BSG Annual Liver Pathology Update Meeting
Harrogate
10 December 2015

in liver pathology?

Dina G. Tiniakos

Dept of Cellular Pathology, Royal Victoria Infirmary
Institute of Cellular Medicine, Newcastle University
Newcastle upon Tyne

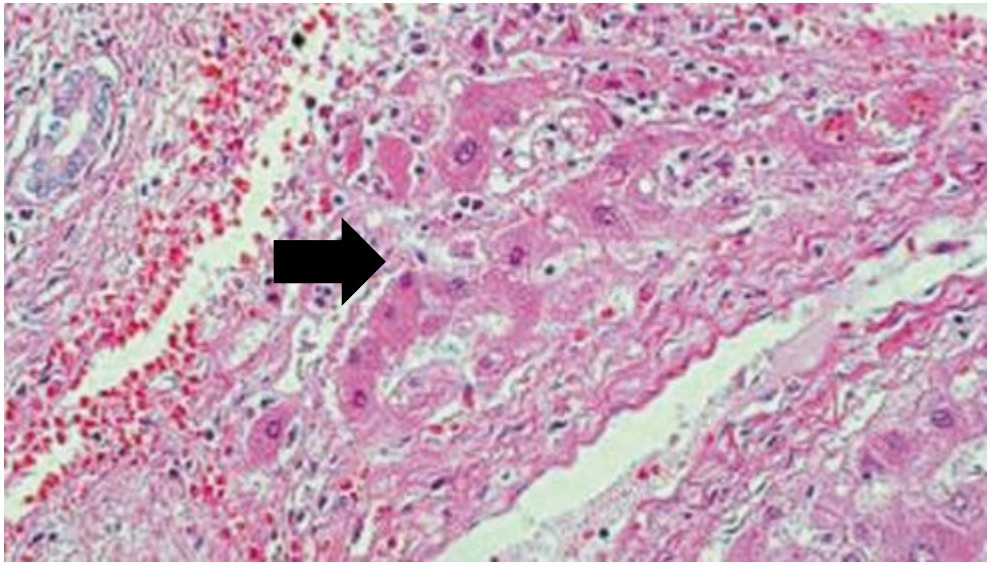
- **Chronic liver disease**
  - **Repair in Cirrhosis**
  - **Autoimmune Hepatitis**
  - **Drug-induced liver injury**
  - **Biliary disease**

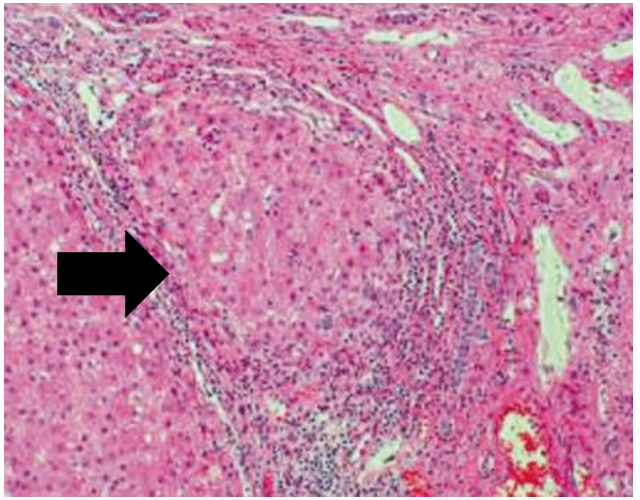
Repair in cirrhosis

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD
2015; 61: 1696-707

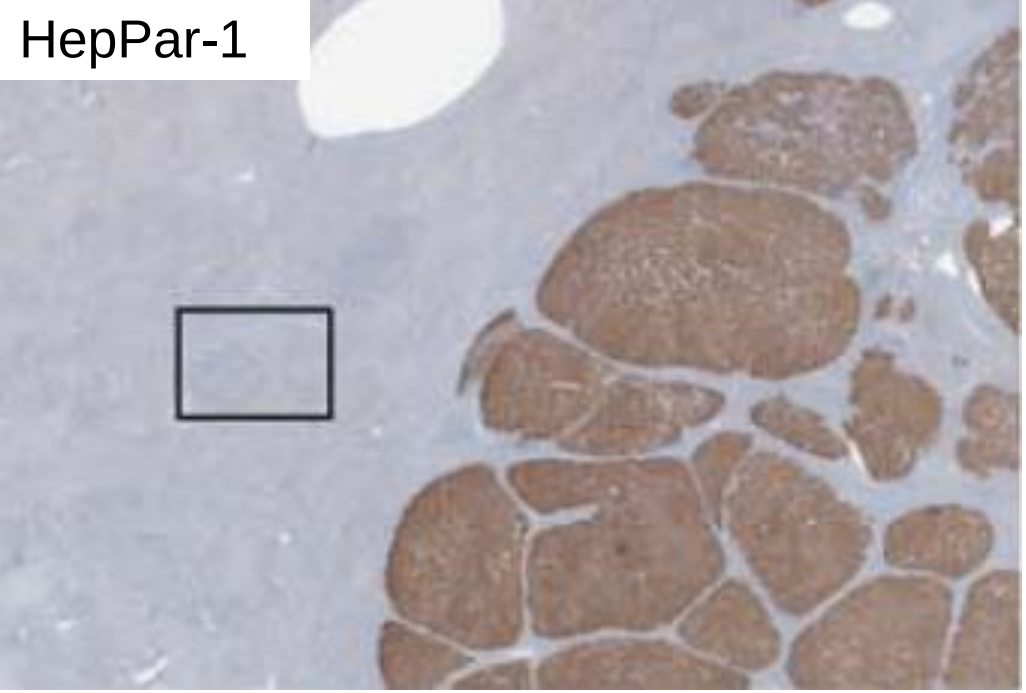
Hepatocyte Buds Derived From Progenitor Cells Repopulate Regions of Parenchymal Extinction in Human Cirrhosis

