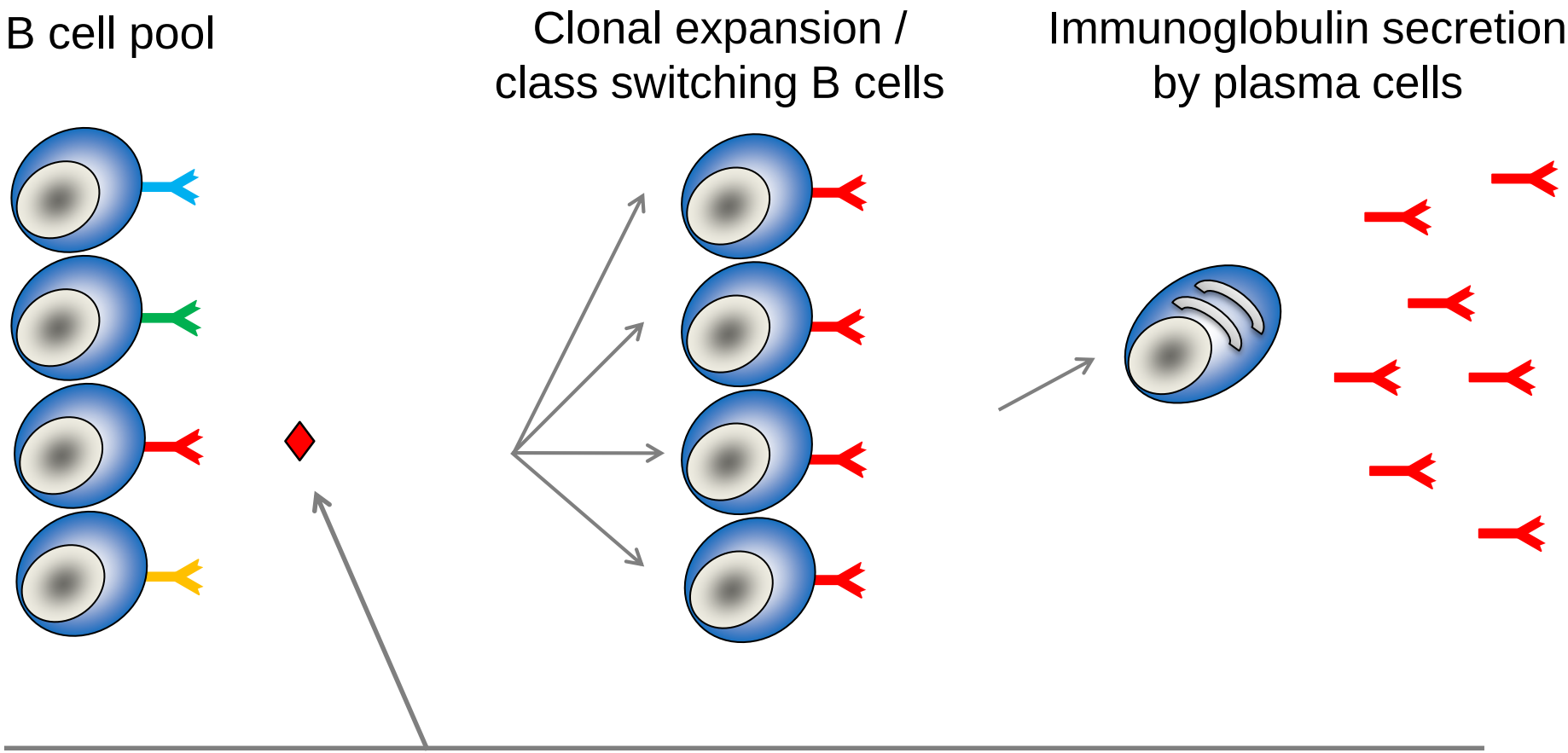
Stone et al., *New Engl J Med* 2012; 366: 539-51

Disease pathways involved in IgG4-RD



Smit et al., *Clin Liver Dis* 2016; 20: 47-65

Clonal expansion of IgG4+ B cells suggests (auto)antigen stimulation



Annexin A11 is the first IgG4 autoantigen identified in IgG4-RD

Slide Courtesy U. Beuers, Amsterdam

Hubers et al., *Gut* 2018; 67(4):728-735

IAC as blue collar worker‘s disease

Maillette de Buy Wenniger et al., Hepatology 2014; 60: 1453-4

- Exposure to occupational antigens might predispose to IgG4-related disease
- Majority had a career in blue collar occupations with prolonged exposures to potentially hazardous occupational antigens (pat. history!)
- Chronic antigenic load associated with ‘dirty’ jobs may predispose to IAC (toxin-induced B cell clone expansion?)
- IgG4 may have immuneregulatory function?

Exposure to occupational antigens might predispose to IgG4-related disease

Job history of 25 patients from the Amsterdam cohort (> 1 year)	Recalled regular occupational exposures (> 1 year)
1. Musician, painter, metal worker, carpenter	solvents, car paint, metal, pigments
2. Carpenter	solvents, sawdust, wood, chipboard
3. Glass worker, project manager at multinational	glass dust, glass components, lead, barium, cobalt, nickel, lead, silica, industrial dust, bu
4. Plasterer	solvents, chalk dust, sawdust, wood, chipwood
5. Industrial warehouse forklift driver	unknown (deceased)
6. Industrial fuel/waste oil laboratory, skipper	solvents, crude oil, ship waste oil, chemicals
7. Miner, tiler, bath superintendent	solvents, silica dust, mine dust, asbestos, glue
8. Metal worker, textile worker	solvents, metal dust, textiles, pigments, paints
9. Shipping	solvents, asbestos, crude oil
10. Painter, army officer, flight arrangements, tomato farmer	solvents, paint, pigments, kerosene, pesticides, friction plate dust
11. Painter	solvents, paint, pigments, dust
12. Small machine factory owner	solvents, car paint, metal dust, asbestos, oils
13. Builder, plumber	plumbing materials, dust, sawdust, glue, lead
14. Self-employed optometrist	lense glass dust, lense plastic dust, acetone
15. Carpenter	solvents, sawdust, clipboard, glue
16. Bricklayer, industrial cleaner of house walls	solvents, silica dust, concrete dust, brick dust, asbestos
17. Mud worker, shipping, mud industry manager	solvents, oil products, dust
18. Builder, painter	solvents, sawdust, clipboard, paints
19. Car industry worker	solvents, oil products
20. Historian, rebuilt 3 houses during last 20 years	solvents, sawdust, silica dust, paint
21. Builder, wall miller	solvents, sawdust, silica dust, dust
22. Hospital cleaner	cleaning products
23. Teacher	no known exposures
24. Nurse	no known exposures
25. Unknown (deceased)	unknown (deceased)

de Buy Wenniger et al., *Hepatology* 2014; 60: 1453-4

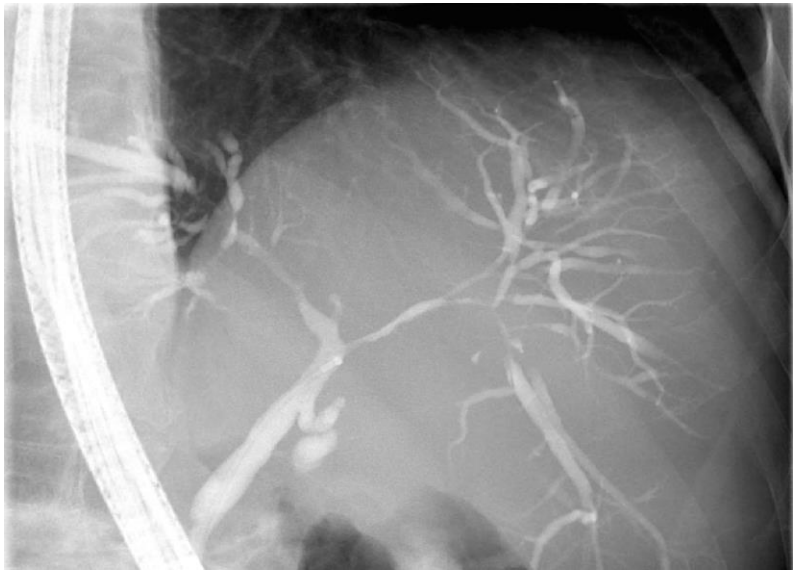
Chronic Exposure to Occupational Antigens May Play a Key Role in the Initiation / Maintenance of IgG4-Related Disease

“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 %

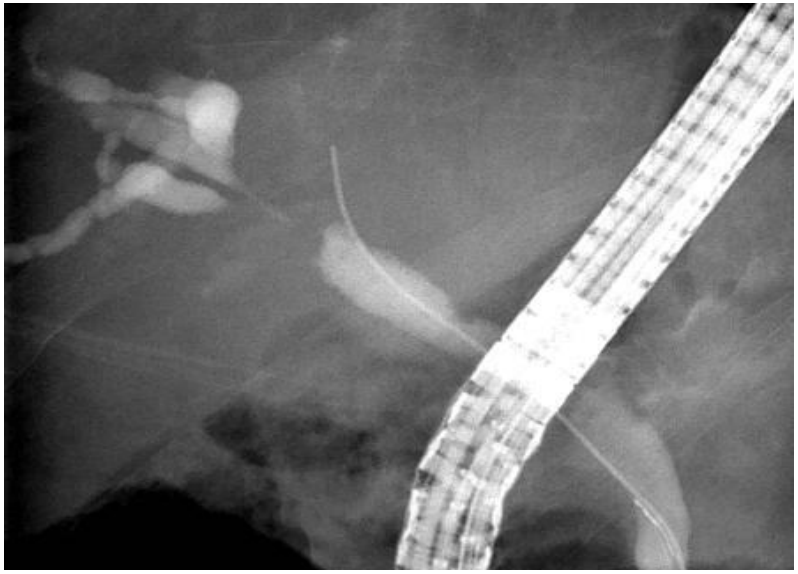
Maillette de Buy Wenniger, Curver, Beuers. *Hepatology* 2014: 60:1453

Slide Courtesy U. Beuers, Amsterdam

IgG4 cholangiopathy mimics PSC and CCA



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



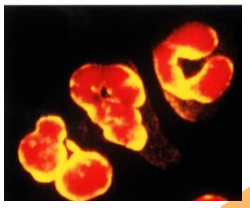
Cholangiographic appearance mimicking cholangiocarcinoma (**CCA**)

Misdiagnosis is common!

Slide Courtesy U. Beuers, Amsterdam

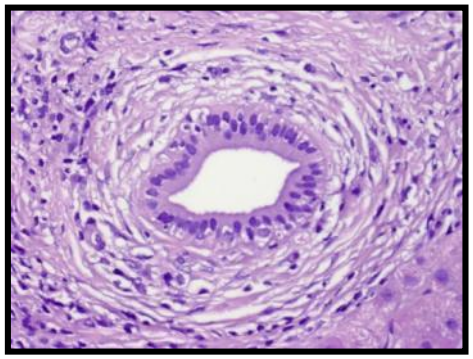
Hubers & Beuers, *Viszeralmedizin* 2015;31:185

Clinical Features & Diagnosis of PSC



Atypical
pANCA

~5%
Small Duct PSC



Obliterative fibrosis
of bile ducts

HCC

CCA
160x
~15%

GB-
Ca

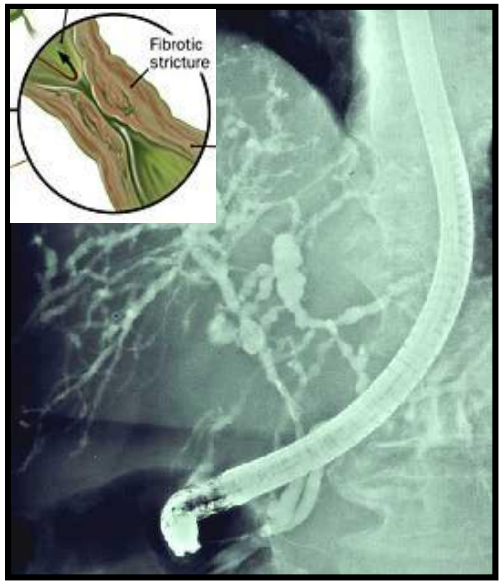
Gut-primed
T cells

LPS

CRC
10x

PSC-IBD

Large Duct PSC



Modified after
G. Paumgartner

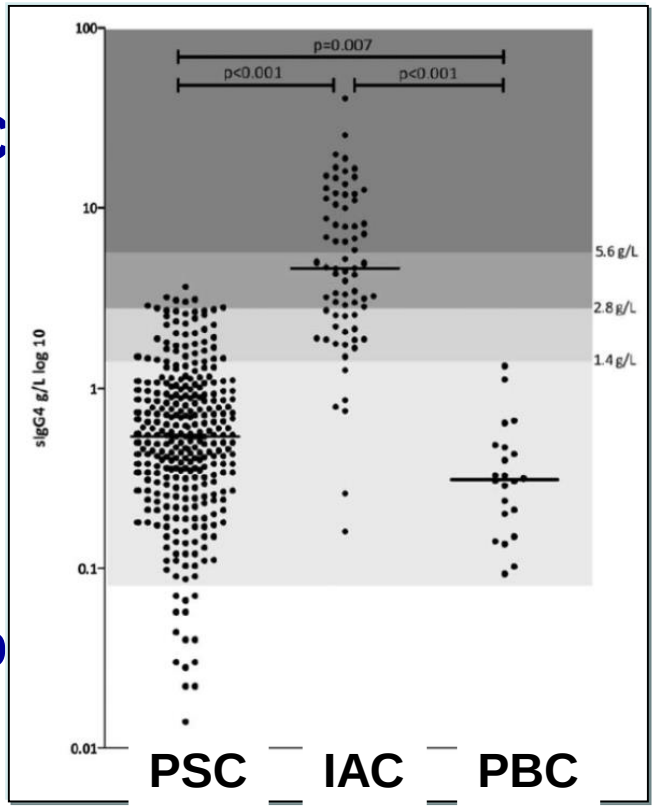
Review: Halilbasic et al., *Dig Dis* 2015

Challenge of Excluding Secondary Causes

- Diagnosis of PSC requires exclusion of secondary causes
  - **IgG4-associated cholangitis (IAC**
  - Recurrent bacterial cholangitis
  - Critically ill patients (SC-CIP)
  - Ischemic cholangitis (vs. rPSC)
  - AIDS cholangiopathy
  - Portal hypertensive biliopathy
  - Histiocytosis X, mast cell cholangio
  - Eosinophilic cholangitis
  - Surgical trauma

Serum IgG4

Boonstra et al., *Hepatology* 2014



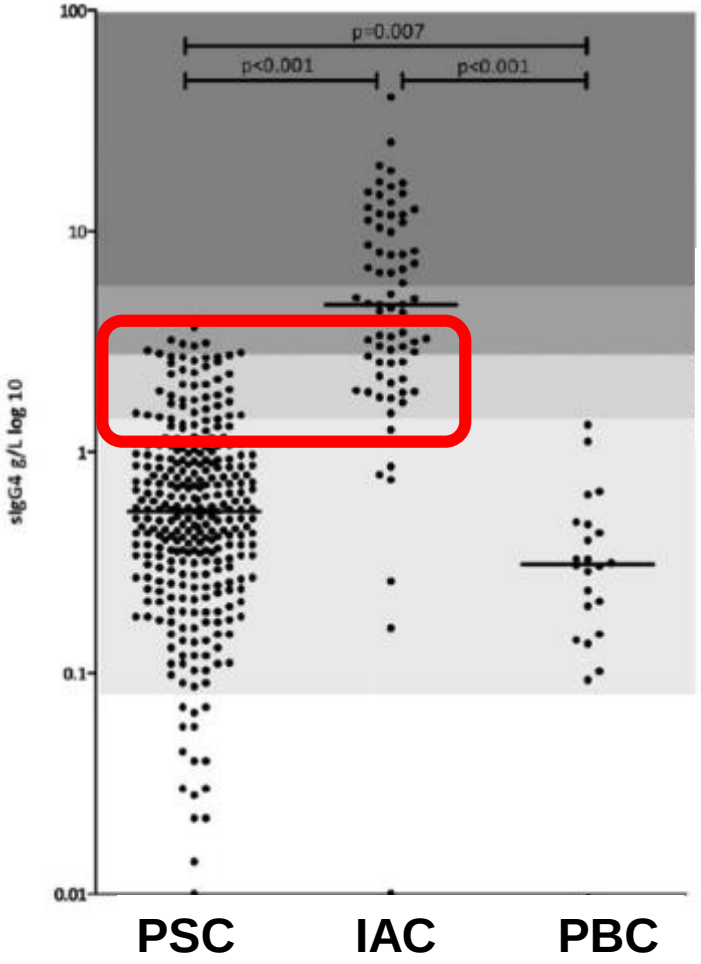
Abdalian & Heathcote, *Hepatology* 2006; 44: 1063

Leonhardt et al., *Medicine* 2015; 94: e2188

Guidelines: EASL *J Hepatol* 2009, ACG *Am J Gastro* 2015

Role of Elevated Serum IgG4 in PSC

?