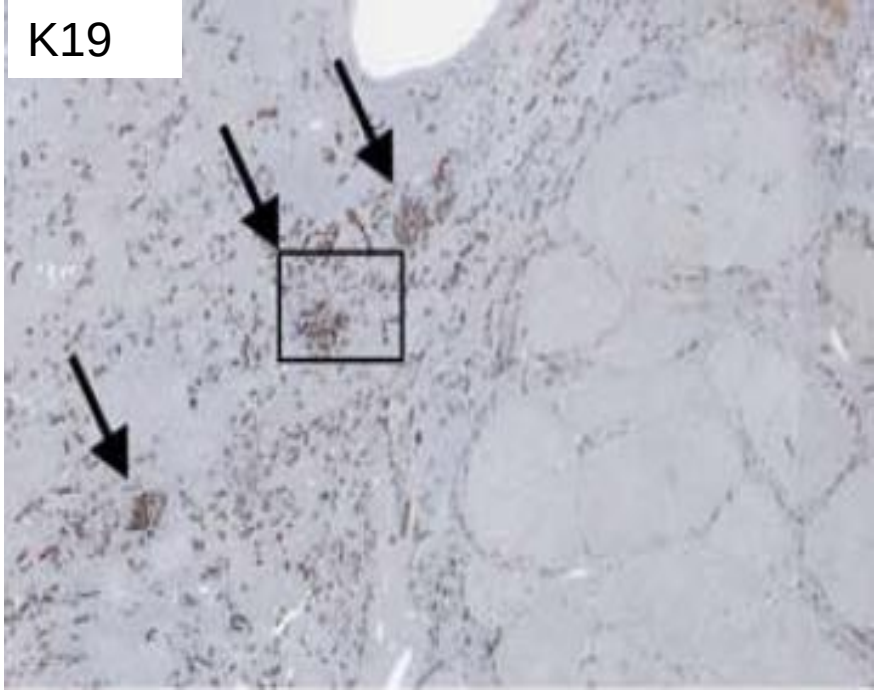
Ashley E. Stueck and Ian R. Wanless

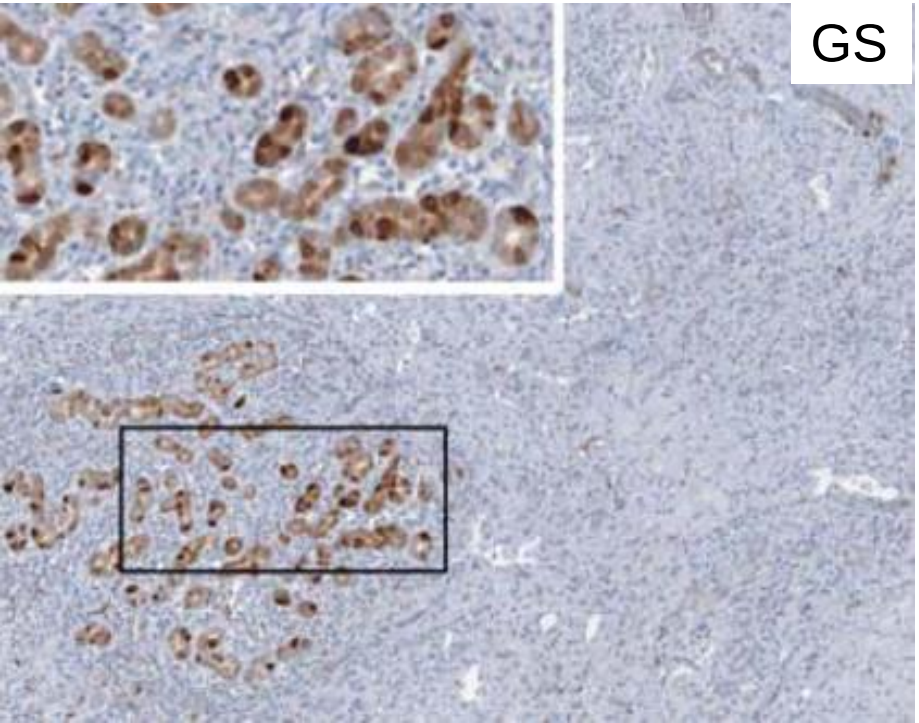


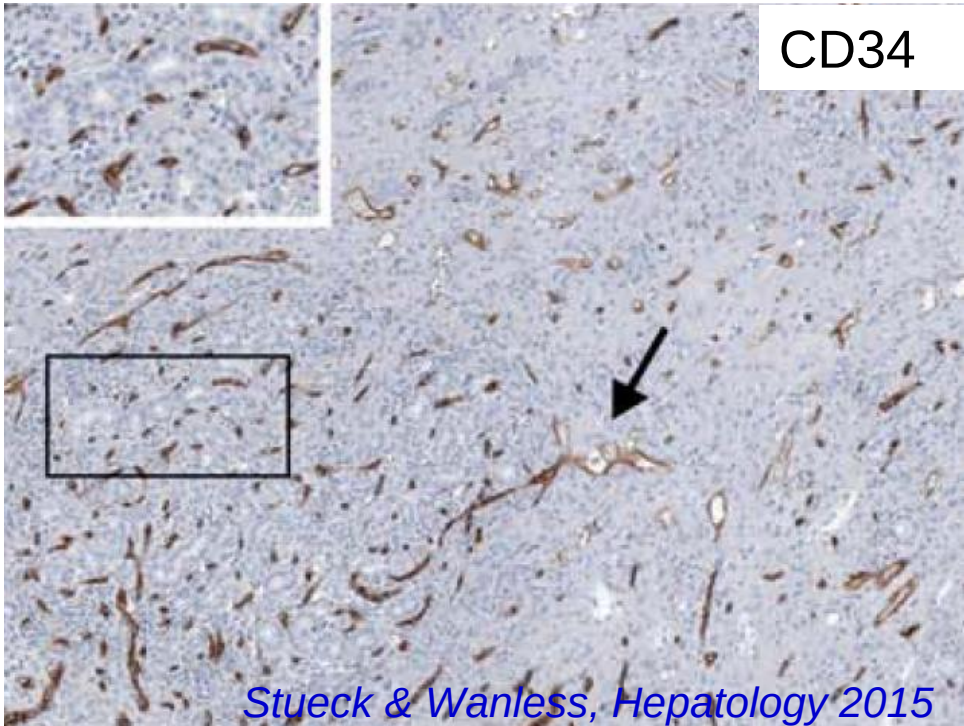


Falkowski et al, J Hepatology 2003

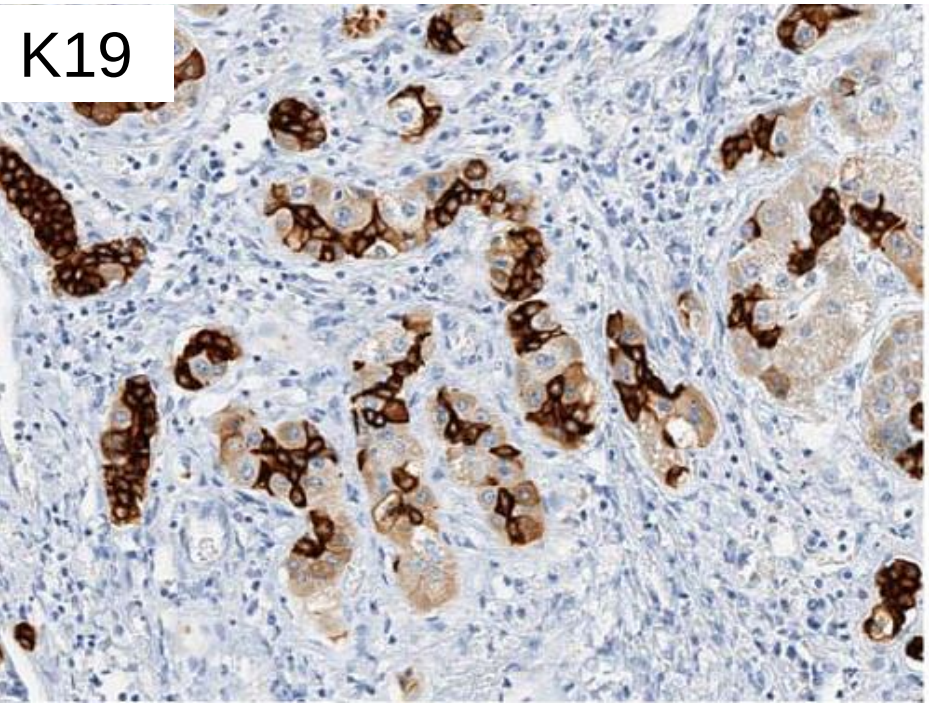


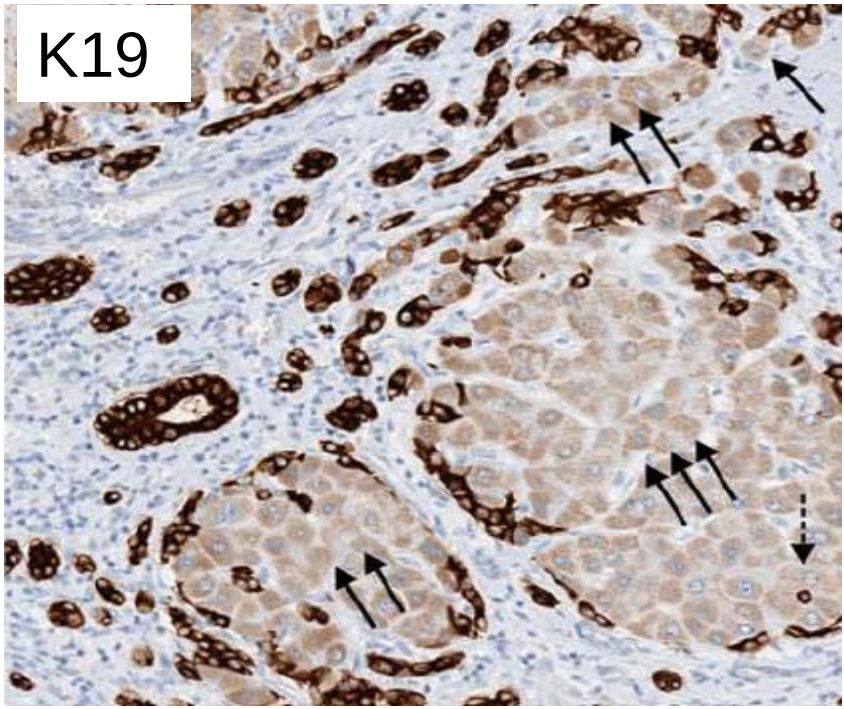


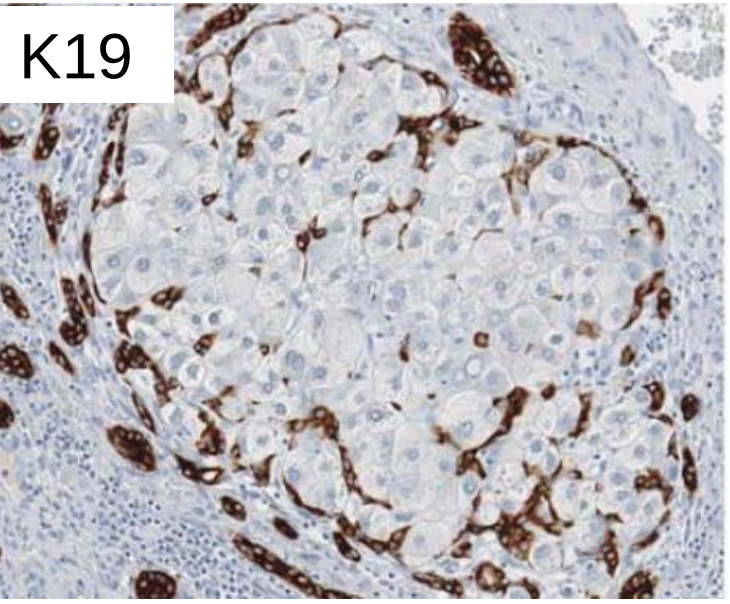


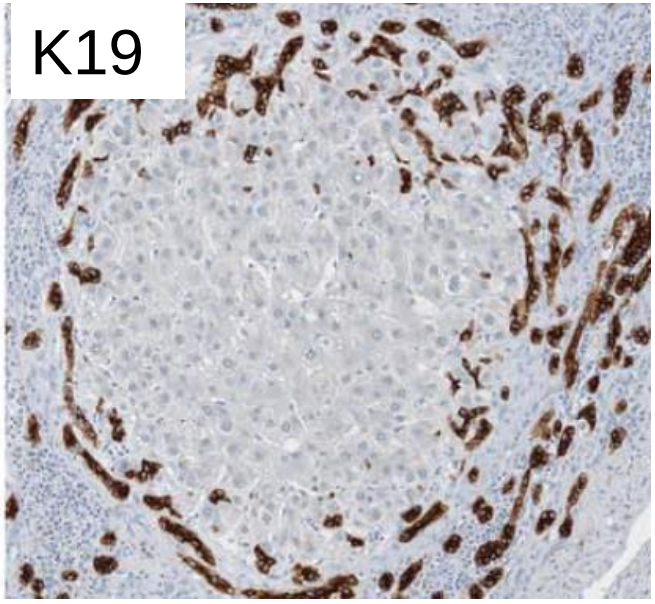


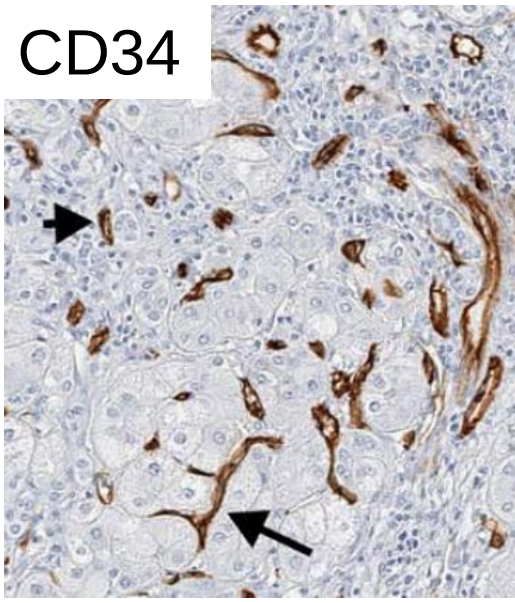
Stueck & Wanless, Hepatology 2015



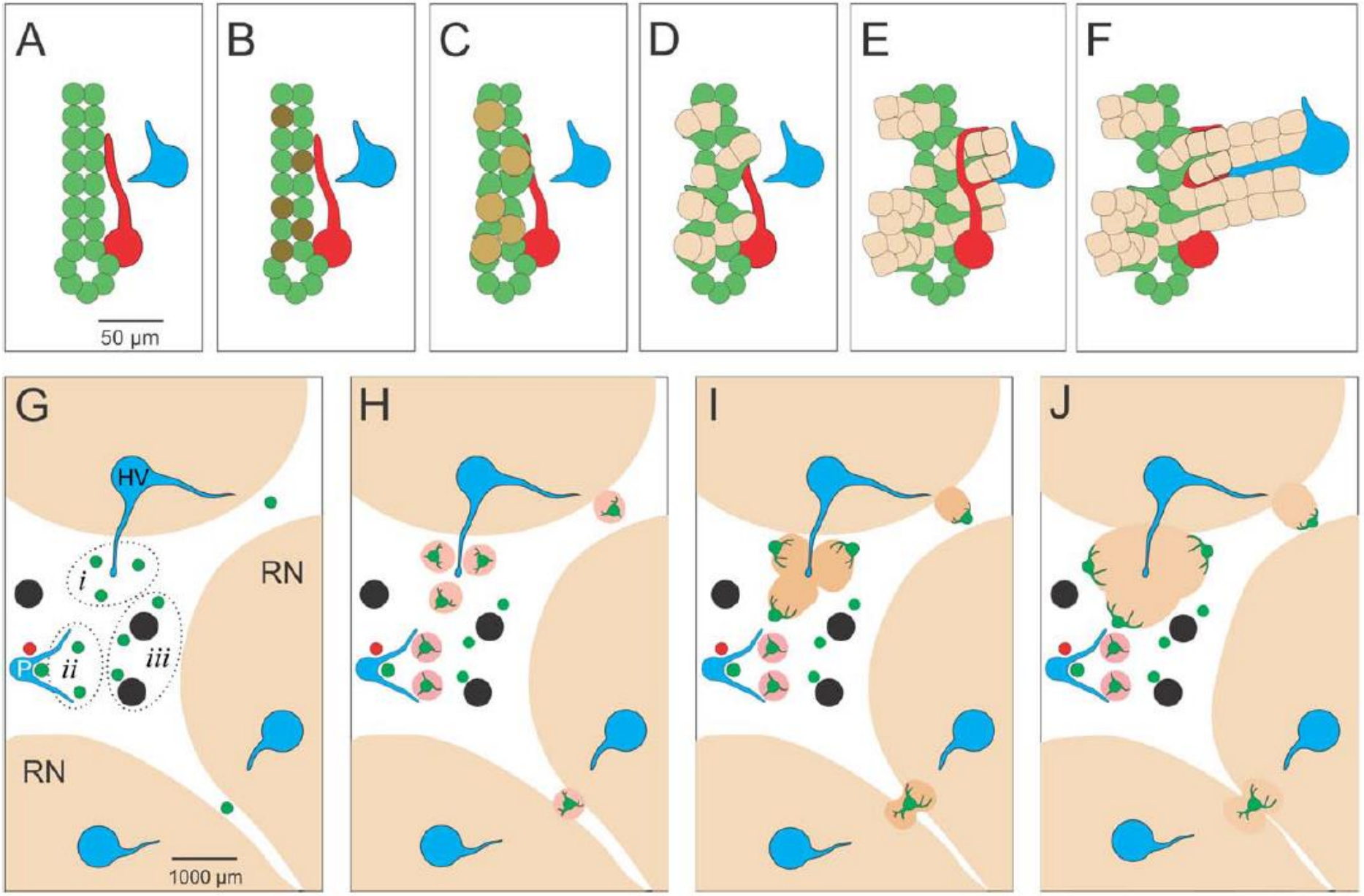




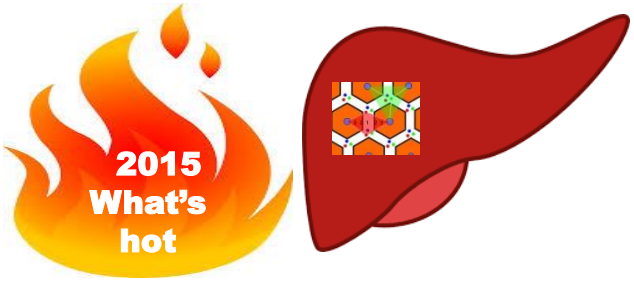




Stueck & Wanless, Hepatology 2015



Stueck & Wanless, Hepatology 2015



- **Chronic liver disease**
  - Repair in Cirrhosis
  - **Autoimmune Hepatitis**
  - Drug-induced liver injury
  - Biliary disease

Diagnostic scoring systems for AIH

Simplified diagnostic criteria, 2008

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		≥6: probable AIH ≥7: definite AIH

*Addition of points achieved for all autoantibodies (maximum, 2 points).

81-88% sensitivity, 97-99% specificity

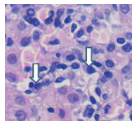
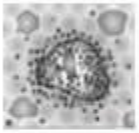
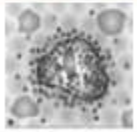
Hennes et al, Hepatology 2008

Diagnostic scoring systems for AIH

Simplified diagnostic criteria, 2008

Variable	Cutoff	Points

Histologic component of the simplified criteria for the diagnosis of AIH

Histologic Category	Description	Points
Typical    	Includes interface hepatitis, lymphocytic or lymphoplasmacytic infiltrates in portal tracts extending into the lobule, emperipolesis, and hepatocyte rosette formation	2
Compatible 	Chronic hepatitis with lymphocytic infiltration without all the features considered typical	1
Atypical	Includes evidence of another diagnosis	0

hepatitis

≥6: probable AIH
≥7: definite AIH

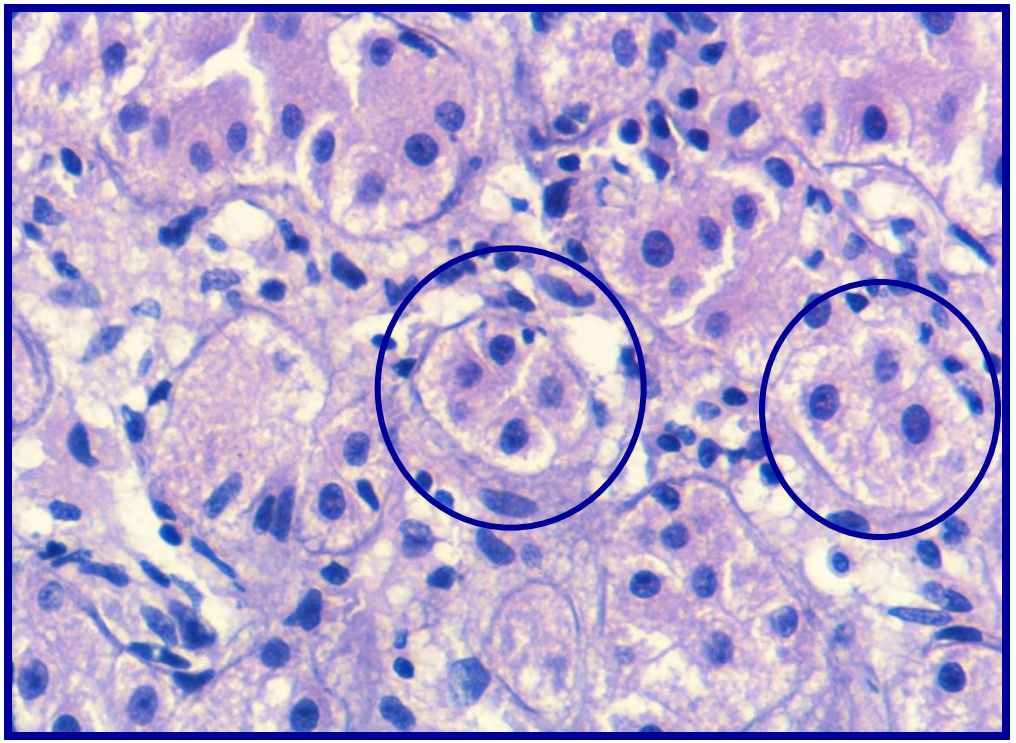
*Addition of points achieved for all autoantibodies (maximum, 2 points).

Hennes et al, Hepatology 2008

Autoimmune hepatitis (AIH)

Other typical (but non-specific) histological features

- hepatocellular rosettes



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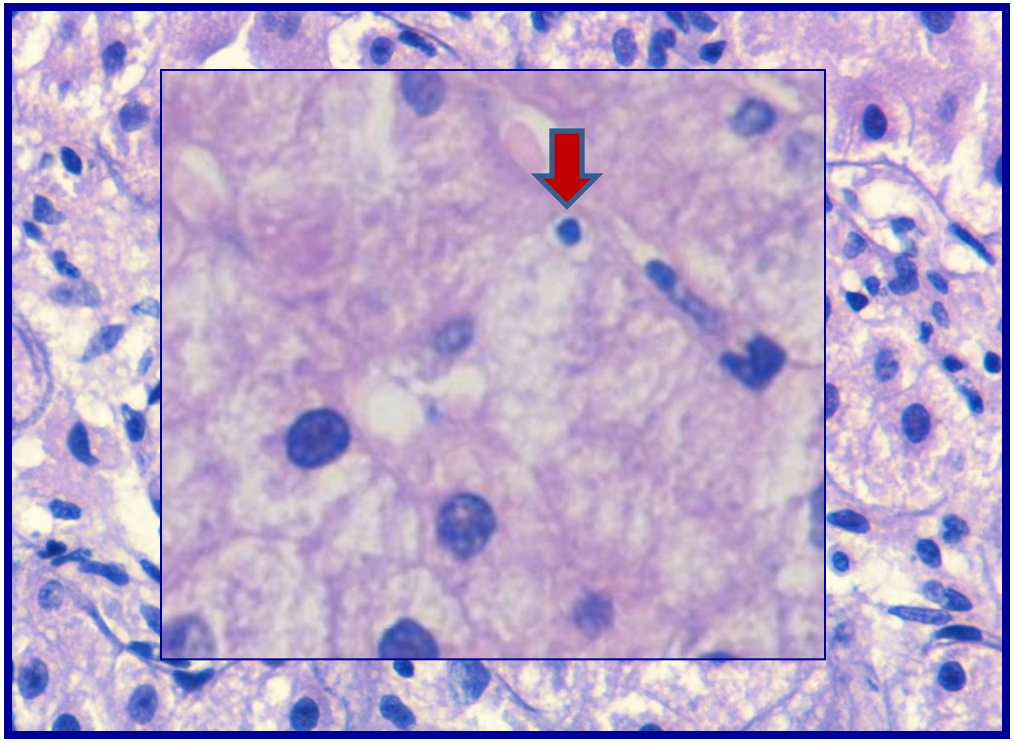
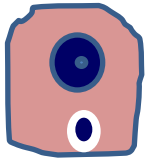


- emperipolesis
  (presence of inflammatory cell/s within hepatocytes)



Histological predictors of AIH

Histopathology

Histopathology 2015, **66**, 351–362. DOI: 10.1111/his.12558

Assessment of the histopathological key features in autoimmune hepatitis

Ynto S de Boer,[1] Carin M J van Nieuwkerk,[1] Birgit I Witte,[2] Chris J J Mulder,[1] Gerd Bouma[1] & Elisabeth Bloemena[3]

[1]*Department of Gastroenterology and Hepatology,* [2]*Department of Epidemiology and Biostatistics, and* [3]*Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands*

Histological predictors of AIH

Table 5. Univariate and multivariate logistic regression analysis on 'typical' histological autoimmune hepatitis (AIH) features

	Probable + definite AIH (IAIHG score of ≥10)			Definite AIH (IAIHG score of ≥15)		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
1999 and 2008 criteria (fixed model)						
 Interface hepatitis (≥2)	1.5	0.5–4.9	0.5	2.1	0.5–8.4	0.3
 Plasma cells (≥2)	1.4	0.5–3.6	0.5	1.2	0.4–3.4	0.8
Rosettes (≥2)	2.9	1.2–7.0	0.02	3.5	1.3–9.1	0.01
Emperipolesis	2.2	0.8–6.4	0.13	3.0	0.9–9.8	0.07
1999 and 2008 criteria (stepwise selection)						
 Rosettes (≥2)	3.0	1.2–7.2	0.02	3.6	1.4–9.5	<0.01
 Emperipolesis	3.0	1.2–7.5	0.02	4.0	1.4–11.7	0.01

Definite AIH n=45, chronic viral hepatitis n=56

de Boer, Histopathology 2015

Emperipolesis and rosettes are the only significant independent predictors of AIH in adult patients with chronic hepatitis patients

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

European Association for the Study of the Liver*

Journal of Hepatology **2015** vol. 63 | 971–1004

15. Histological demonstration of hepatitis is a prerequisite for the diagnosis of AIH and needs to be part of the initial diagnostic work-up **(II-2)**

- **Chronic liver disease**
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Drug-induced liver injury (DILI)

- Idiosyncratic DILI is an important cause of clinically significant liver injury that is associated with a **10% 6-month mortality**

- Little is known about the long-term outcomes of DILI patients including the evolution of liver histology

Persistent Liver Biochemistry Abnormalities Are More Common in Older Patients and those With Cholestatic Drug Induced Liver Injury

The American Journal of GASTROENTEROLOGY VOLUME 110 | OCTOBER 2015 www.amjgastro.com

Robert J. Fontana, MD[1], Paul H. Hayashi, MD[2], Huiman Barnhart, PhD[3], David E. Kleiner, MD, PhD[4], K. Rajender Reddy, MD[5], Naga Chalasani, MD[6], William M. Lee, MD[7], Andrew Stolz, MD[8], Thomas Phillips, MS[3], Jose Serrano, MD, PhD[9] and Paul B. Watkins, MD[2] for the DILIN Investigators

Long-term outcomes of DILI

- Amongst 99 patients with probable DILI, 75% had laboratory evidence of persistent liver injury at 12 months after DILI onset

- Older patient age and a cholestatic lab profile at DILI onset were associated with a greater likelihood of persistent liver injury during follow-up.