5.6g/l
2.8g/l
1.4g/l

Boonstra et al., *Hepatology* 2014; 59: 1954-63

Role of Elevated Serum IgG4 in PSC

- Elevated IgG4 in 10-15% of PSC patients
  - More progressive course; therapeutic implications?[1]
- Patients with PSC should be tested at least once for elevated serum IgG4 levels
- Distinction from IAC challenging (overlap?)
- When ↑ serum IgG4 is < 2 x ULN (‘grey zone‘), a IgG4/IgG1 ratio >0,24 indicative for IgG4-RD[2]
- IgG4(+) BCR clones or IgG4/IgG RNA ratio in blood (PCR) can assist differential diagnosis[3]

1: Mendes et al., *Am J Gastro* 2006; 101: 2070-6
2: Boonstra et al., *Hepatology* 2014; 59: 1954-63
3: Doorenspleet et al., *Hepatology* 2016: 64: 501-7
ACG Guidelines, Lindor et al., *Am J Gastro* 2015; 110: 646-59

Novel Approach to Diagnosis & Monitoring of IgG4-related Disease

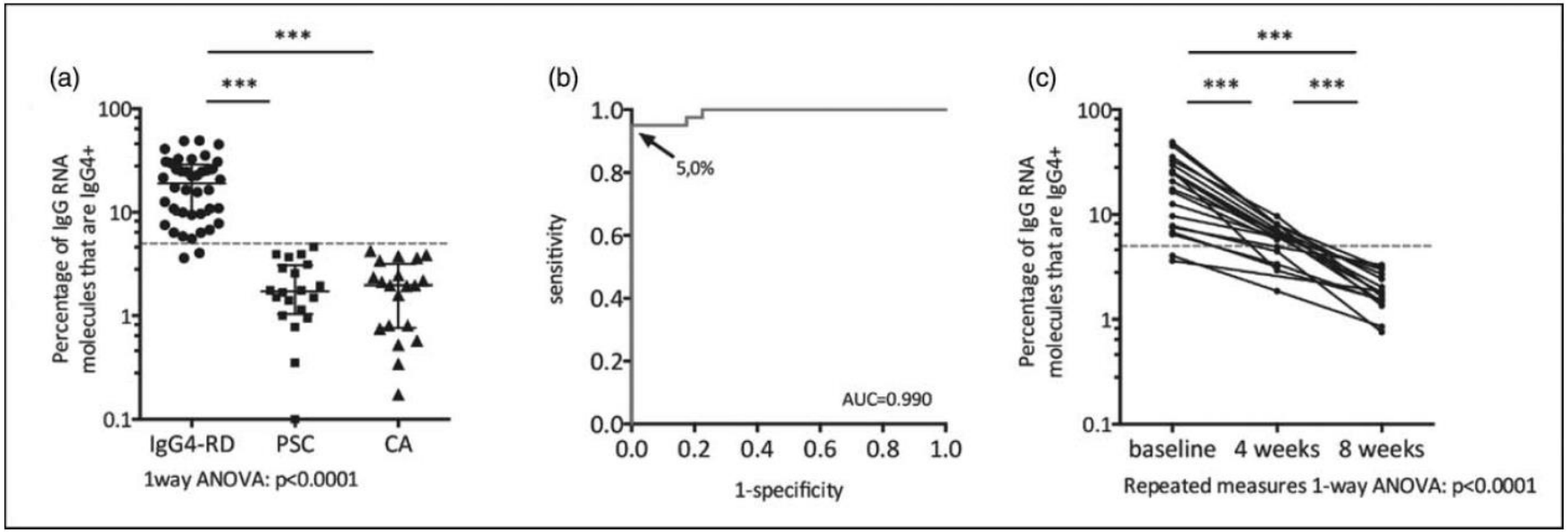
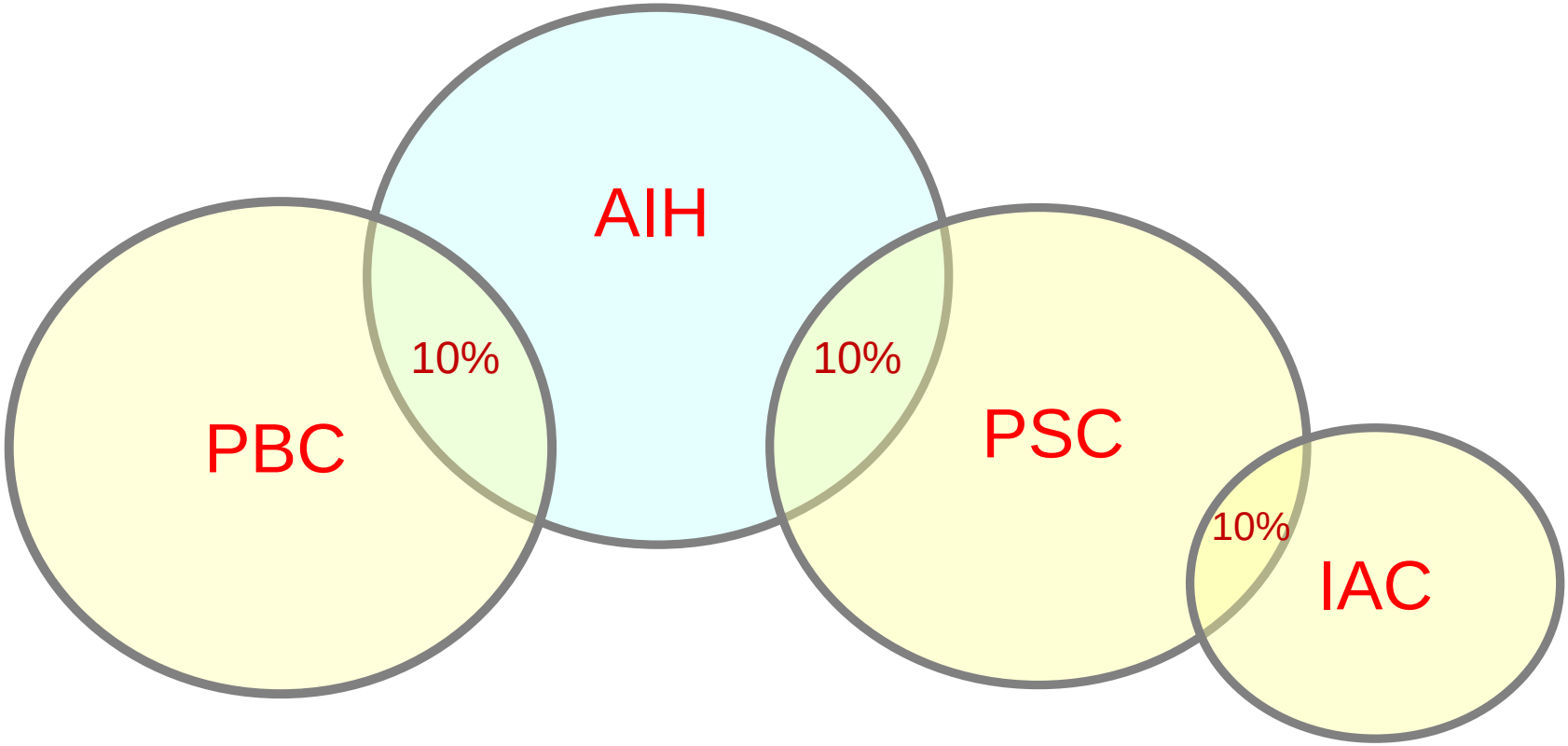


FIGURE 1. Novel approach to diagnosis and monitoring of IgG4-RD of bile ducts and pancreas. (a): The IgG4/IgG RNA ratio distinguishes IgG4-RD from PSC and hepatobiliary/pancreatic malignancies (cutoff level = 5%, $n = 125$); (b): AUROC analysis 0.99 ($n = 125$); (c): Monitoring disease activity by IgG4/IgG RNA during corticosteroid treatment ($n = 20$).

Hubers & Beuers, *Curr Opin Gastroenterol* 2017; 33: 310-14
Doorenspleet et al., *Hepatology* 2016: 64: 501-7

Autoimmune & Immune-mediated Liver- & Biliary Diseases Can Overlap



IAC= IgG4-associated cholangitis (2007)
often used synonymously for
IgG4-SC = IgG4-related sclerosing cholangitis (2011)