Table 3. Histological and clinical features of DILI patients with follow-up liver biopsies

Age/ sex	Primary implicated (days of therapy)	*R* value at DILI onset	Histological diagnosis on 1st biopsy	Time between biopsies (days)	*R* value closest to second biopsy	Histological diagnosis on f/u biopsy	[a]Stage at 1st/ 2nd	Initial duct loss/ ductular reaction	Duct loss/ductular reaction on F/U
53 F	Trimethoprim-sulfamethoxasole	1.9	Chronic cholestasis	490	1.0	Chronic cholestasis	0/0	No/no	No/no
38 F	Celecoxib	8.4	Cholestatic hepatitis	382	0.7	Chronic cholestasis	0/0	No/no	No/no
20 F	Azithromycin	7.3	Acute hepatitis	283	4.5	Chronic cholestasis	0/2	No/no	Yes/no
45 M	Azithromycin	62.6	Chronic hepatitis	392	18.6	Chronic hpatitis	1/1	No/no	No/no
58 F	Ultravist vitamin preparation	0.42	Steatohepatitis+ Cholestasis	246	27.3	Steatohepatitis+ cholestasis	4/6	No/yes	No/yes
37 F	Tamoxifen	17.0	Steatohepatitis	675	1.3	Steatohepatitis	3/0	No/no	No/no
20 F	Olanzapine	1.6	Cholestatic hepatitis	633	1.8	Chronic cholestasis	0/4	No/no	Yes/yes
52 M	Metoclopramide	1.8	Cholestatic hepatitis	404	0.7	Chronic cholestasis	1/2	No/no	Yes/yes
54 F	Omeprazole	2.5	Cholestatic hepatitis	331	1.0	Chronic cholestasis	0/2	No/no	Yes/no
64 M	Amoxicillin-clavulanate	6.8	Cholestatic hepatitis	183	0.8	Chronic cholestasis	0/2	No/no	No/yes
56 M	Gluco-ease Plus	1.1	Chronic hepatitis	522	0.2	Chronic cholestasis	0/2	No/no	Yes/no
70 F	Lansoprazole	2.4	Cholestatic hepatitis, granulomas	217	3.7	Duct paucity with cholestasis	0/1	No/no	Yes/no

- n=12 DILI patients with follow-up (f/u) biopsies (mean time interval 397 days)
- chronic cholestasis (9/12): most common pattern of liver injury on f/u biopsy
- fibrosis progression 8/12
- bile duct loss 7/12

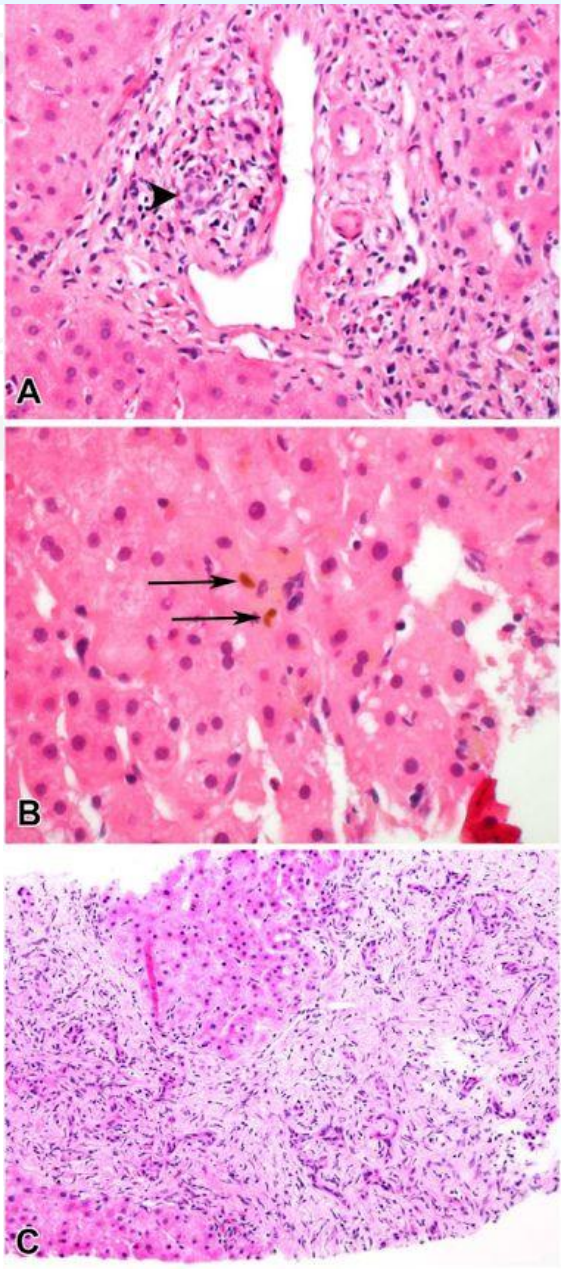
→ most had cholestatic hepatitis in 1st biopsy

Long-term outcomes of DILI

- Amongst 99 patients with probable DILI, 75
evidence of persistent liver injury at 12 mon
onset

- Older patient age and a cholestatic lab prof
were associated with a greater likelihood of
injury during follow-up.

- Serial liver biopsies demonstrate evidence of progressive liver injury with chronic cholestasis, bile duct loss and progressive hepatic fibrosis in >2/3 of the patients



DILI in Chronic Hepatitis C patients

- Major advances in CHC treatment with oral direct acting antivirals (DAA)
  - sofosbuvir - SOF *(NS5B inhibitor)*
  - daclatasvir - DCV *(NS5A inhibitor)*
  - ledispasvir - LDV *(NS5A inhibitor)*

- Combination of SOF, LDV or DCV +/- ribavirin (phase 3 studies) for 12 or 24 weeks ➡ sustained virological response (SVR) >95%

- No or very rare serious adverse effects in HCV genotype 1 infected patients

Charlton M, Gastroenterology 2015
Alqahtani S, Hepatology 2015

Case Report

EASL JOURNAL OF HEPATOLOGY 2015

Liver toxicity associated with sofosbuvir, an NS5A inhibitor and ribavirin use

Jessica K. Dyson[1,2,*], John Hutchinson[3], Laura Harrison[3], Olorunda Rotimi[4], Dina Tiniakos[2,5], Graham R. Foster[6], Mark A. Aldersley[3], Stuart McPherson[1,2]

Review

Drug-Induced Liver Injury

Kurt Fisher, MD, PhD; Raj Vuppalanchi, MD; Romil Saxena, MBBS, FRCPath

Arch Pathol Lab Med—Vol 139, July 2015:876-887

United States National Library of Medicine

NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

LiverTox

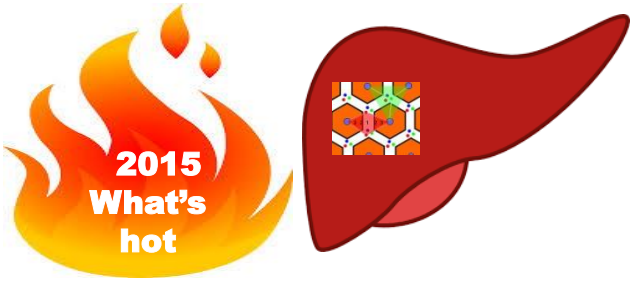
Clinical and Research Information on Drug-Induced Liver Injury

http://livertox.nih.gov/

Free database of drugs linked to liver injury launched in 2012

Up-to-date and accurate information and case registry of DILI

>1000 medications, herbals and dietary supplements.



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HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

CORRESPONDENCE

Wahl, Hepatology 2015

Primary Biliary "Cirrhosis": Time to Replace a Misnomer

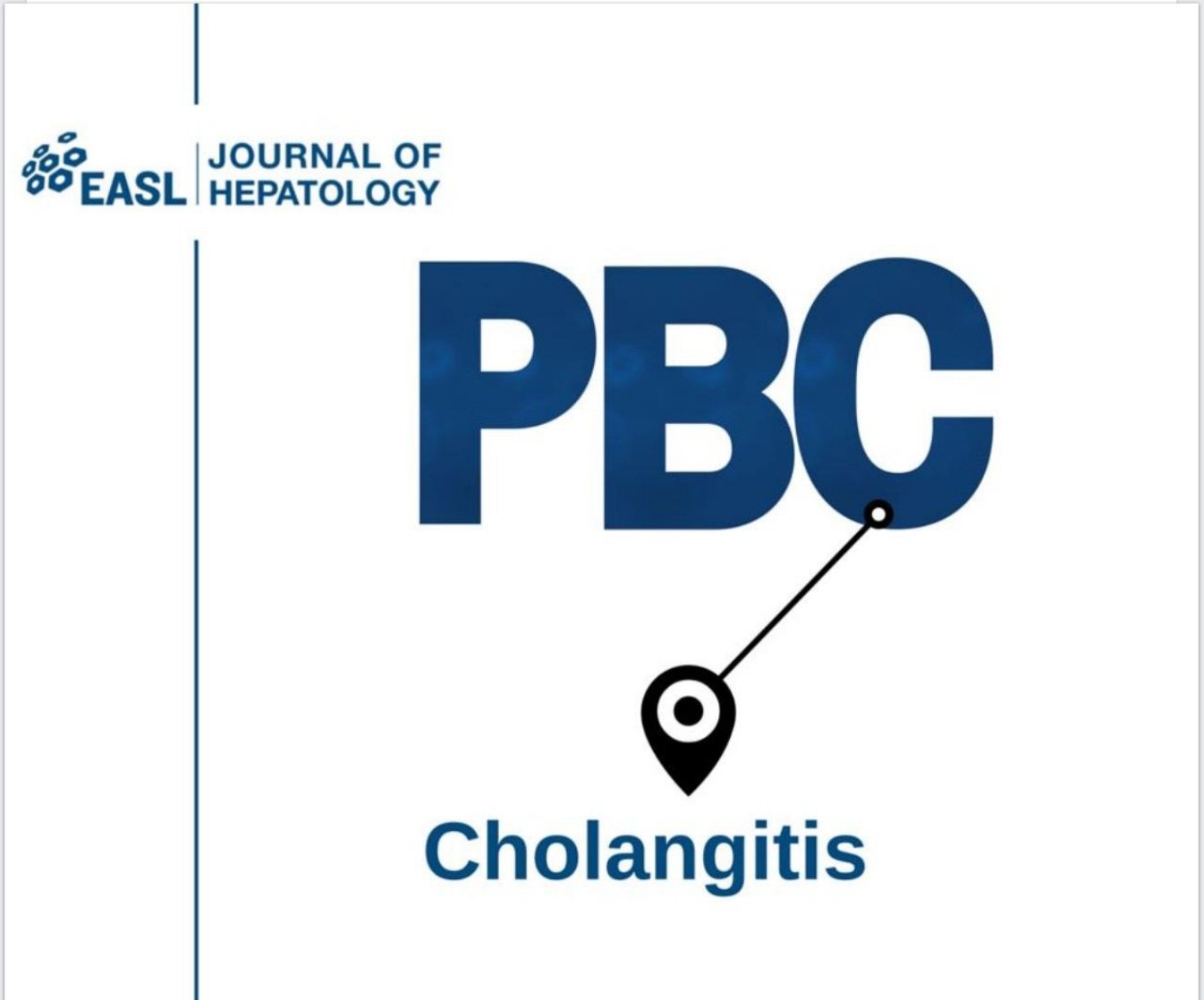
this diagnosis term has become a misnomer, as Rubin et al. called it already in 1965,[2] and should be replaced.

Rubin E, Schaffner F, Popper H. Primary biliary cirrhosis. Chronic non-suppurative destructive cholangitis. Am J Pathol 1965;46:387-407.

EASL - European Association for the Study of the Liver

September 15, 2015

65 years later the community has changed the nomenclature for #**PBC**: From ‘cirrhosis’ to ‘cholangitis’
http://buff.ly/1Nti6mY



Gastroenterology 2015;■:1–3

AGA SECTION

Changing Nomenclature for PBC: From 'Cirrhosis' to 'Cholangitis'

Ulrich Beuers,[1] M. Eric Gershwin,[2] Robert G. Gish,[3] Pietro Invernizzi,[4] David E. J. Jones,[5] Keith Lindor,[6] Xiong Ma,[7] Ian R. Mackay,[8] Albert Parés,[9] Atsushi Tanaka,[10] John M. Vierling,[11] and Raoul Poupon[12]

[1]Department of Gastroenterology & Hepatology and Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [2]Division of Rheumatology, Allergy and Clinical Immunology, The University of California School of Medicine, Davis, CA, USA; [3]Department of Medicine, Division of Gastroenterology & Hepatology, Stanford University, Stanford, CA, USA; [4]Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Rozzano (Milan), Italy; [5]Institute of Cellular Medicine, Ne[illegible]stle University, Newcastle upon Tyne, UK; [6]College of Health Solutions, Arizona State University, Phoenix, AZ, USA; [7][illegible] Gastroenterology & Hepatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai [illegible] Disease, Shanghai, China; [8]Department of Biochemistry & Molecular Biology, Monash University, Clayto[illegible]er Unit, Hospital Clinic, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain; [10]Depa[illegible]ity School of Medicine, Tokyo, Japan; [11]Departments of Medicine and Surgery, Baylor C[illegible] Reference Center for Inflammatory Biliary Diseases, Service d'Hépat[illegible]

Primary Biliary Cholangitis

Novel histological features in Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis *Am J Clin Pathol* April 2015;143:505-513

Detailed Histologic Assessment and Integration Using Bioinformatics Highlights Arterial Fibrointimal Hyperplasia as a Novel Feature

Gonzalo Carrasco-Avino, MD,[1] Thomas D. Schiano, MD,[2] Stephen C. Ward, MD, PhD,[1] Swan N. Thung, MD,[1] and M. Isabel Fiel, MD[1]

From the [1]Department of Pathology and [2]Division of Liver Diseases and Recanati-Miller Transplant Institute, Icahn School of Medicine at Mount Sinai, New York, NY.

- **36 PSC** vs 10 CHC and 10 PBC explant livers
- Demographic, gross and histological variables
- Integrative bioinformatics approach and hierarchical clustering analysis

Novel histological features in Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis *Am J Clin Pathol* April 2015;143:505-513

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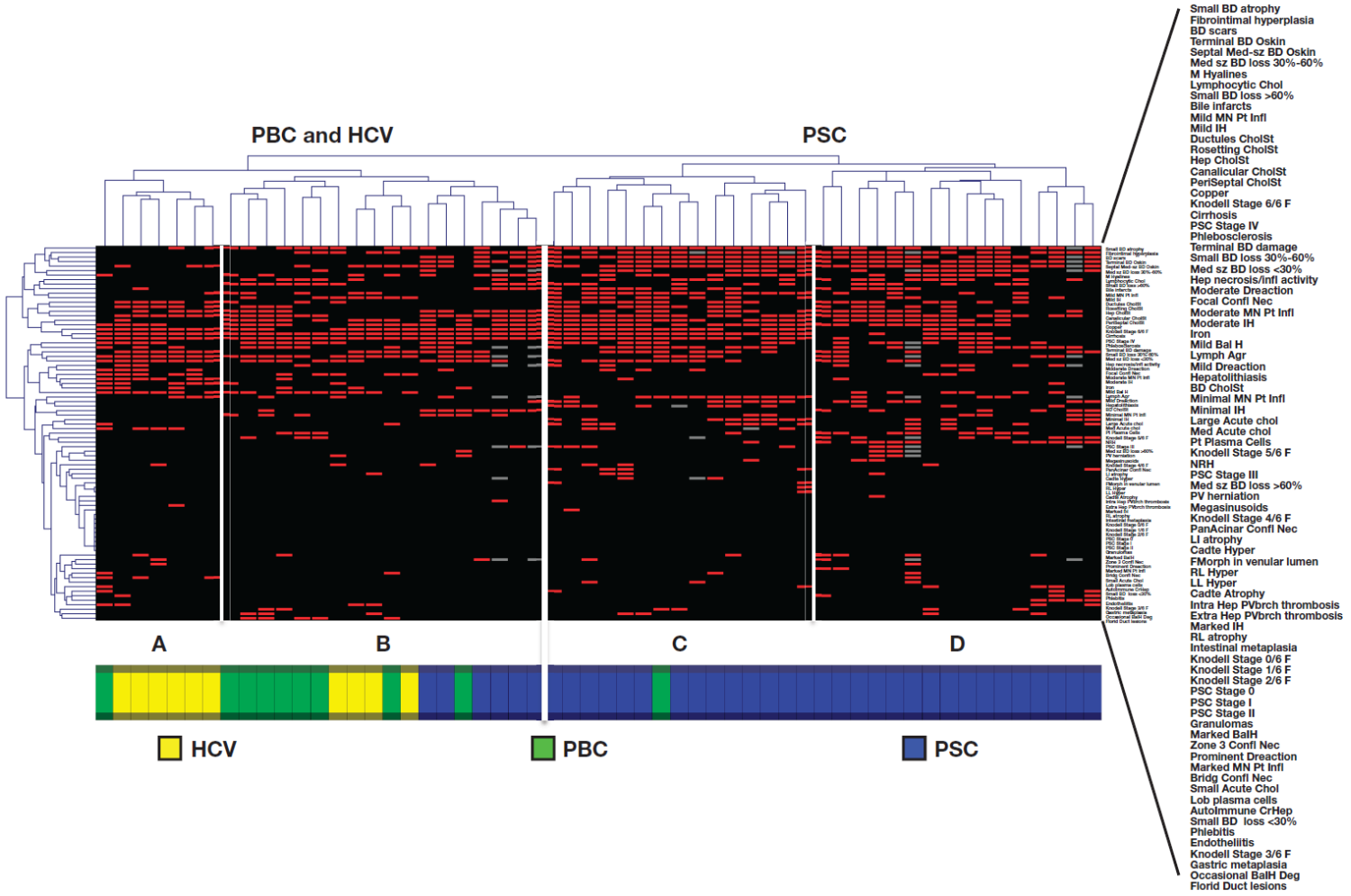

Novel histological features in Primary Sclerosing Cholangitis (PSC)

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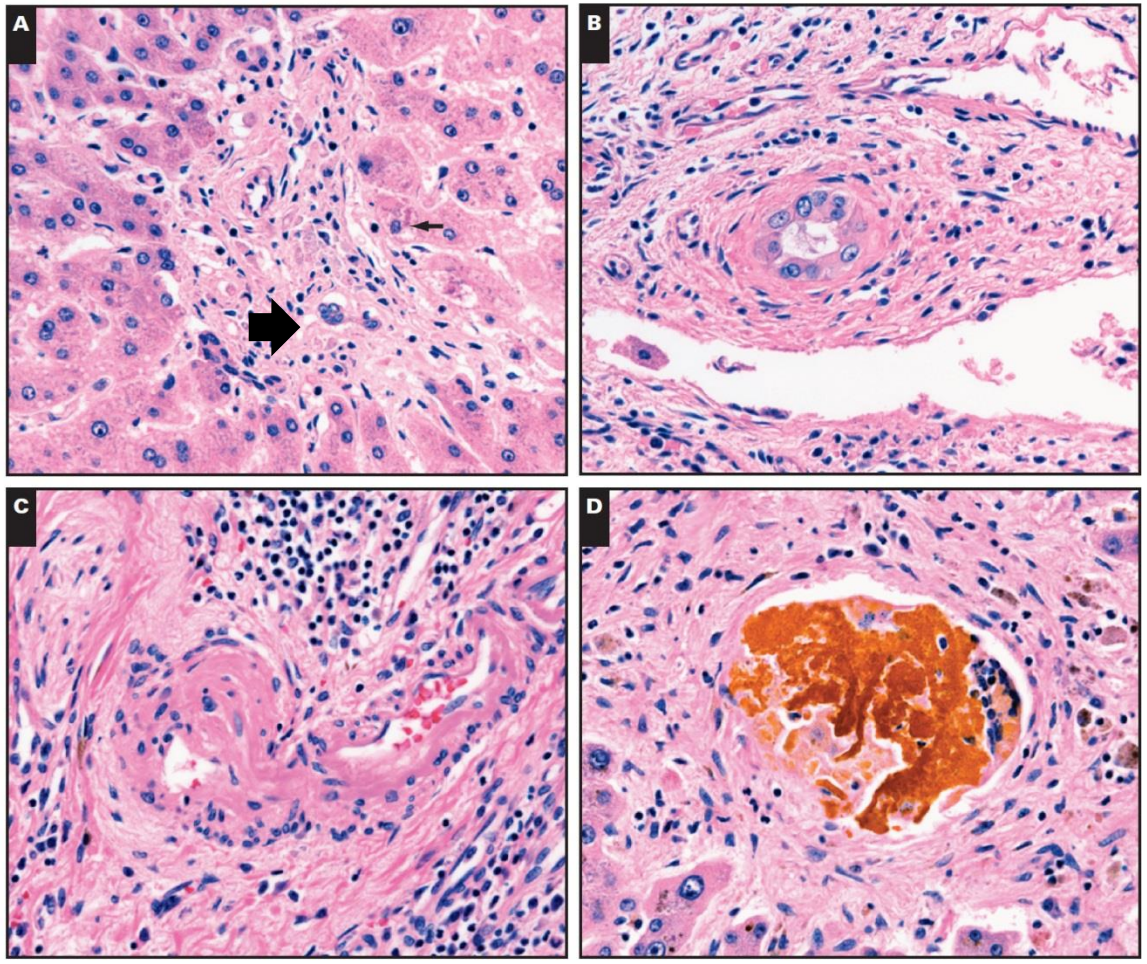


Small-size BD "onion-skin" fibrosis

Arterial fibrointimal hyperplasia

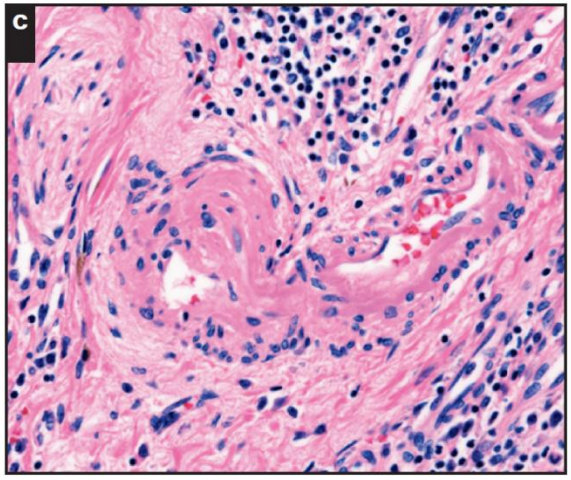
Novel histological features in Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis *Am J Clin Pathol* April 2015;143:505-513

Detailed Histologic Assessment and Integration Using Bioinformatics Highlights Arterial Fibrointimal Hyperplasia as a Novel Feature

? Primary or secondary vasculopathy in PSC => initial and/or subsequent damage in BD vascular supply => secondary BD injury and loss

Arterial fibrointimal hyperplasia



Fiel MI, Virchows Arch 2015; 466:143-9

Novel histological features in Primary Sclerosing Cholangitis (PSC)

Histopathology

Histopathology 2015 DOI: 10.1111/his.12857

Bile duct basement membrane thickening in primary sclerosing cholangitis

Richard Colling,* Clare Verrill,* Eve Fryer, Christiana Kartsonaki,[1] Lai M Wang, Roger Chapman,[2] Naayil Rajabally[3] & Kenneth Fleming[2]

Cellular Pathology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK, [1]Department of Oncology, University of Oxford, Oxford, UK, [2]Medical Sciences Division, University of Oxford, Oxford, UK, and [3]Department of Hepatology, Oxford University Hospitals NHS Trust, Oxford, UK

Novel histological features in Primary Sclerosing Cholangitis (PSC)

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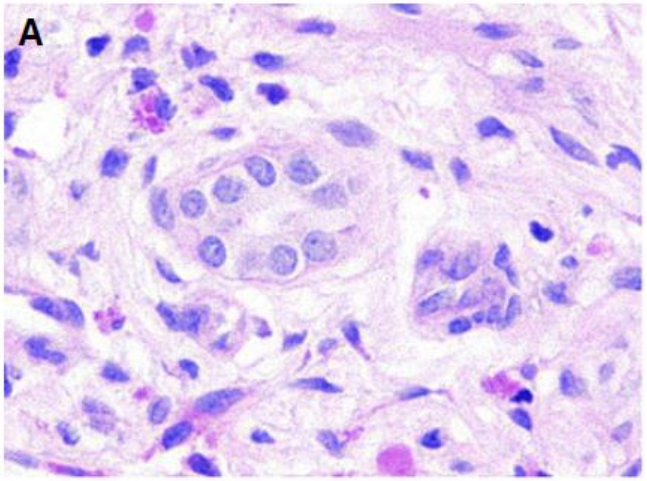
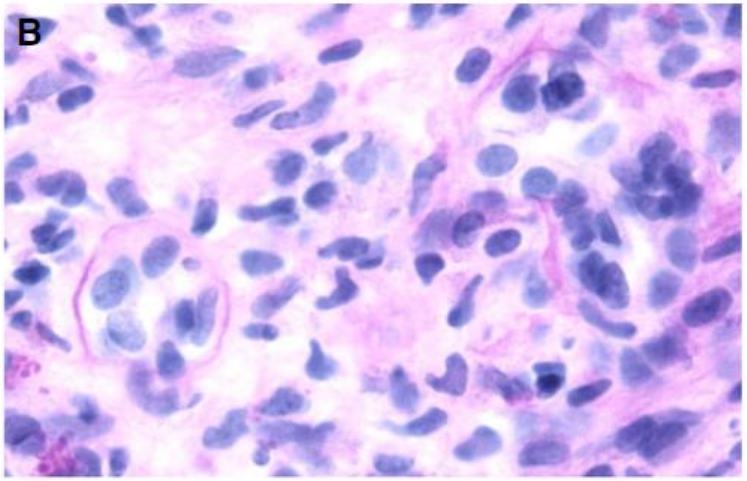
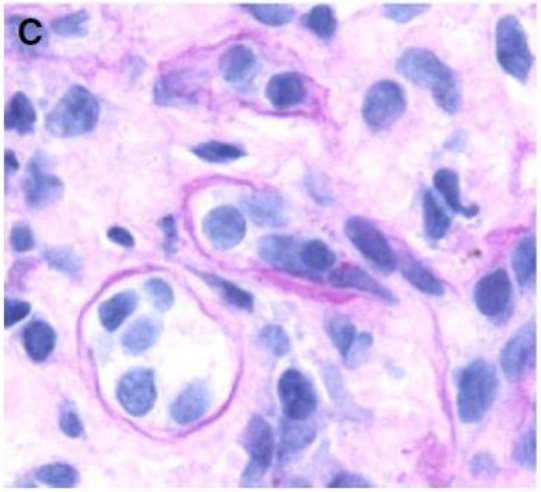
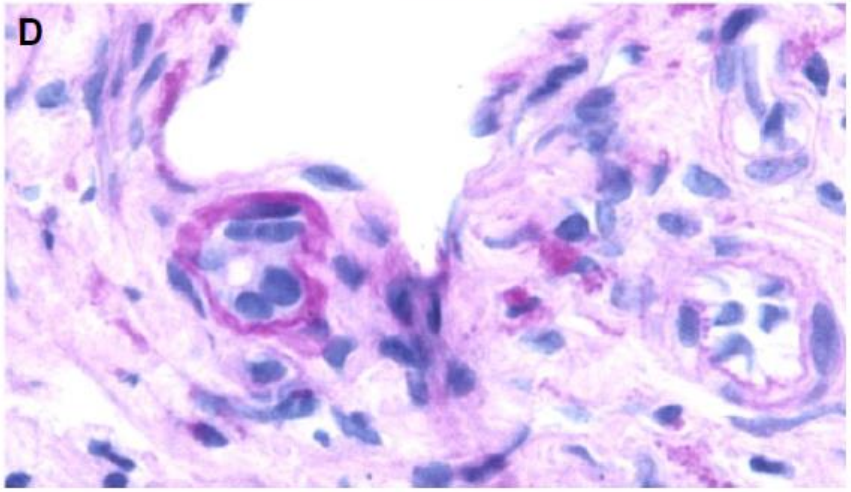




G1

G2





G3

- 128 medical liver core biopsies
- H-E and D-PAS stain blinded review by two histopathologists
- Basement membrane thickening assessed as G0-G3.

Novel histological features in Primary Sclerosing Cholangitis (PSC)

Histopathology

Histopathology 2015 DOI: 10.1111/his.12857

Bile duct basement membrane thickening in primary sclerosing cholangitis

Bile duct basement membrane thickening (BD BMT)

- reliable marker of PSC
- good inter-observer correlation
- may represent a reaction to recurrent biliary injury and regeneration
- any BD BMT thickening warrants alerting the clinician to a possible differential diagnosis of PSC
- G2/G3 BMT is highly suggestive of PSC

Nodular regenerative hyperplasia (NRH) post-chemotherapy

Three main forms of chemotherapy associated liver injury (CALI)

- ✓ steatosis
- ✓ steatohepatitis
- ✓ sinusoidal obstruction syndrome (SOS)/toxic microvascular injury
  - sinusoidal dilatation
  - THV fibrosis
  - zone 3 sinusoidal fibrosis
  - peliosis
  - **NRH ⇨ the most dangerous form of CALI**

- SOS has been associated with increased postoperative morbidity
- steatohepatitis has even been associated with higher 90-day mortality rates

Nodular regenerative hyperplasia (NRH) post-chemotherapy

Ann Surg Oncol (2015) 22:4149–4157
DOI 10.1245/s10434-015-4533-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

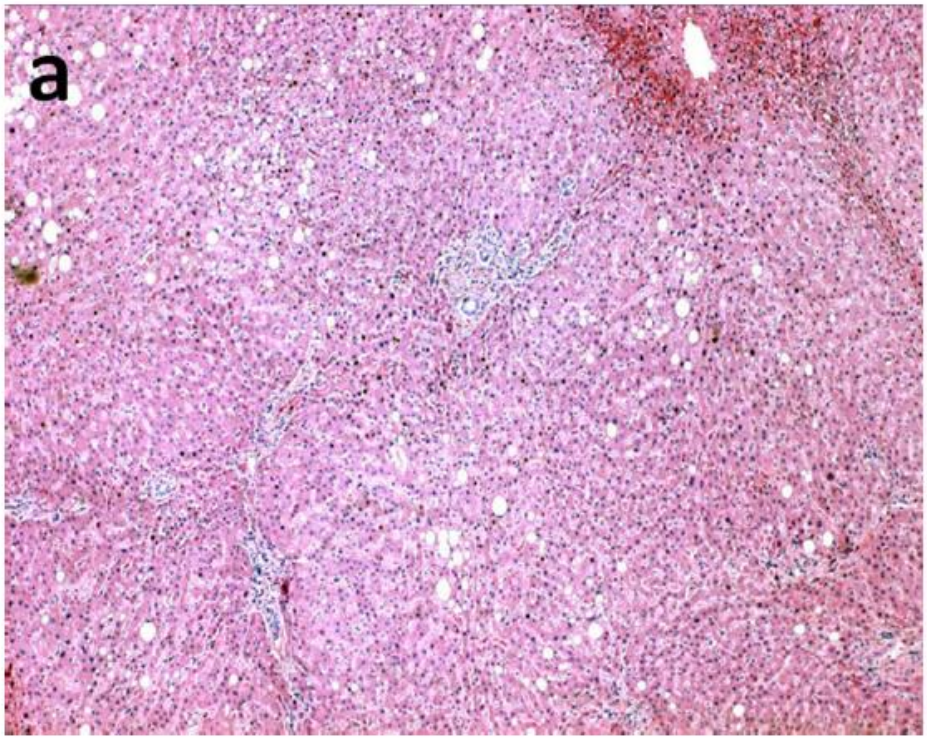
CrossMark

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Nodular Regenerative Hyperplasia in Patients Undergoing Liver Resection for Colorectal Metastases After Chemotherapy: Risk Factors, Preoperative Assessment and Clinical Impact

Luca Viganò, MD[1,2], Laura Rubbia-Brandt, MD[3,6], Giovanni De Rosa, MD[4], Pietro Majno, MD[5,6], Serena Langella, MD[2], Christian Toso, MD, PhD[5,6], Gilles Mentha, MD[5,6], and Lorenzo Capussotti, MD[2]

n=406



Reticulin

Nodular regenerative hyperplasia (NRH) post-chemotherapy

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- **18% NRH, 68% sinusoidal dilatation, 24% steatosis, 10% SH**
- NRH was the most severe form of chemotherapy-related liver injury
- NRH increases the risk of post-op liver failure in resections for colorectal metastases (14% for grade 2/3 NRH)
- NRH incidence : ↑ by oxaliplatin, ↓ by bevacizumab

PLOS ONE DOI:10.1371/journal.pone.0120299 June 8, 2015

RESEARCH ARTICLE

Diagnosing Nodular Regenerative Hyperplasia of the Liver Is Thwarted by Low Interobserver Agreement

Bindia Jharap[1]*, Dirk P. van Asseldonk[1], Nanne K. H. de Boer[1], Pierre Bedossa[2], Joachim Diebold[3], A. Mieke Jonker[4], Emmanuelle Leteurtre[5], Joanne Verheij[6], Dominique Wendum[7], Fritz Wrba[8], Pieter E. Zondervan[9], Jean-Frédéric Colombel[10], Walter Reinisch[11], Chris J. J. Mulder[1], Elisabeth Bloemena[12], Adriaan A. van Bodegraven[1,13], NRH-pathology Investigators[¶]

- 48 NRH reviewed by 7 liver pathologists
- needle biopsies and wedge resection specimens (n=5)
- H-E, reticulin & Sirius red or Masson trichrome stains

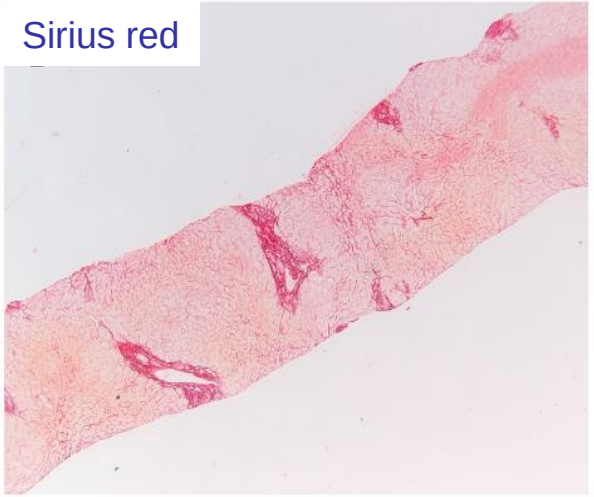
PLOS ONE | DOI:10.1371/journal.pone.0120299 June 8, 2015

Table 3. Diagnosis of nodular regenerative hyperplasia on re-examination of all 48 liver specimen

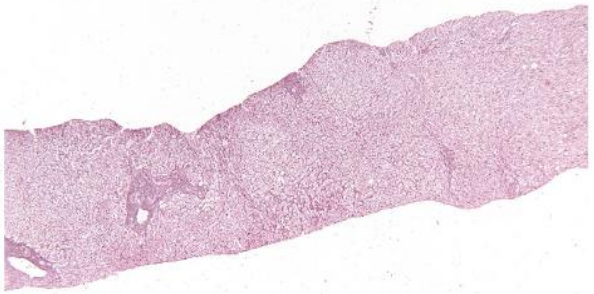
Pathologist	1	2	3	4
Definite NRH	38%	23%	13%	35%
Inconclusive NRH	19%	21%	13%	27%
No NRH	44%	56%	75%	38%