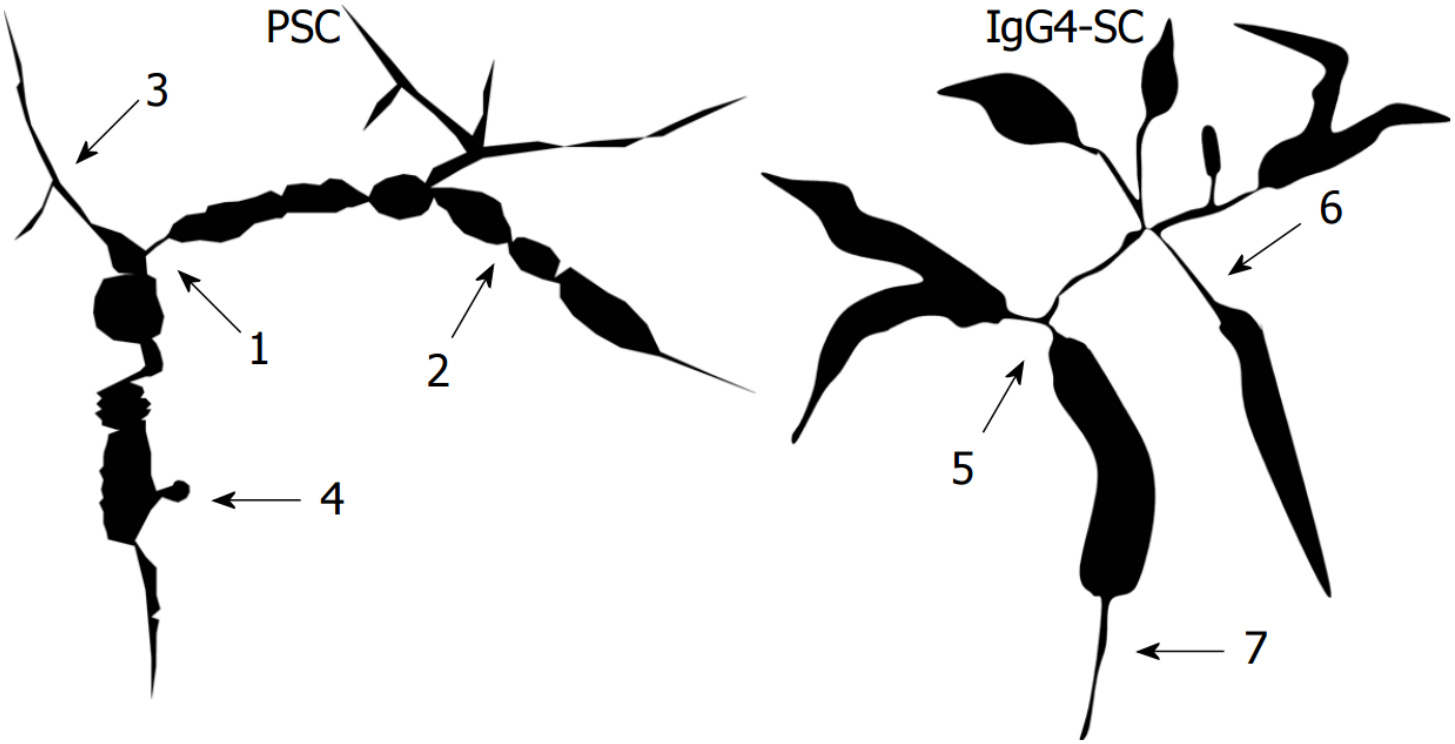
Comparison of PSC and IgG4-SC

	PSC	IgG4-SC
Gender	M:F 1.5:1	M:F 7:1
Age of onset	Young age (< 40 years)	Older (>50 years)
Presentation	Cholestatic liver biochemistry	Obstructive jaundice
Biliary abnormalities	Beading, band-like strictures, peripheral pruning	Long smooth strictures, low CBD stricture
Raised serum IgG4 levels	**<20%**	**> 70%**
Pancreatic involvement	<5%	> 80%
Multi-organ involvement	No	Yes
Association with IBD	80%	< 10%
Response to steroids	Rare (IgG4 +ve PSC)	Yes (relaps: azathioprine, rituximab?)

- MRI patterns (Tokala et al., *Am J Roentgenol* 2014)
- IDUS (Naitoh et al., *J Gastroenterol Hepatol* 2015)

Joshi & Webster, *Aliment Pharmacol Ther* 2014; 40: 1251-61

Comparison of PSC and IgG4-SC

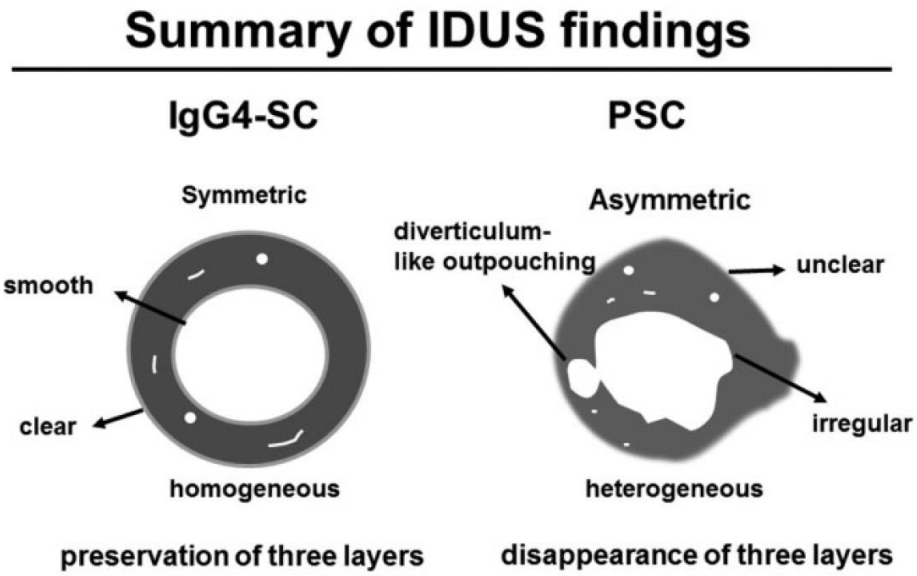


Nakazawa et al., *World J Gastroenterol* 2013; 19: 7661–7670

Comparison of PSC and IgG4-SC

	Type1 – lower CBD stricture
	Type 2 – Intrahepatic stenosis with pre-stenotic dilatation and lower CBD stricture
	Type 3 – Hilar stricture and lower CBD stricture
	Type 4 – Hilar stricture

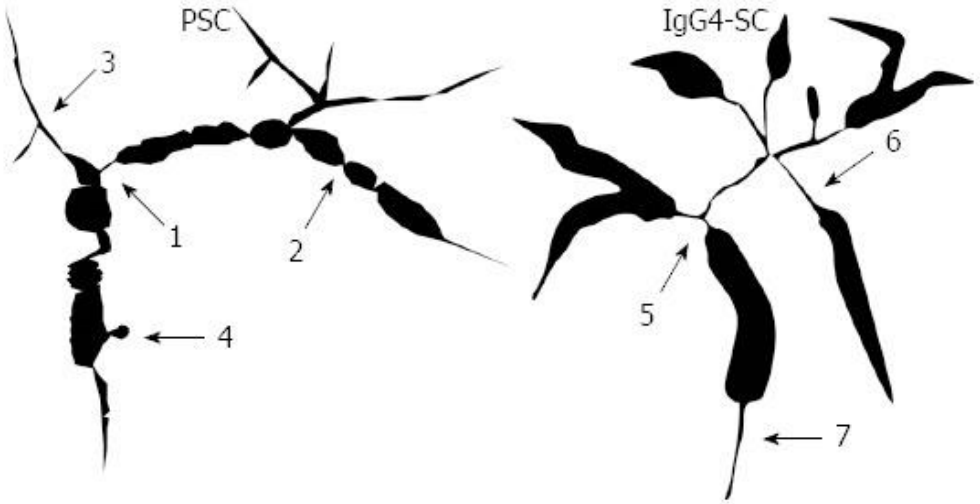
Adapted after Nakazawa et al., *WJG* 2013

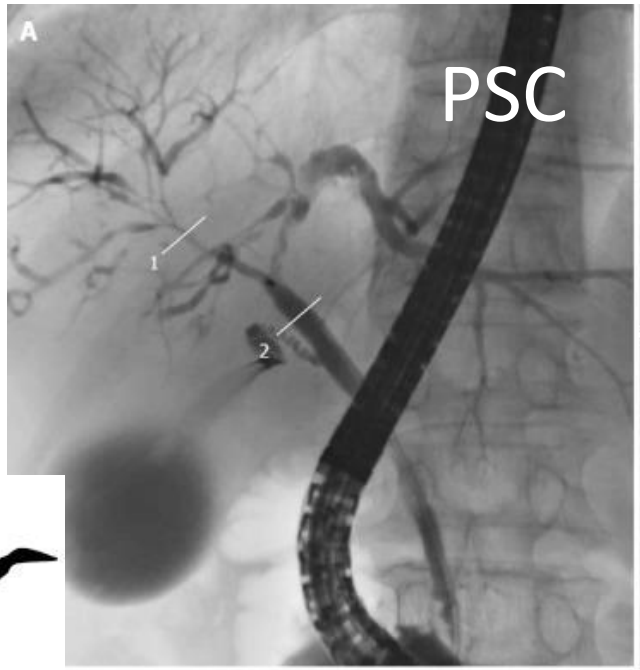


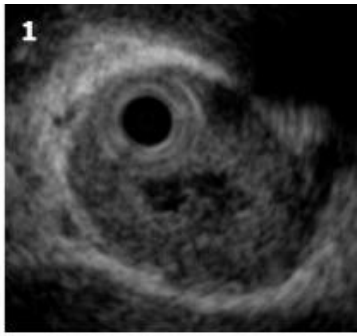
Naitoh et al., *J Gastroenterol Hepatol* 2015

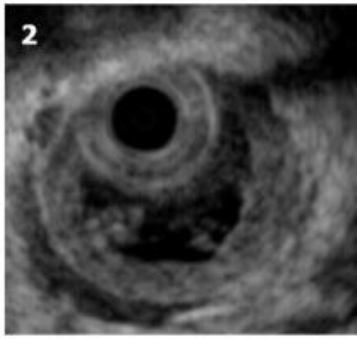
Joshi & Webster, *Aliment Pharmacol Ther* 2014; 40: 1251-61
Okazaki et al., *J Hepatol* 2014; 690-95