Pathologist	5	6	7
Definite NRH	40%	35%	40%
Inconclusive NRH	40%	21%	13%
No NRH	21%	44%	48%

Sirius red



Reticulin



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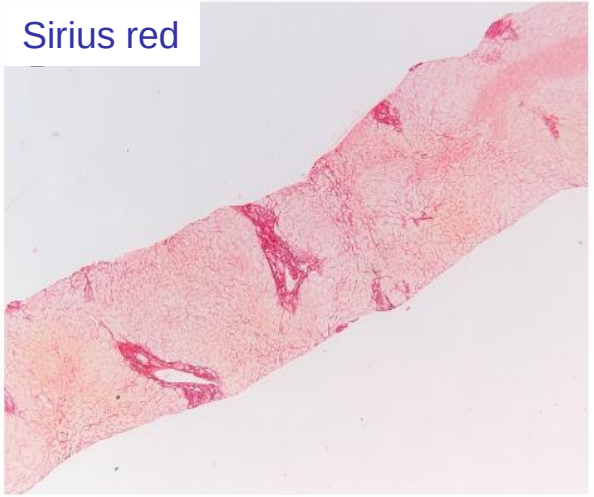

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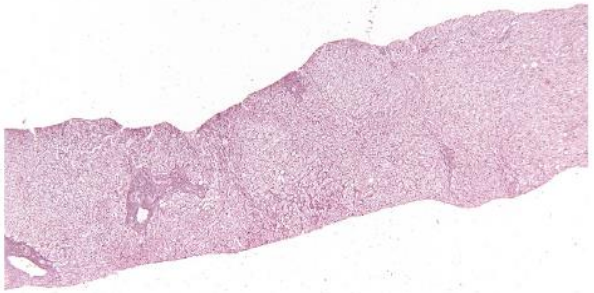

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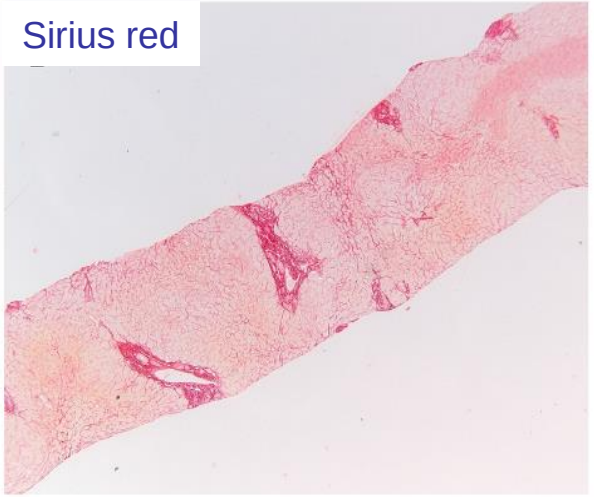
κ=0.20 poor interobserver agreement

Sirius red



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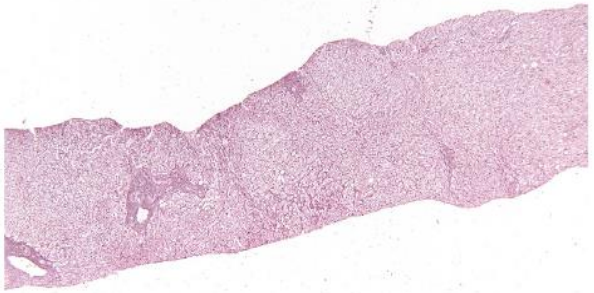

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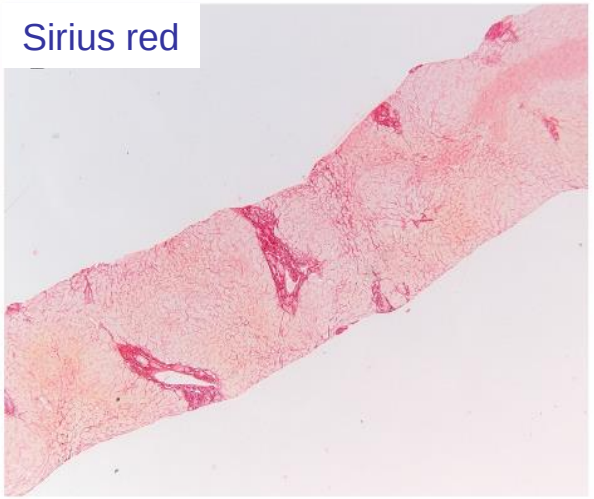
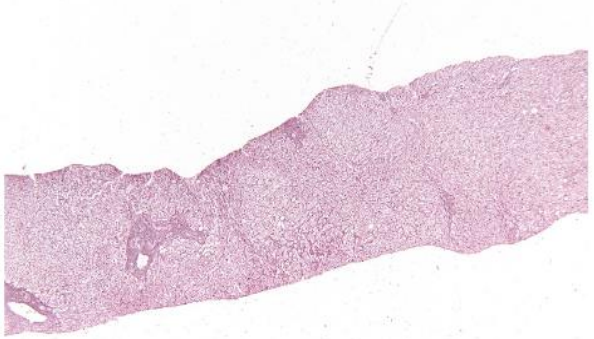


Reticulin



- review with modified criteria
- exclusion of biopsies with technical faults

κ=0.45 poor interobserver agreement

Usefulness of medical liver biopsies
An audit tool

A template for a clinico-pathological audit of medical liver biopsies

J Clin Pathol 2015;**68**:935–937

Richard Colling,[1] Eve Fryer,[1] Jeremy Cobbold,[2] Jane Collier,[2] Elena Collantes,[1] Lai Mun Wang,[1] Stefan Hubscher,[3] Judith Wyatt,[4] Kenneth Fleming[5]

- prospective questionnaire-based review of adult medical liver biopsy reporting in a large UK regional centre
- 50 consecutive liver biopsies

Usefulness of medical liver biopsies

An audit tool

Table 2 The frequency of indications* for liver biopsy from the audit of 50 cases

Indication	Frequency
?Fibrosis/cirrhosis	13 (26%)
Fatty liver disease	11 (22%)
Abnormal liver enzymes	10 (20%)
?Autoimmune hepatitis	7 (14%)
?Biliary disease	6 (12%)
?Drug reaction	5 (10%)
Viral hepatitis	4 (8%)
Alcoholic liver disease	3 (6%)
?Iron overload	3 (6%)
?Nodular regenerative hyperplasia	1 (2%)
?Wilson's disease	1 (2%)
Ascites	1 (2%)
?Transplant rejection	1 (2%)

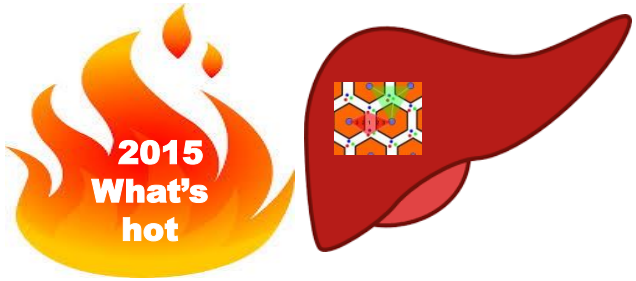
*In many cases, there was more than one indication.

Usefulness of medical liver biopsies

An audit tool

- Clinicians found liver biopsy helpful, contributing to patient management in all of the cases (96%) where biopsy was adequate size.
- Almost a third of liver biopsies result in a clinically unanticipated diagnosis.
- Around three-quarters of liver biopsies result in a change of management.

Reports which resulted in a change of management*	37/50 (74%)
Due to a diagnosis change	15/37 (41%)
Resulting treatment change	19/37 (51%)
Resulting follow-up change	31/37 (84%)



- Chronic liver disease
- **Benign liver tumours**
- Malignant tumours

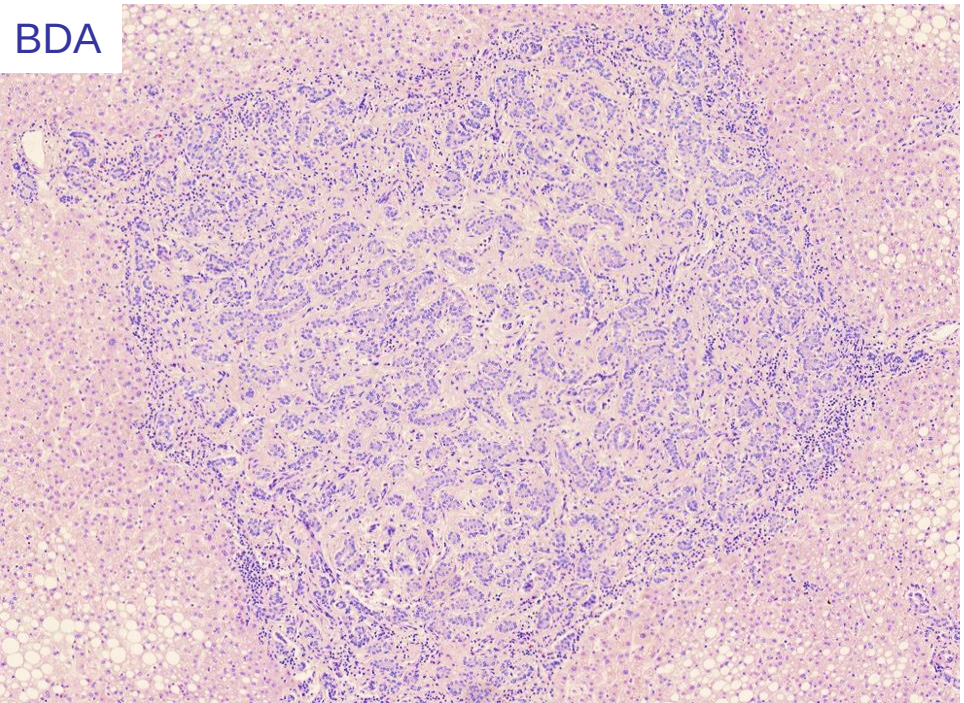
Bile duct adenoma (BDA) *VS* biliary microhamartoma (von Meyenburg complex)

- Previous reports of high prevalence of BRAF V600E mutations in BDA suggestive of neoplastic nature in contrast with previous view that they represent peribiliary gland hamartomas

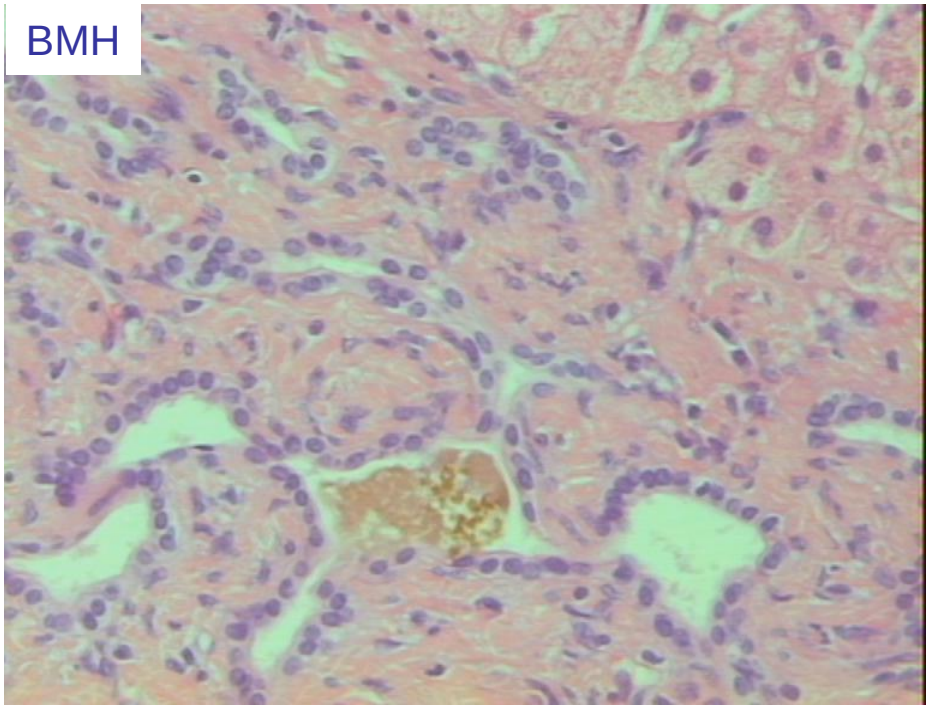
- BDA may be precursors to a subset of intrahepatic cholangiocarcinomas harbouring BRAF V600E mutations

Pujals A, Hepatology 2014; 61; 403–405.

BDA



BMH



Histopathology 2015, **67**, 562–567

SHORT REPORT

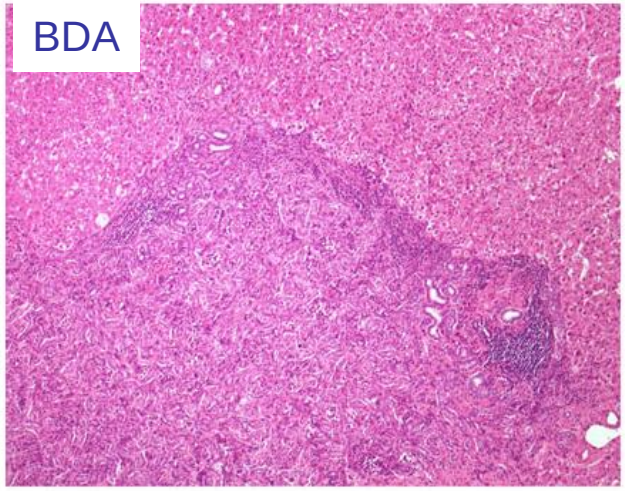
BRAF V600E mutational status in bile duct adenomas and hamartomas

Anaïs Pujals,[1,2,3] Paulette Bioulac-Sage,[4,5] Claire Castain,[4,5] Cécile Charpy,[1] Elie Serge Zafrani[1,2] & Julien Calderaro[1,2,6]

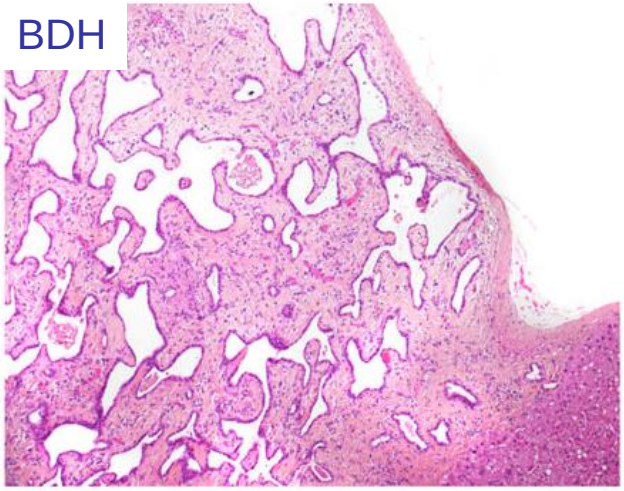
[1]*Department of Pathology, Assistance Publique-Hôpitaux de Paris, CHU Henri Mondor, Créteil, France,* [2]*Faculté de Médecine, Université Paris-Est Créteil, Créteil, France,* [3]*Inserm U955, Equipe 9, Institut Mondor de Recherche Biomédicale, Créteil, France,* [4]*Department of Pathology, CHU de Bordeaux, Pellegrin Hospital, Bordeaux, France,* [5]*Inserm, UMR-1053, Université de Bordeaux, Bordeaux, France, and* [6]*Inserm U955 Equipe 18, Institut Mondor de Recherche Biomédicale, Créteil, France*

Bile duct adenoma (BDA) *VS* bile duct microhamartoma (BDH) (von Meyenburg complex)

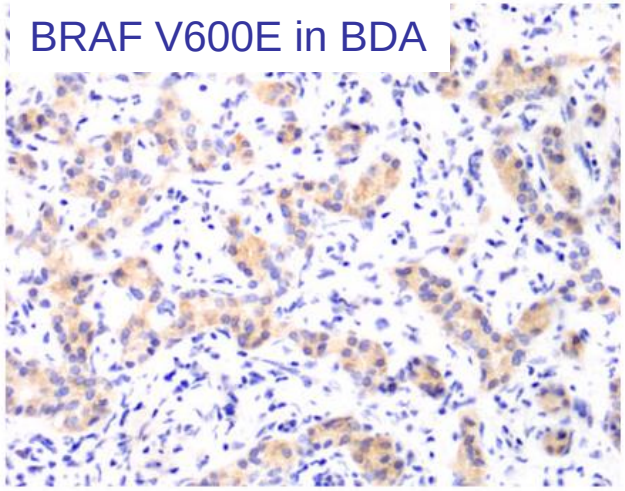
BDA



BDH



BRAF V600E in BDA



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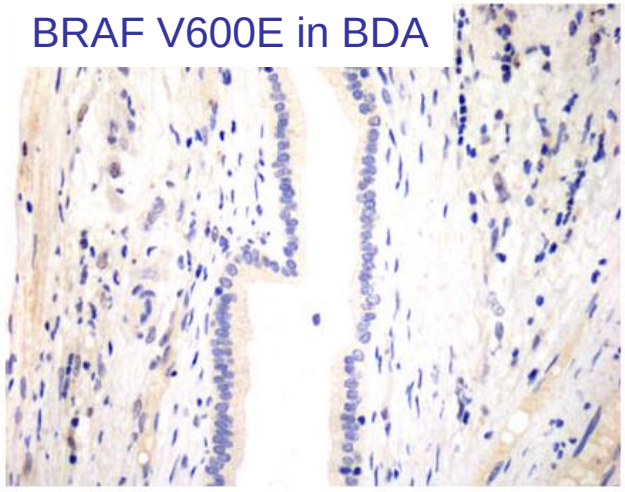
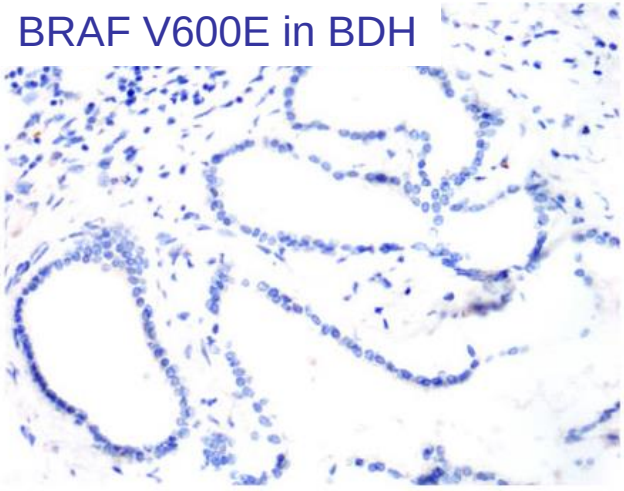
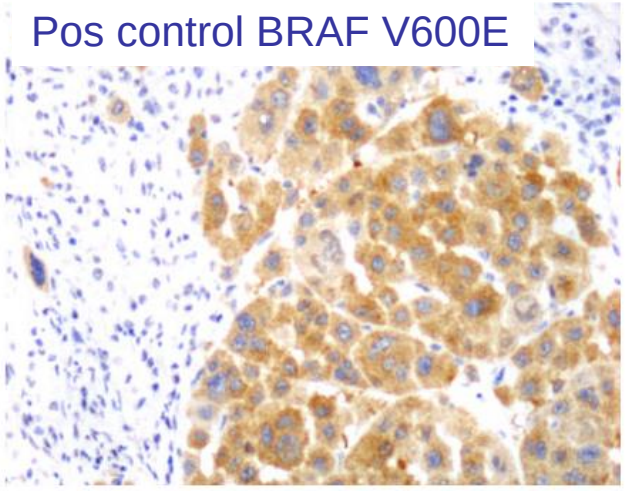


BRAF V600E in BDH



Pos control BRAF V600E



Research Article

EASL JOURNAL OF HEPATOLOGY

2015 vol. 63 | 1173–1180

Hepatocellular nodules expressing markers of hepatocellular adenomas in Budd-Chiari syndrome and other rare hepatic vascular disorders

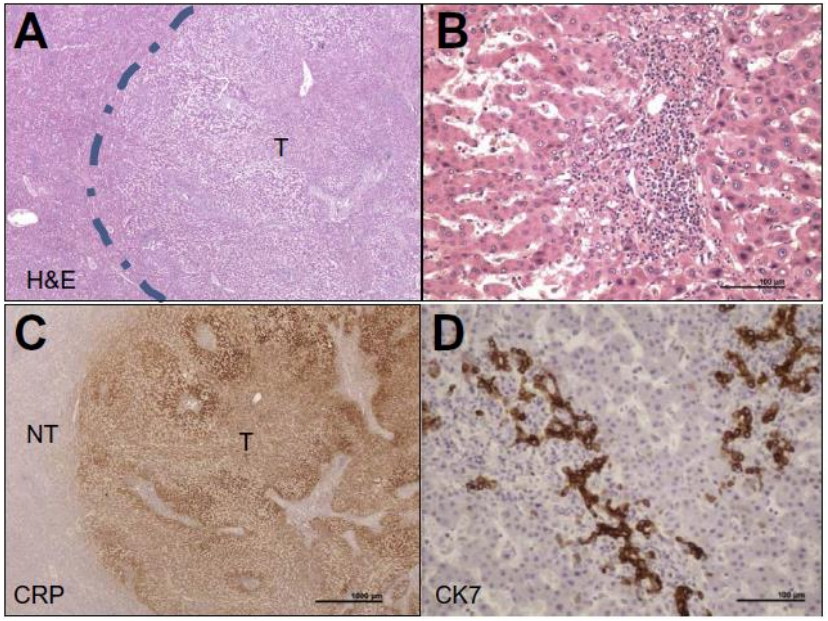
Christine Sempoux[1,†], Valérie Paradis[2], Mina Komuta[3,‡], Aileen Wee[4], Julien Calderaro[5,6], Charles Balabaud[7], Alberto Quaglia[8], Paulette Bioulac-Sage[7,9,*]

- retrospective study
- n=45 (Budd-Chiari n=32)

Table 2. Diagnosis of liver nodules at pre- and post-central review examination.

Type of liver nodules	Pathological report	Reinterpretation of the data using the HCA classification	
Nodule	4	4	
LRN/FNH like	27	23	+ HCA (1b-HCA, 1IHCA) + 2 CRP positive nodules
LRN/FNH-like with HCC	3	3	
HCA	9*	9*	4 H-HCA 3 b-HCA 2 IHCA
HCC alone	2	2	
Total	45		

Inflammatory-HCA



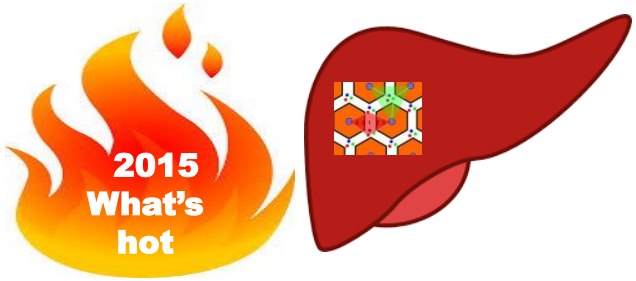
Hepatocellular nodules in hepatic vascular disorders

- often are large regenerative nodules (LRN)
- 25% hepatocellular adenomas (HCA)
- HCA have IHC phenotype similar to conventional HCA subtypes
- HCA difficult to differentiate from LRN, particularly the small ones
- **increased risk of malignant transformation**

HCA in vascular disorders should be managed differently

from conventional HCA

Sempoux C, J Hepatol 2015; 63:1173-80

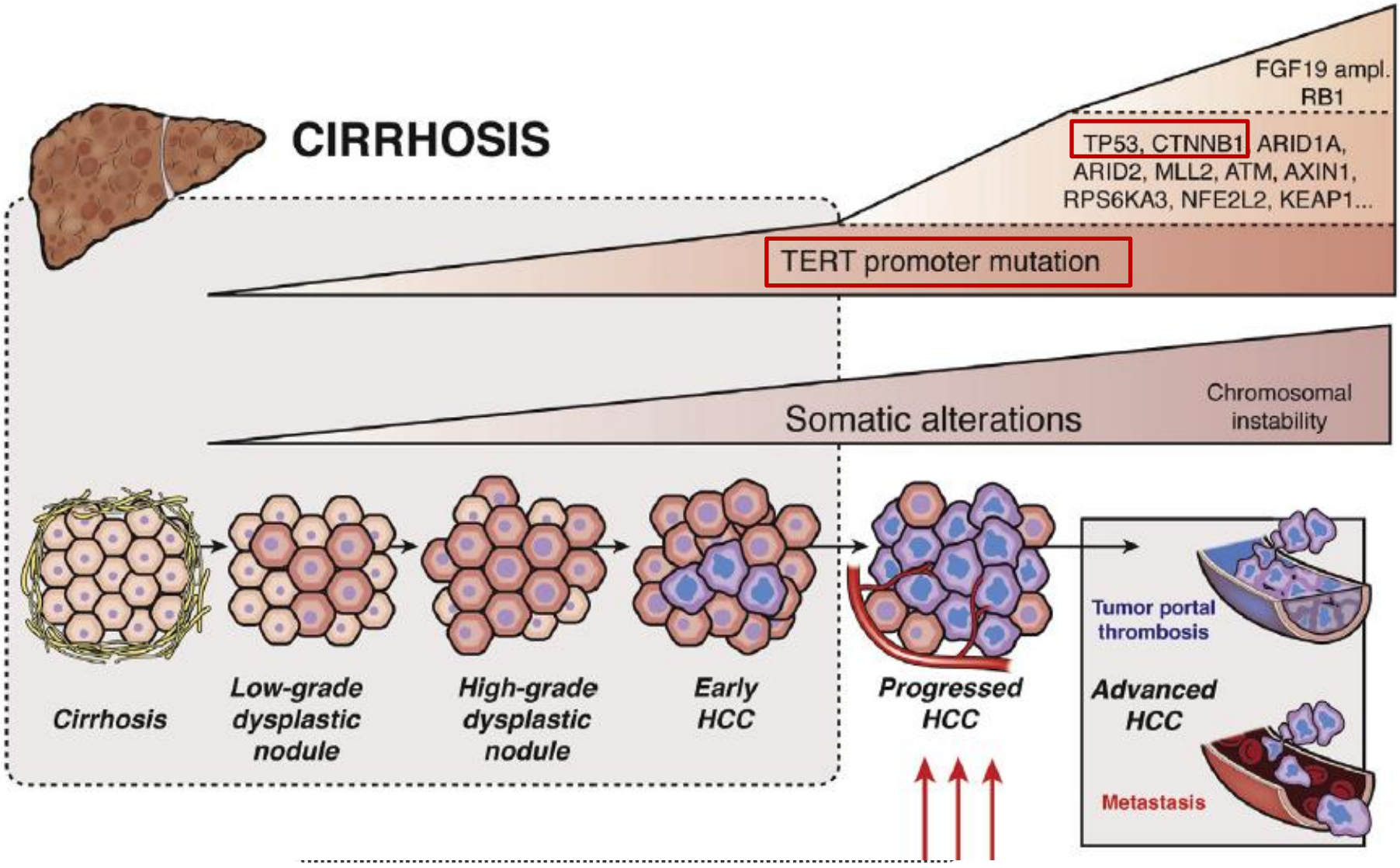


- Chronic liver disease
- Benign liver tumours
- **Malignant liver tumours**
  - **HCC**
  - **Combined HCC-CC**

Genetic Landscape and Biomarkers of Hepatocellular Carcinoma

Gastroenterology 2015;149:1226–1239

Zucman-Rossi et al

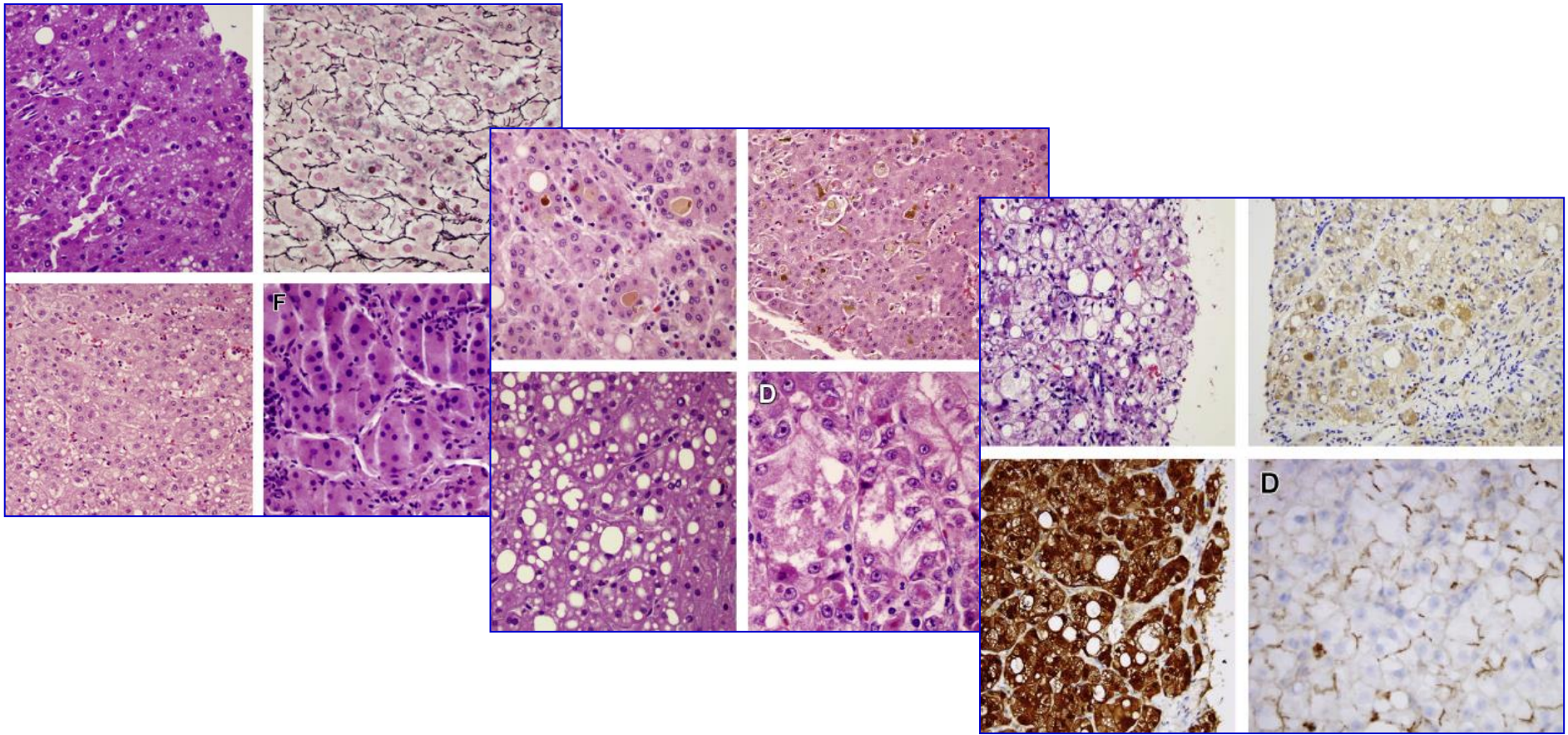


Clin Liver Dis 19 (2015) 239–259

Anatomic Pathology of Hepatocellular Carcinoma

Histopathology Using Classic and New Diagnostic Tools

Meredith E. Pittman, MD[a], Elizabeth M. Brunt, MD[b,*]



HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Editor's Note

Unlike most malignancies, suspected hepatocellular carcinomas are not routinely biopsied to establish a diagnosis or to direct treatment. Following are opposing views on whether the approach should be changed.

DOI: 10.1002/hep.27683

Pro # Liver Cancer Biopsy – Back to the Future?!

Michael TORBENSON, Mayo Clinic, MN, USA
Peter SCHIRMACHER, University of Heidelberg, Germany

Con # Biopsy for Liver Cancer: How to Balance Research Needs With Evidence-Based Clinical Practice

Morris SHERMAN, Toronto General Hospital, Canada
Jordi BRUIX, Barcelona Clinic Liver Cancer (BCLC), Spain

Symposium - Liver biopsy in HCC 17 April 2016

Peter Schirmacher, Germany

- Liver biopsy from the clinicians perspective - do we need to change the guidelines?
- Liver biopsy from the pathologist' perspective - do the guidelines meet reality?
- Liver biopsy in clinical trials - needless or necessity?
- Liver biopsy - options to come

IHC markers for diagnosing HCC

Most frequently used:

- HepPar1
- arginase 1

} Hepatocellular differentiation

- polyclonal CEA
- CD10

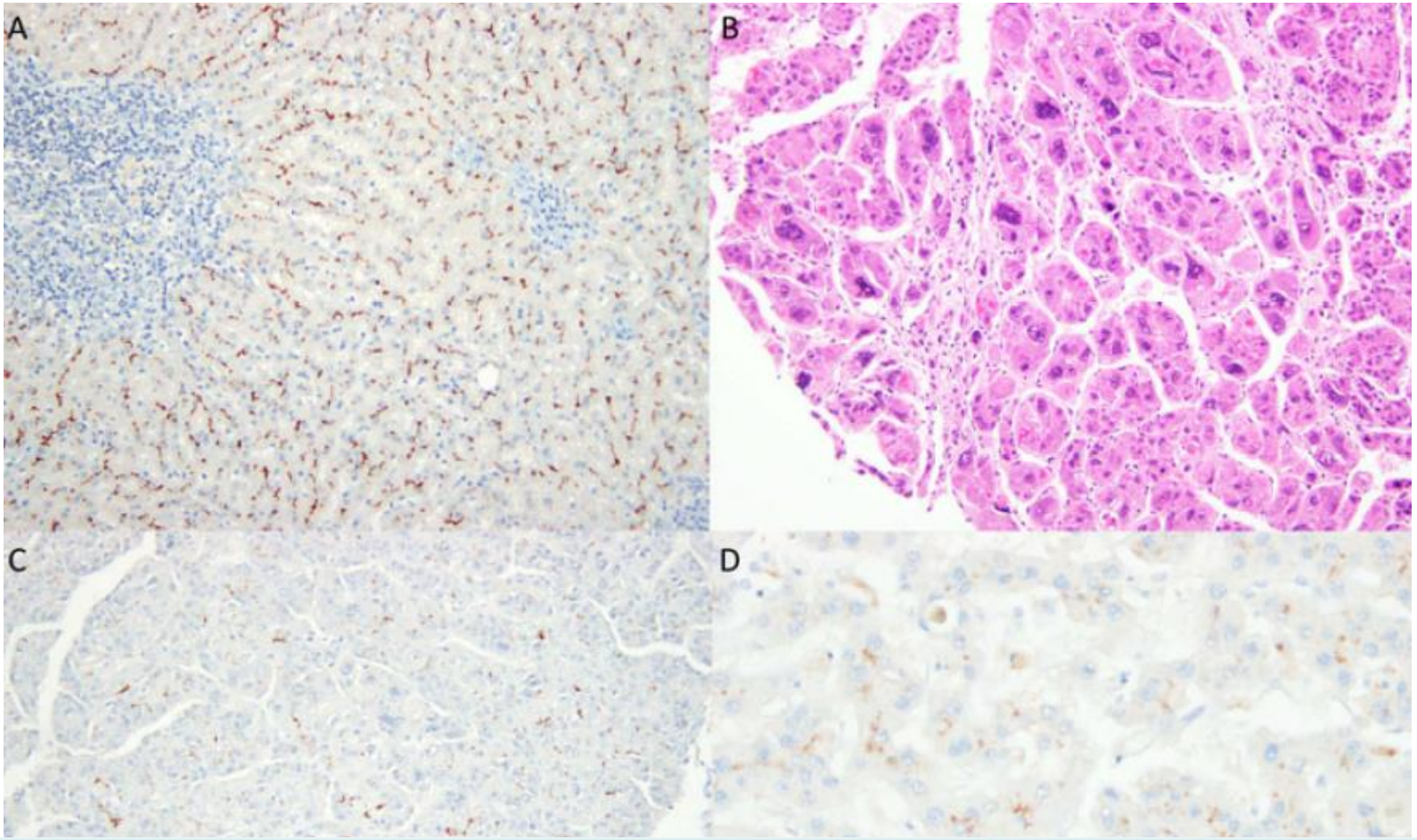
} Canalicular markers

Yan, Am J Surg Pathol 2010

- Glypican-3 (GPC-3) → - marks HCC, but generally not benign hepatocytes
  - therapeutic target in HCC

Filmus & Capurro, FEBS J 2013

Bile Salt Export Pump as a marker of HCC



BSEP is a highly sensitive and specific marker for HCC

No need to identify a “canalicular” pattern!