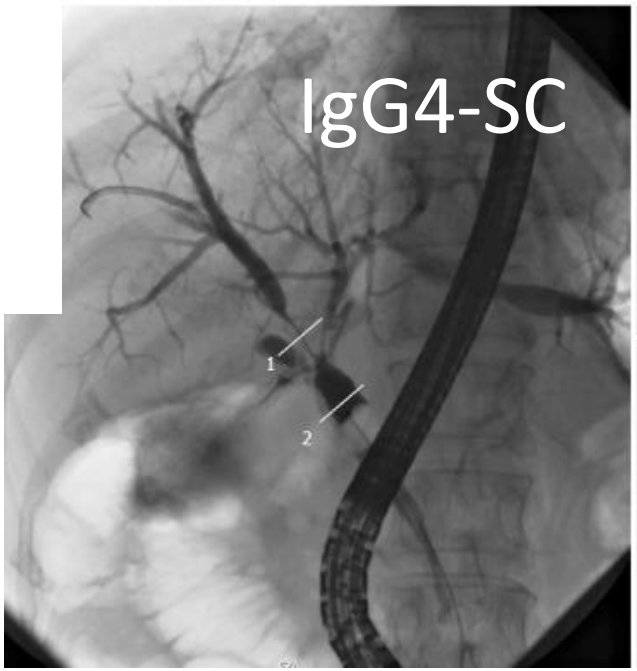
Cholangiography of PSC versus IgG4-SC

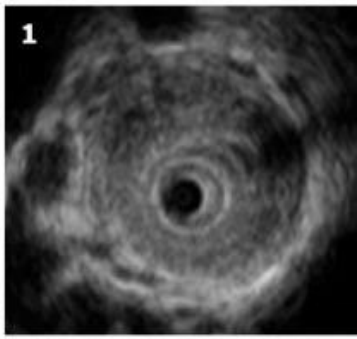


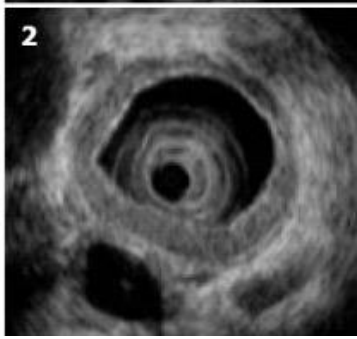












Nakazawa et al., *World J Gastroenterol* 2013; 19: 7661–7670

Diagnosis of IgG4-related Cholangitis

- HISORt Criteria -

Biliary strictures: intrahepatic, proximal and/or distal extrahepatic

A

Previous pancreatic / biliary resection or core biopsy of pancreas (EUS) showing diagnostic features of AIP / IAC

B

Classical imaging findings of AIP
+
Elevated serum IgG4

C

Two or more of following:

- Elevated serum IgG4
- Suggestive pancreatic imaging
- Other organ involvement
- Bile duct / ampullary biopsy with > 10 IgG4-pos. cells/HPF

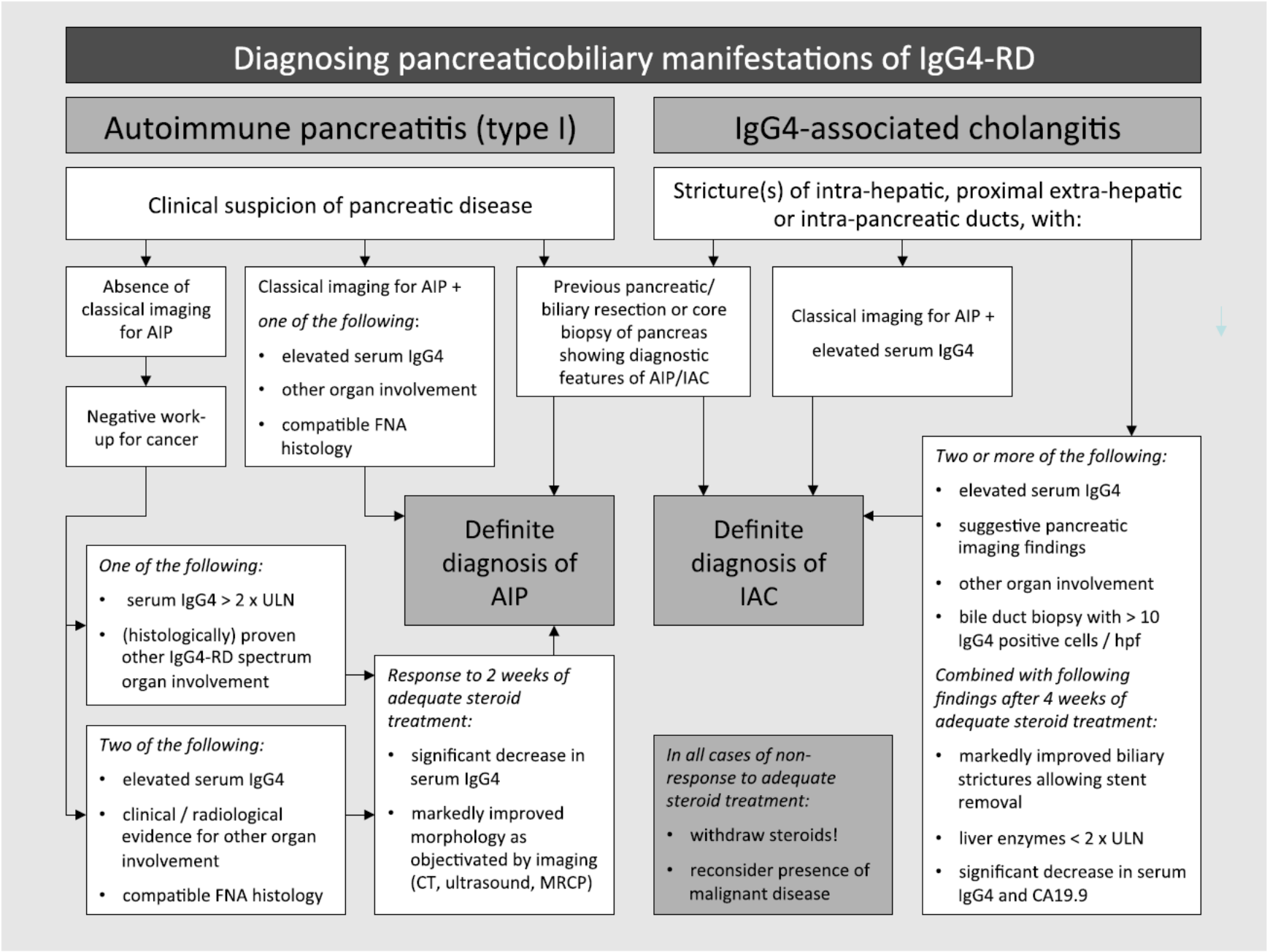
Probable IAC

Definite IAC

Improvement after 4 wks of steroid Rx

- Strictures - stent removal
- Liver enzymes < 2 x ULN
- Serum IgG4, CA 19-9

Ghazale et al., *Gastroenterology* 2008;134:706
EASL Clinical Practice Guidelines *J Hepatol* 2009; 51: 237-67
Review: Hubers et al., *Clin Rev Allergy Immunol* 2015; 48: 198-206



Hubers et al., *Clin Rev Allergy Immunol* 2015; 48: 198-206

Pitfalls of Elevated Serum IgG4

- sIgG4 normal in >30% of pts. with type I AIP
- Elevated sIgG4 in 5% of healthy individuals
- Elevated sIgG4 in 10% of patients with pancreatic or cholangio ca (no overlap >4.5 g/L)
- Elevated sIgG4 in various other autoimmune, allergic, inflammatory and infective conditions including PSC
- Elevated sIgG4 does not reliably determine disease activity, disease relapse or organ involvement in AIP (more in systemic disease)

Slide Courtesy R. Chapman, Oxford

Elevated serum IgG4 is not disease specific

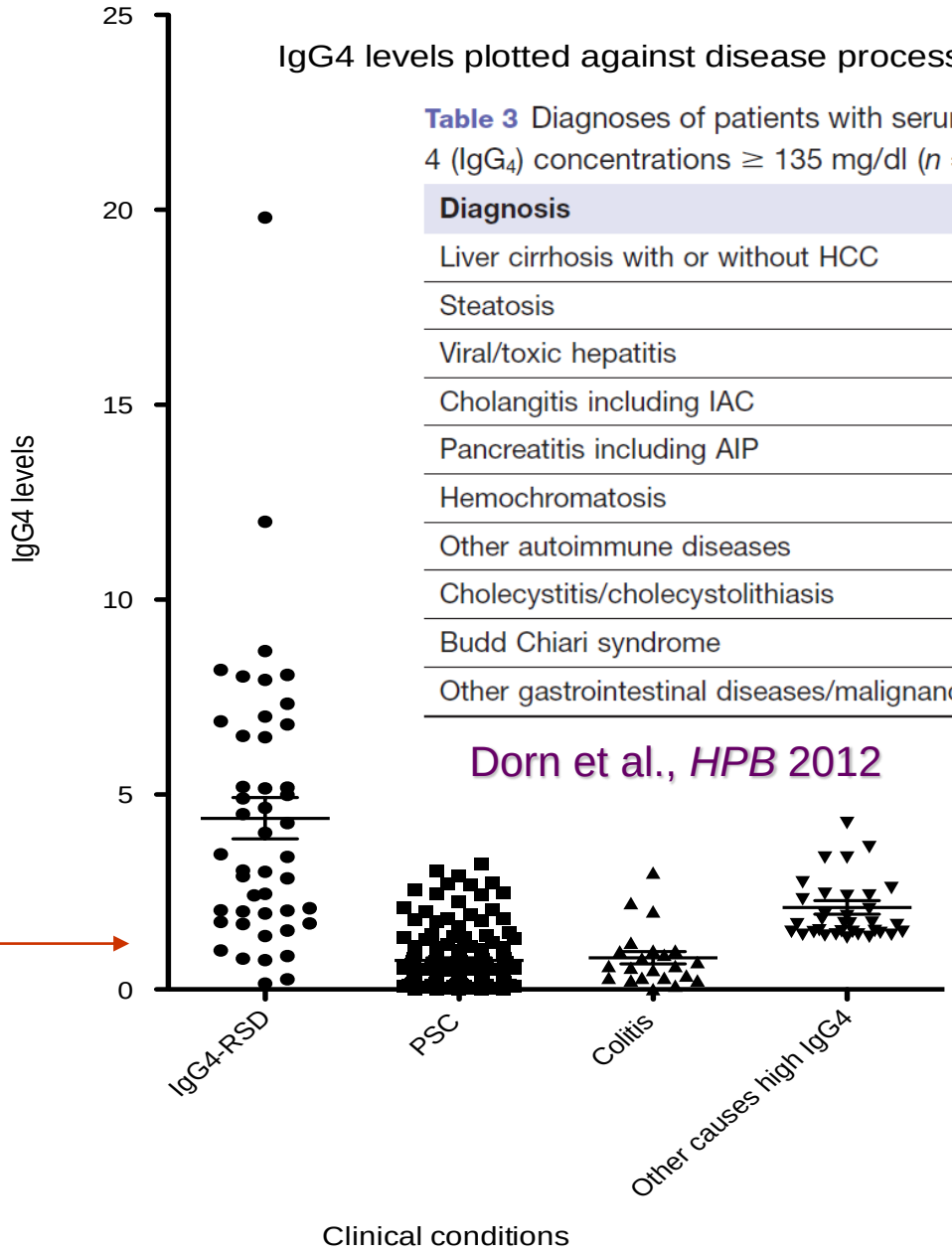


Table 3 Diagnoses of patients with serum immunoglobulin subclass 4 (IgG_4) concentrations ≥ 135 mg/dl (n = 210)