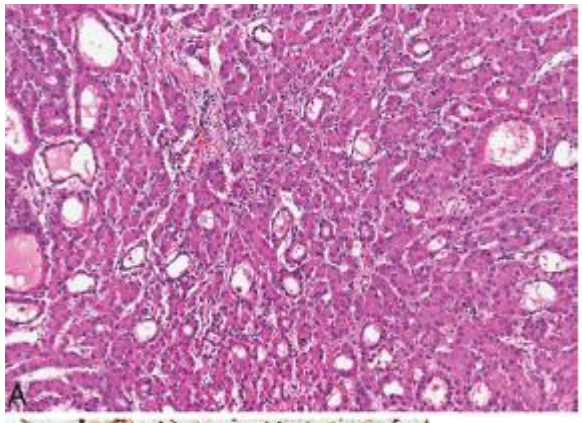
Lagana, Histopathology 2015; 66:598-602

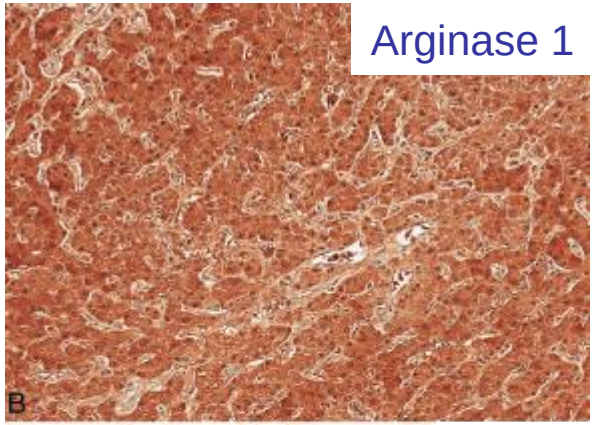
Arch Pathol Lab Med—Vol 139, August 2015

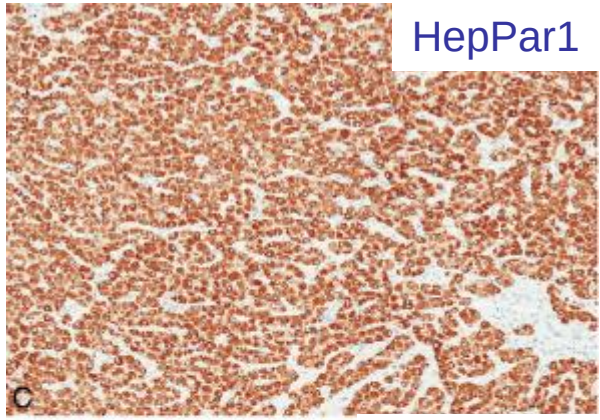
Comparison of 5 Immunohistochemical Markers of Hepatocellular Differentiation for the Diagnosis of Hepatocellular Carcinoma

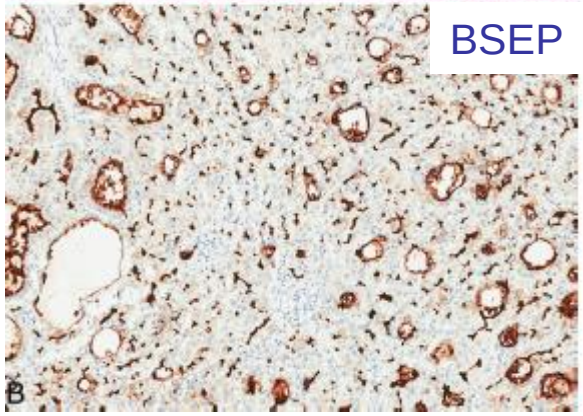
Thuy Nguyen, MD; Daniel Phillips, MD; Dhanpat Jain, MD; Michael Torbenson, MD; Tsung-Teh Wu, MD, PhD; Matthew M. Yeh, MD, PhD; Sanjay Kakar, MD

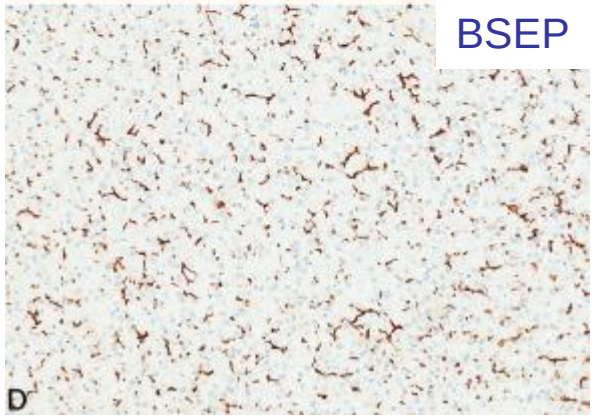
Well differentiated HCC

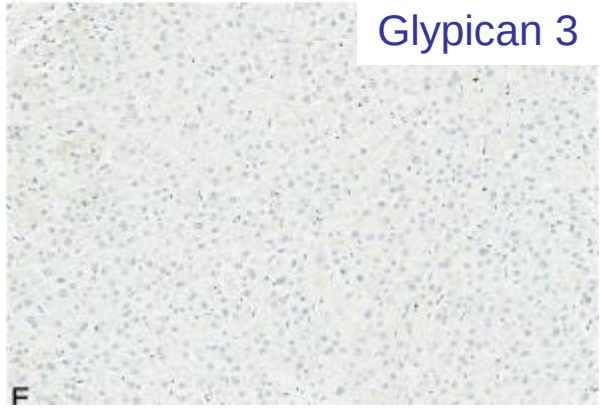












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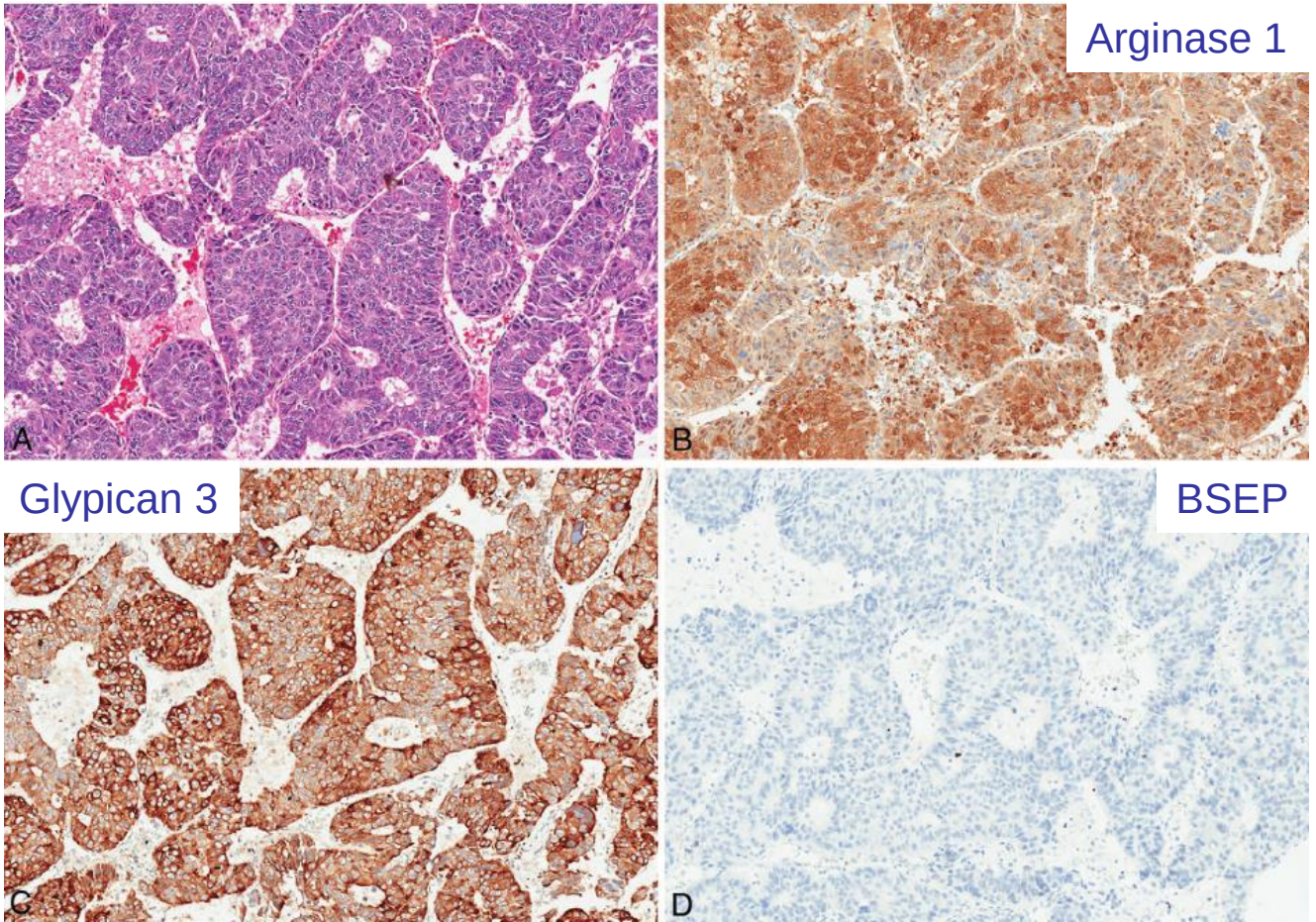
Poorly differentiated HCC



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Comparison of 5 Immunohistochemical Markers of Hepatocellular Differentiation for the Diagnosis of Hepatocellular Carcinoma

Thuy Nguyen, MD; Daniel Phillips, MD; Dhanpat Jain, MD; Michael Torbenson, MD; Tsung-Teh Wu, MD, PhD; Matthew M. Yeh, MD, PhD; Sanjay Kakar, MD

Table 2. Immunohistochemical Markers in Hepatocellular Carcinoma With 5%[a] Staining Considered Positive

Differentiation	Arginase-1, No. (%)	Glypican-3, No. (%)	Hep Par-1, No. (%)	pCEA, No. (%)	BSEP, No. (%)
Well, n = 13	13 (100)	8 (62)	13 (100)	12 (92)	12 (92)
Moderately, n = 41	41 (100)	33 (80)	40 (98)	36 (88)	37 (95)[b]
Poorly, n = 39	38 (97)	33 (85)	25 (64)	21 (54)	14 (45)[c]

Abbreviations: BSEP, bile salt export pump; Hep Par-1, hepatocyte paraffin antigen 1; pCEA, polyclonal carcinoembryonic antigen.

- Arginase-1 (Arg-1) is the most sensitive marker of HCC irrespective of differentiation
- Glypican-3 (GLP3) has high sensitivity for poorly differentiated HCC
- Combination of GLP3 and Arg-1 identifies ~all cases of poorly diff HCC
- BSEP has good sensitivity but limited role in establishing hepatocellular differentiation when added to a panel of Arg-1 with GLP3 or HepPar1

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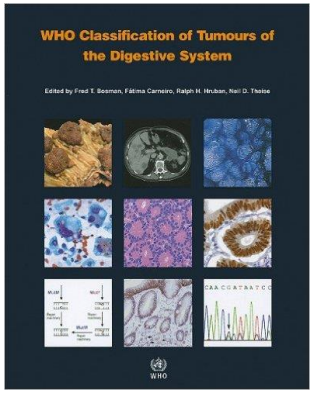
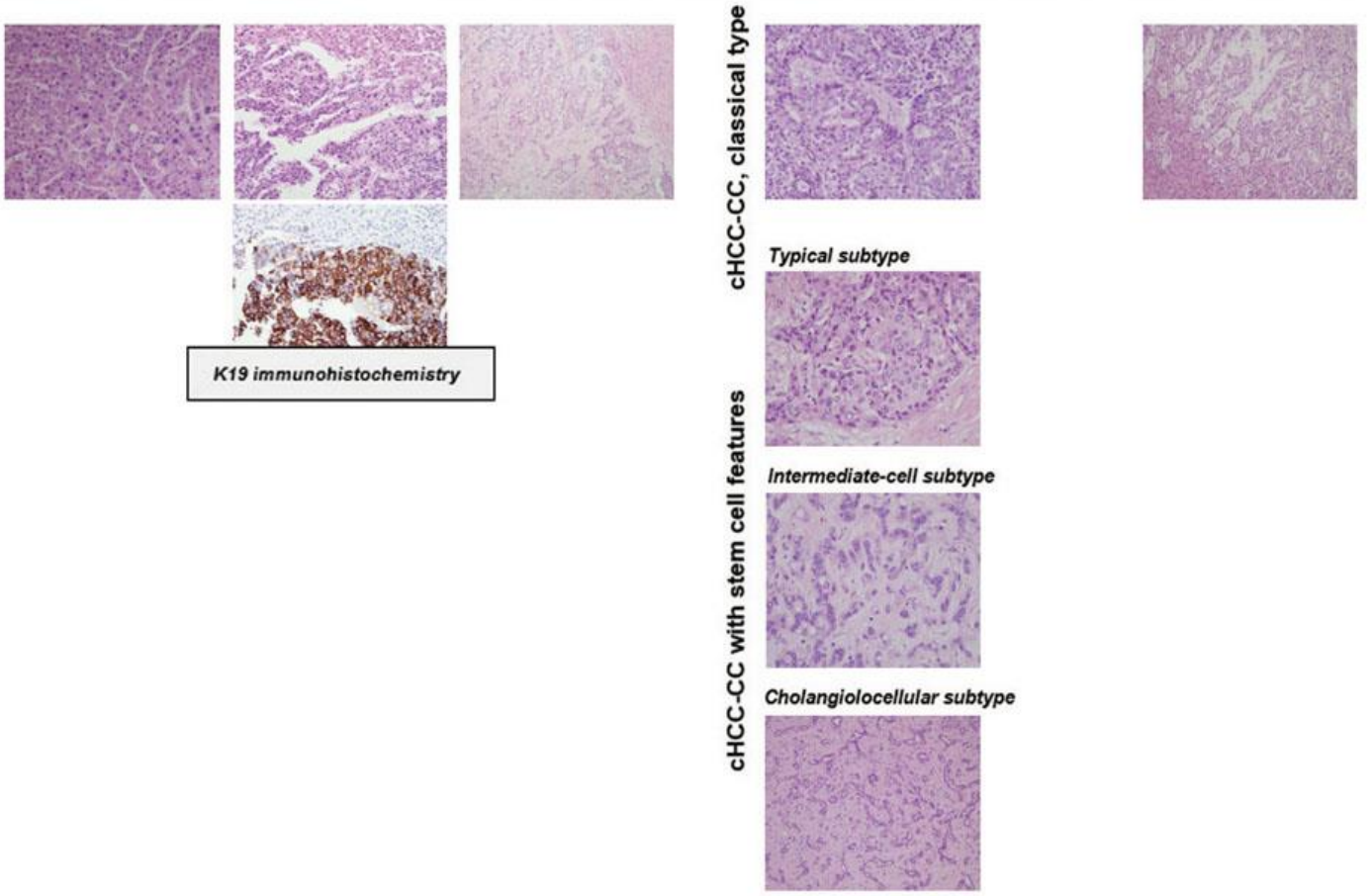


WHO classification 2010
Combined hepatocellular–cholangiocarcinoma and stem cell subtypes

Cellular differentiation	Hepatocyte differentiation → Cholangiocyte differentiation
WHO classification 2010	HCC / cHCC-CC / CC
Histologic subtypes	Classical HCC; HCC with "stemness" -related marker expression; Scirrhous HCC; cHCC-CC, classical type; cHCC-CC with stem cell features; CC
Pathologic features	

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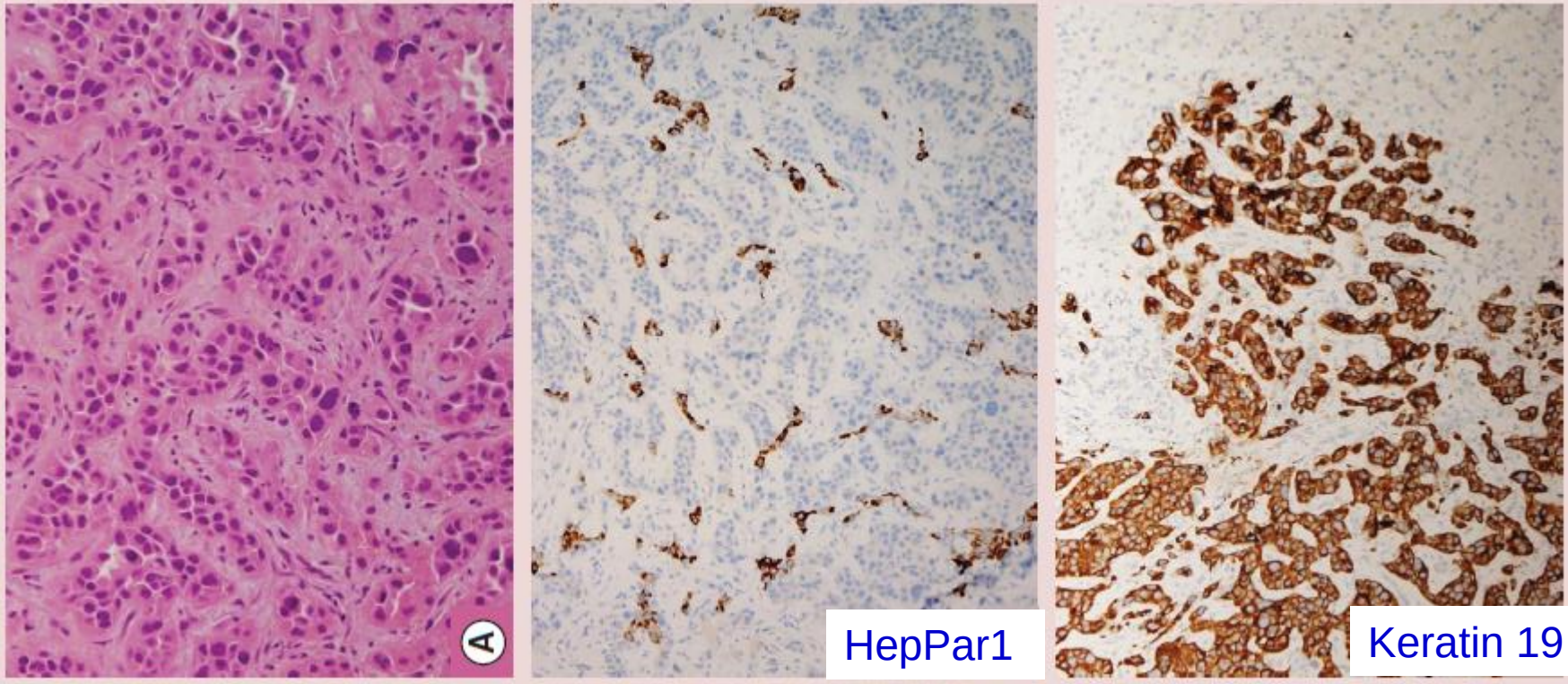
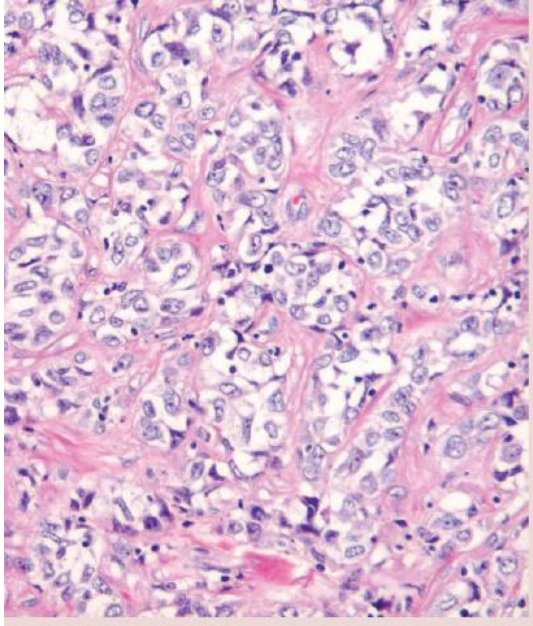
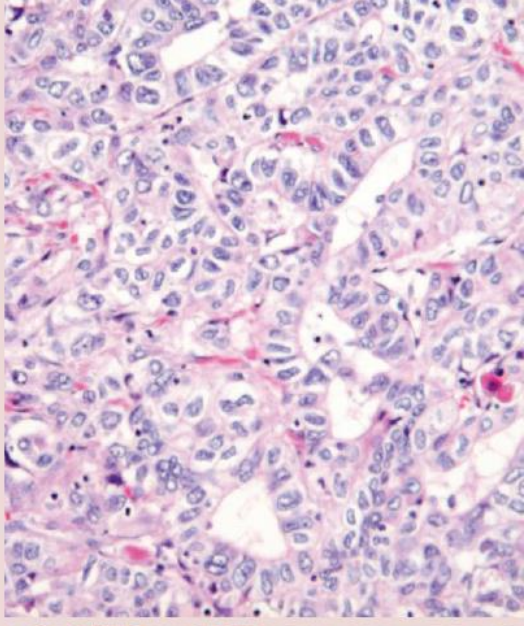
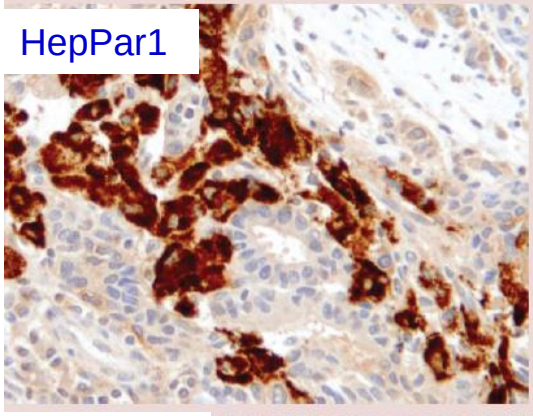
Biphenotypic (hepatobiliary) primary liver carcinomas: the work in progress

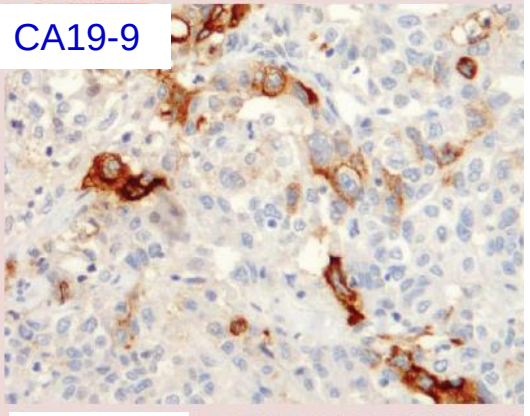
Elizabeth M Brunt[1], Valerie Paradis[2], Christine Sempoux[3] & Neil D Theise*[,4]

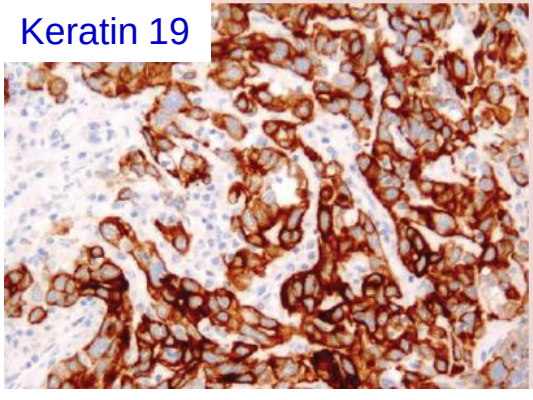












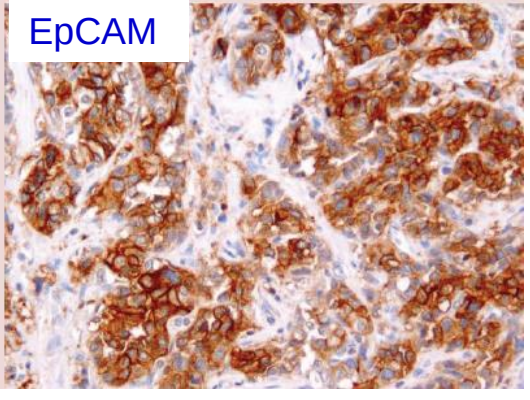


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Table 2. Descriptive versus WHO classification of primary (mixed hepatobiliary) liver carcinomas.

Descriptive classification	2010 WHO classification
Stem cell/biliary marker positive (particularly K19+) 'pure' HCC	HCC
HCC, small cell subtype	HCC
HCC with stem cell features and IHC markers	Unclassified
Hepatocyte marker positive pure CC	Unclassified
cHCC-CC	cHCC-CC
cHCC-CC with 'typical' stem cell features	cHCC-CC, typical stem cell subtype
cHCC-CC with 'intermediate' features	cHCC-CC, intermediate stem cell subtype
Cholangiolocellular carcinomas with HCC component	Unclassified
Cholangiolocellular carcinomas with cHCC-CC	cHCC-CC, cholangiolocellular subtype
Primary liver carcinoma with mixed hepatobiliary IHC features (non-HCC, non-CC)	Unclassified

CC: Cholangiocarcinoma; cHCC-CC: Combined hepatocellular–cholangiocarcinoma; IHC: Immunohistochemistry.

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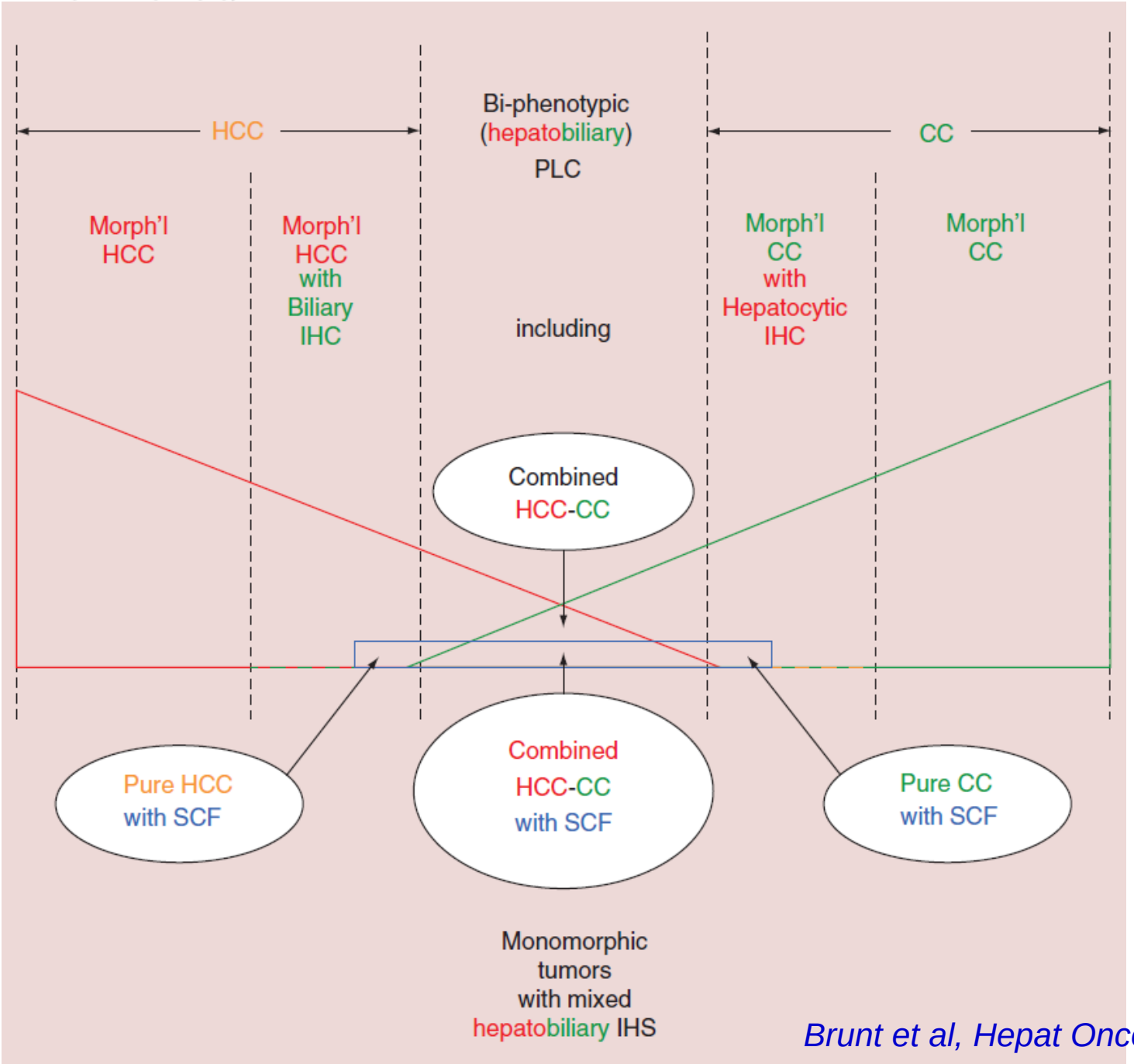

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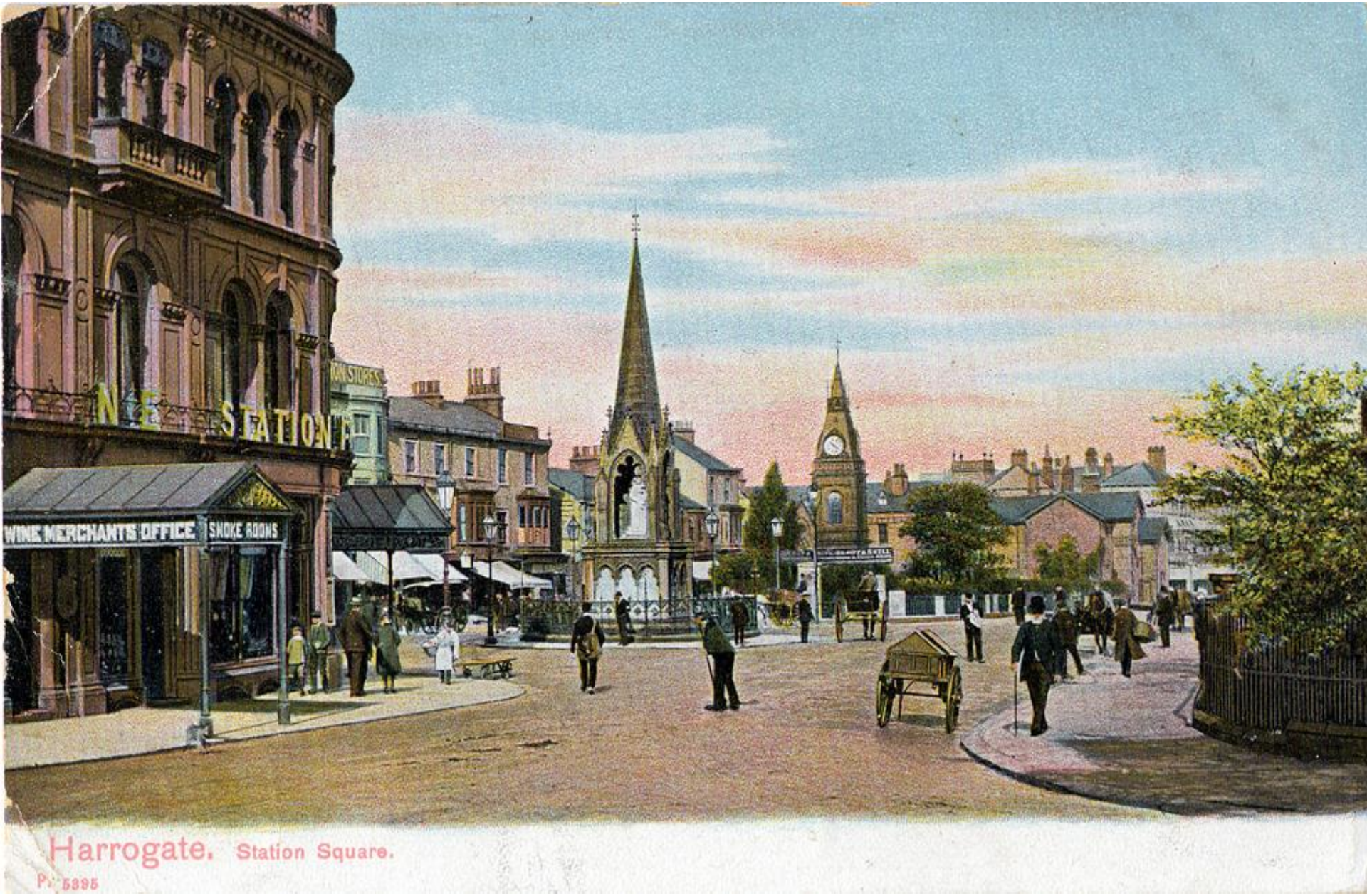

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