Diagnosis	*n* (%)
Liver cirrhosis with or without HCC	72 (35%)
Steatosis	35 (17%)
Viral/toxic hepatitis	24 (11%)
Cholangitis including IAC	21 (10%)
Pancreatitis including AIP	8 (4%)
Hemochromatosis	8 (4%)
Other autoimmune diseases	6 (3%)
Cholecystitis/cholecystolithiasis	3 (1%)
Budd Chiari syndrome	2 (1%)
Other gastrointestinal diseases/malignancies	30 (14%)

Dorn et al., *HPB* 2012

IgG4 level >1.4 g/L

Slide Courtesy R. Chapman, Oxford

EL Culver, R Sadler et al, GUT suppl, 2012

Diagnostic HISORt Criteria

Category	Criteria
Histology	- Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis - Lymphoplasmacytic infiltrate with > 10 IgG4+ plasma cells/HPF
Pancreatic **I**maging	Typical: diffuse gland enlargement; diffuse attenuated pancreatic duct. Others: focal mass/stricture; atrophy; calcification; pancreatitis
Serology	Elevated serum IgG4
Other organs	Biliary strictures; salivary/lacrimal gland enlarged; mediastinal lymphadenopathy; retroperitoneal fibrosis; lung disease; tubulointerstitial nephritis
Response to Steroids	Resolution/marked improvement of pancreatic/extrapancreatic manifestation

Chari ST, et al. Clin Gastro Hepatol, 2006

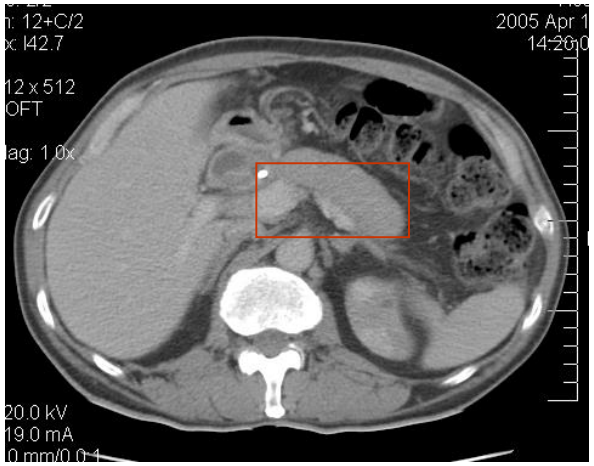
Slide Courtesy R. Chapman, Oxford

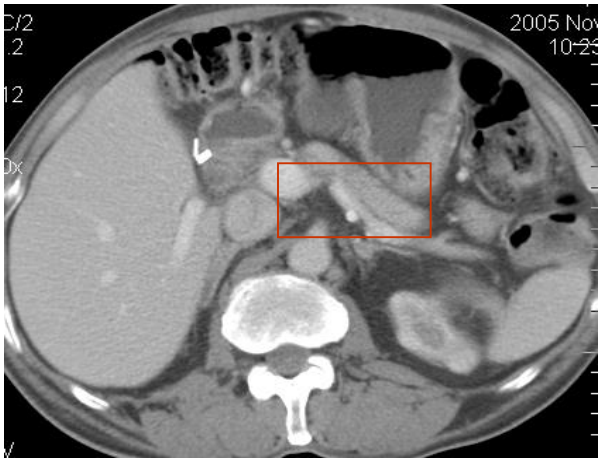
Treatment of IgG4-related Disease
- International Consensus* (but limited evidence) -

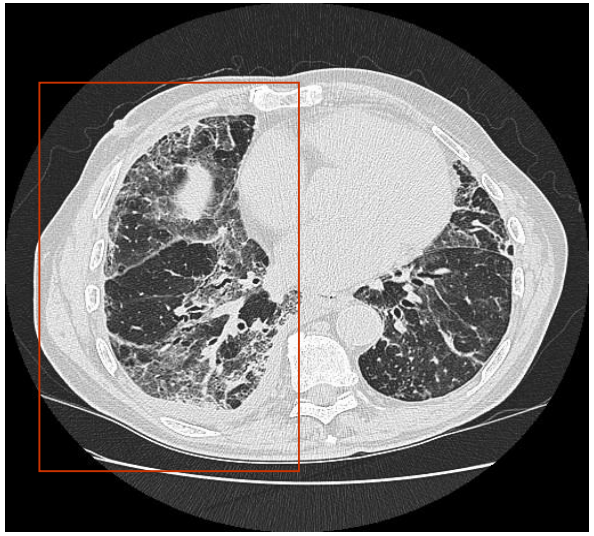
- Multi-system disease
- Frequent pancreatic endocrine and exocrine dysfunction
- Prednisone induction therap similar to AIH
  - Prednisone 30-40mg day and taper by 5mg every 2 weeks
  - Aim at 3-6 mo, some patients require longterm low-dose (5-7,5mg/d)
  - Monitor IgG4 levels (Alk Phos and ALT should also respond)
  - Watch out for hyperglycemia
- Maintenance with Azathioprine, 6-MP or Mycophenolate
- Very bulky pseudo-tumour or early Prednisone relapse
  - Rituximab 1000mg IV q2 weeks for two doses
- Stenting (biliary tract, ureter), rarely surgical debulking

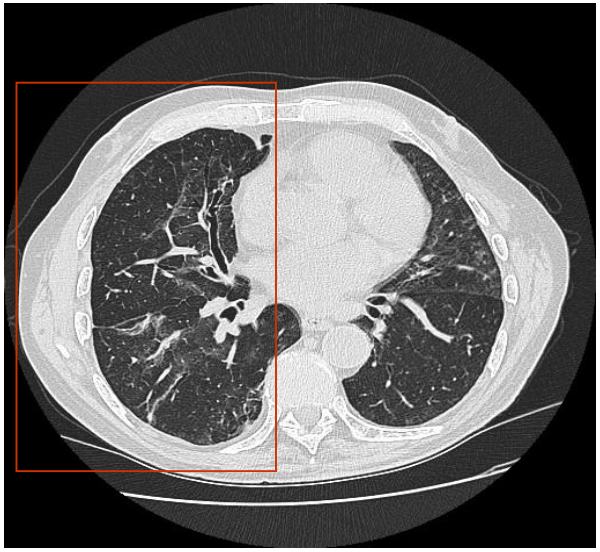
*Khosroshahi et al., *Arthritis Rheum* 2015; EASL CPG *J Hepatol* 2009
Ghazale et al., *Gastro* 2008; Hubers & Beuers, *Curr Opin Gastroenterol* 2017
Culver & Chapman, *Nat Rev Gastro Hepatol* 2016

Resolution with steroids





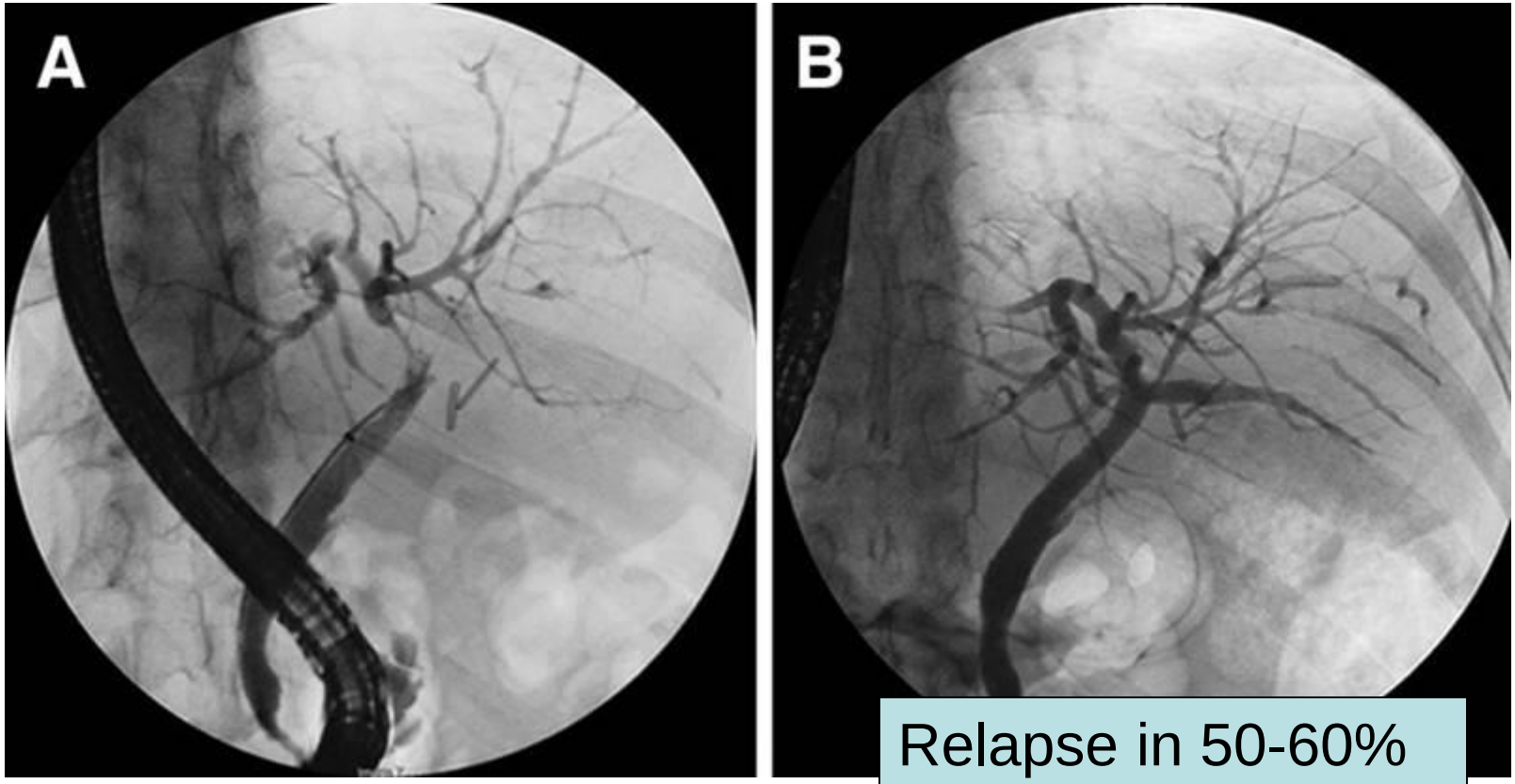




IgG4-associated Cholangitis

Before

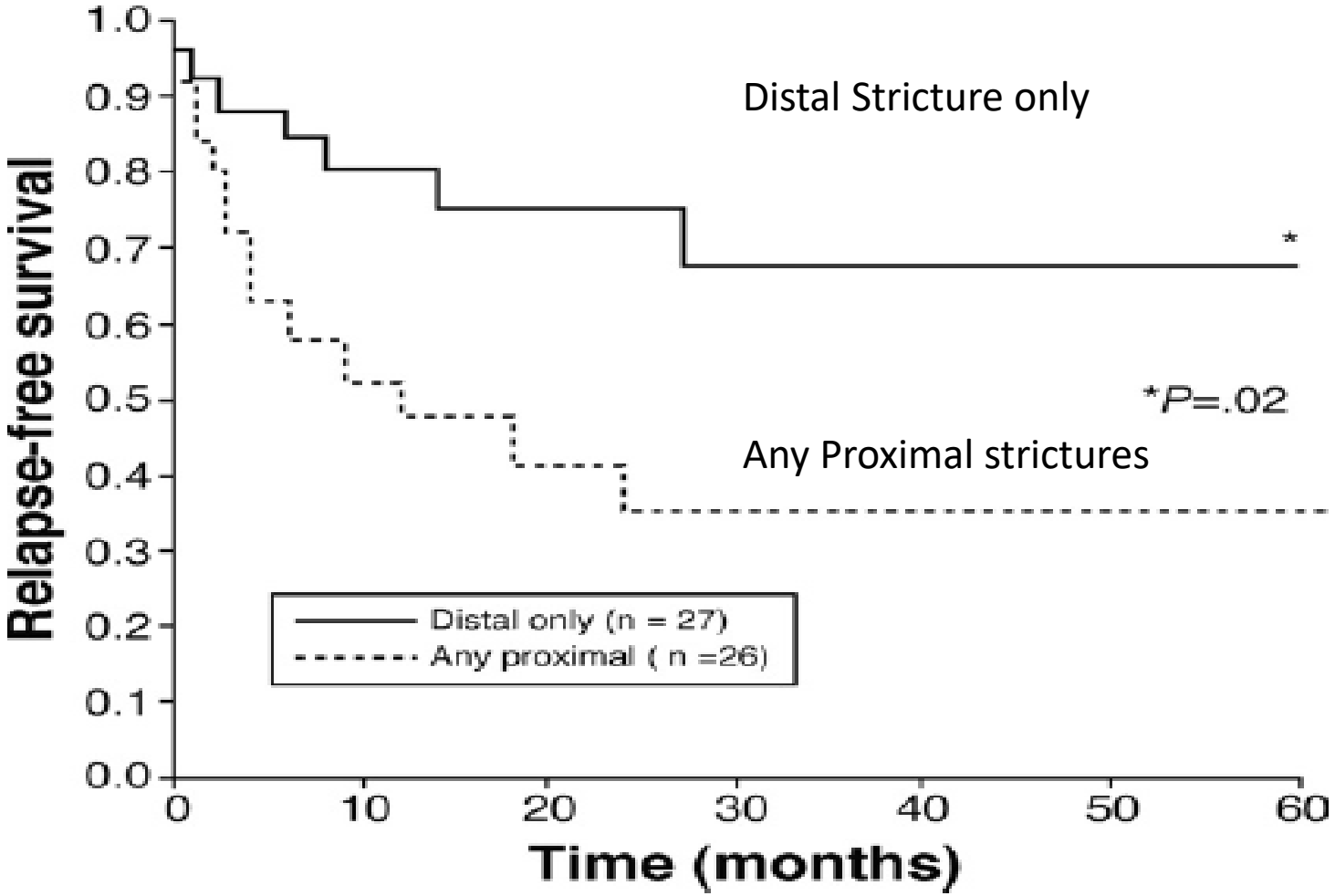
After Steroids (3m)



Relapse in 50-60%
Aza, MMF, rituximab

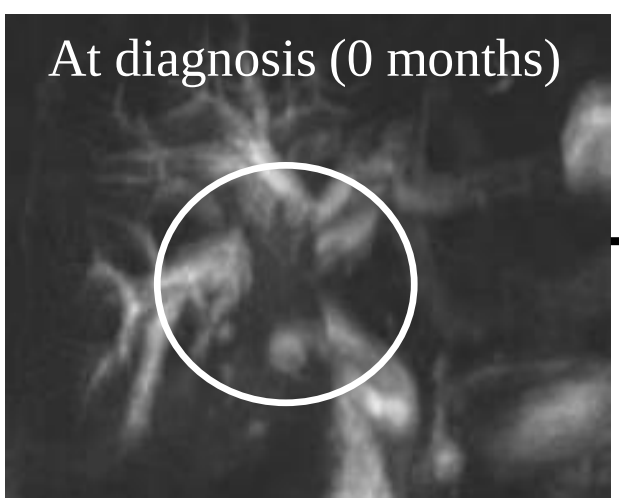
Ghazale et al., *Gastroenterology* 2008; 134: 706
Mailette de Buy Wenninger et al., *Endoscopy* 2012; 44. 66

Localization of Strictures in IgG4-associated Cholangitis-
Treatment Response to Corticosteroids -

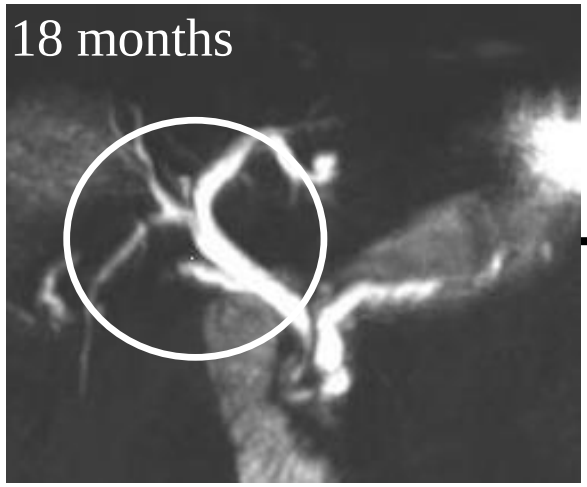


Ghazale et al., *Gastroenterology* 2008;134:706

Sequential MRCPs of remission and relapse in IAC

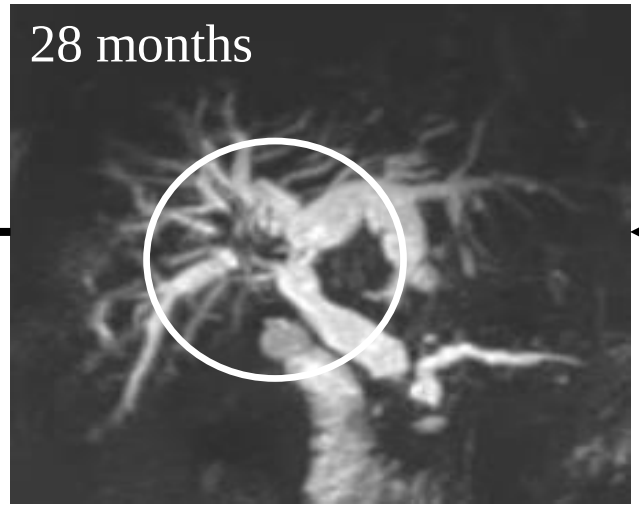


6/12 Pred

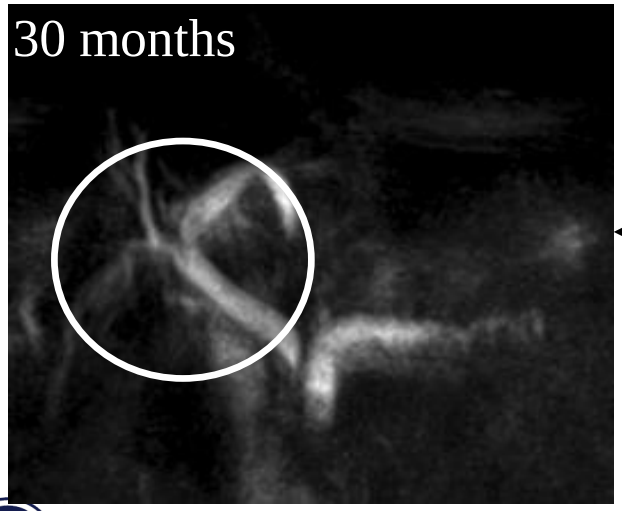


Off steroids

16/12



Pred + AZA



Slide Courtesy G.J.M. Webster, London

Treatment of IgG4-related Disease

- Second Line Options (Relapsers, Non-responders) -

Table 4 | **Immunosuppresive therapies for IgG4-SC***

Agent	Regimen	Mechanism of action
Azathioprine‡	2 mg/kg per day in a single dose	Thiopurine analogue, and is the prodrug of mercaptopurine
Mycophenolate mofetil§	750–1,000 mg twice per day	Inosine-5′-monophosphate dehydrogenase inhibitor
Mercaptopurine§	2.5 mg/kg per day in two divided doses	Thiopurine analogue
Methotrexate‖	10–25 mg per week plus folic acid	Antimetabolite and antifolate agent
Tacrolimus‖	Adjusted to a target blood level range of 4–11 ng/mL	Macrolide calcineurin inhibitor
Rituximab	1,000 mg week 0 and week 2 by intravenous infusions	$CD20^+$ B cell depletion agent

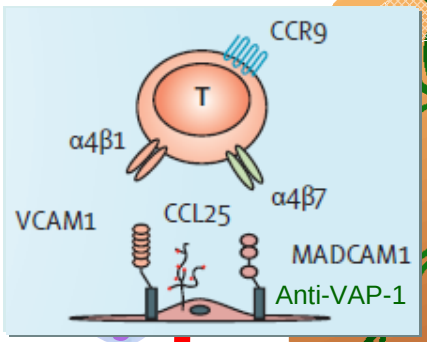
Culver & Chapman, *Nat Rev Gastro Hepatol* 2016; 13: 601-12

Novel Therapeutic Approaches to PSC

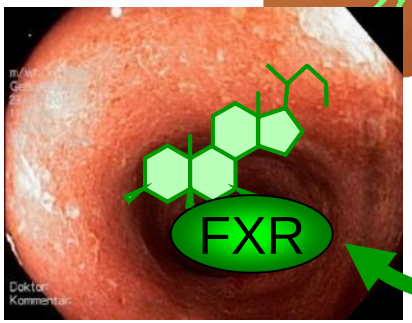
Currently Tested in Clinical Trials

Cenicriviroc

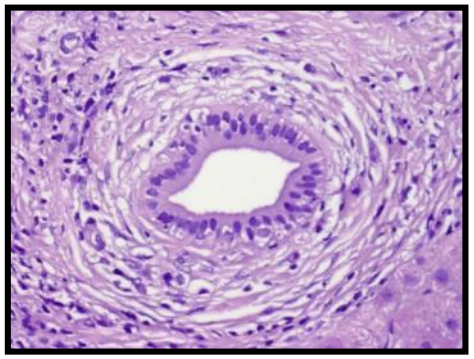
Etrolizumab
Vedolizumab



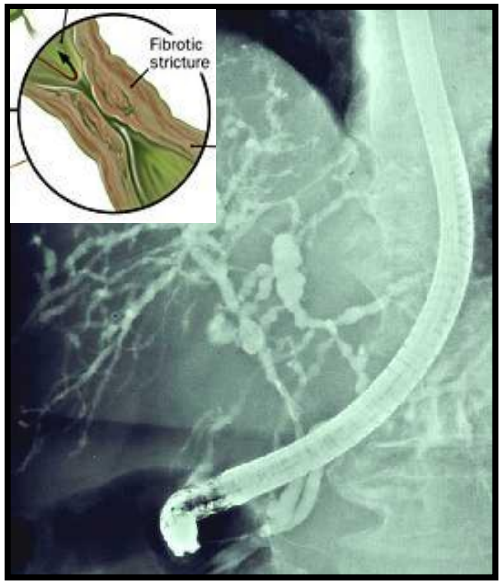
Colitis (~75%)



*nor*UDCA



Obliterative fibrosis of bile ducts



PPAR
FXR
RAR

Antibiotics
(Vancomycin,
Minocyclin,
Metronidazol)

FXR

FMT?

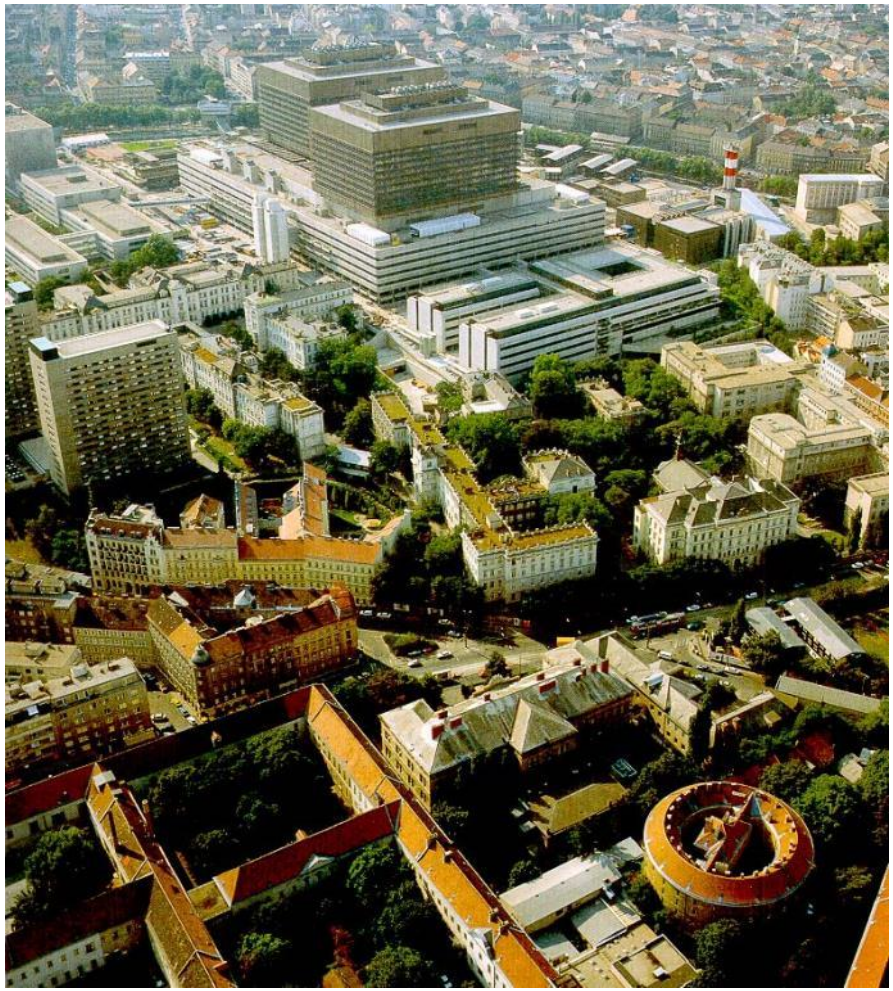
Microbiota (Dysbiosis)

Kowdley et al., AASLD 2017
AESOP trial (OCA in PSC)

Summary & Conclusions

- IgG4-related disease is a systemic / multiorgan fibroinflammatory condition, pathogenesis still unclear
- Environmental risk factors (“blue collar worker“)
- Diagnosis is based on a combination of clinical, biochemical, radiological and histological findings
- Differentiation from other benign and malignant disorders
- Treatment regimens have been reached by international consensus (no RCT). First-line therapy is corticosteroids, often in combination with (biliary) stenting
- The long-term outcome in IgG4-HBD is not well established. Disease-related inflammatory and fibrotic complications and an increased risk of all-cause malignancy have been reported in prospective studies

Culver & Chapman, *Nat Rev Gastro Hepatol* 2016; 13: 601-12
Hubers et al., *Clin Rev Allergy Immunol* 2015; 48: 198-206



Thank you for your attention!

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