

Pathologie bij leverziekten



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Geen disclosures



Leerdoelen

- **Duiding van schadepatronen in de lever**
*acute schade (ontsteking) "grading":
chronische schade (fibrose) "staging"*
- Inzicht plaats van de pathologie bij de diagnostiek en behandeling van leverziekten; **klinisch correlaat!**



Interpretatie leverbiopt

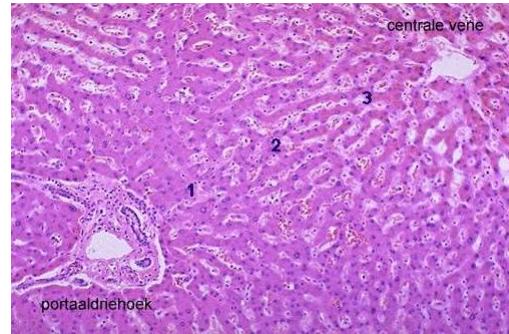
Afwijkingen:

Waar ?

Wat ?

Klinisch correlaat !





Liver acinus

Zone 1: surrounds portal tract

Zone 3: surrounds central vein



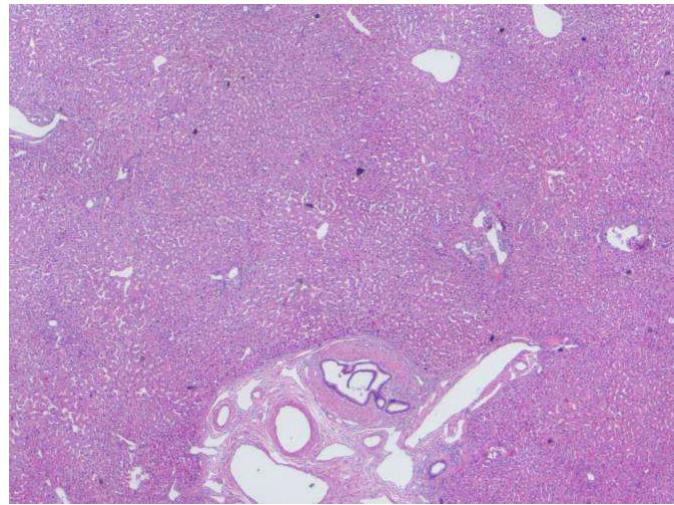
Stainings

HE overall architecture, inflammation, steatosis

PAS stains glycogen, delineates limiting plate

PAS-D ceroid-laden macrophages, $\alpha 1$ -antitrypsin, copper binding protein, basal membrane

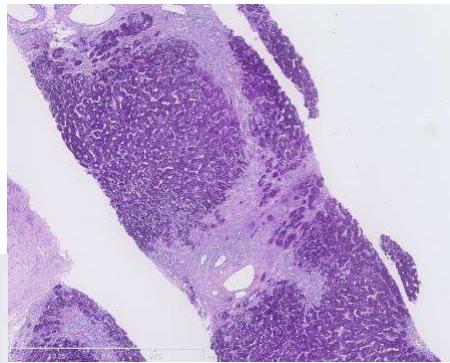
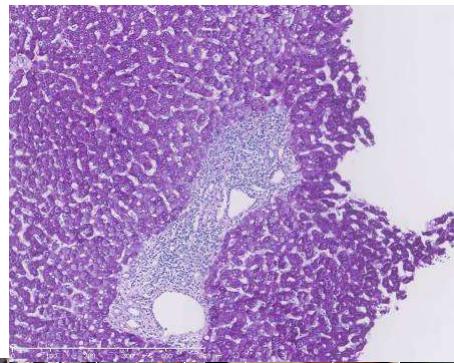


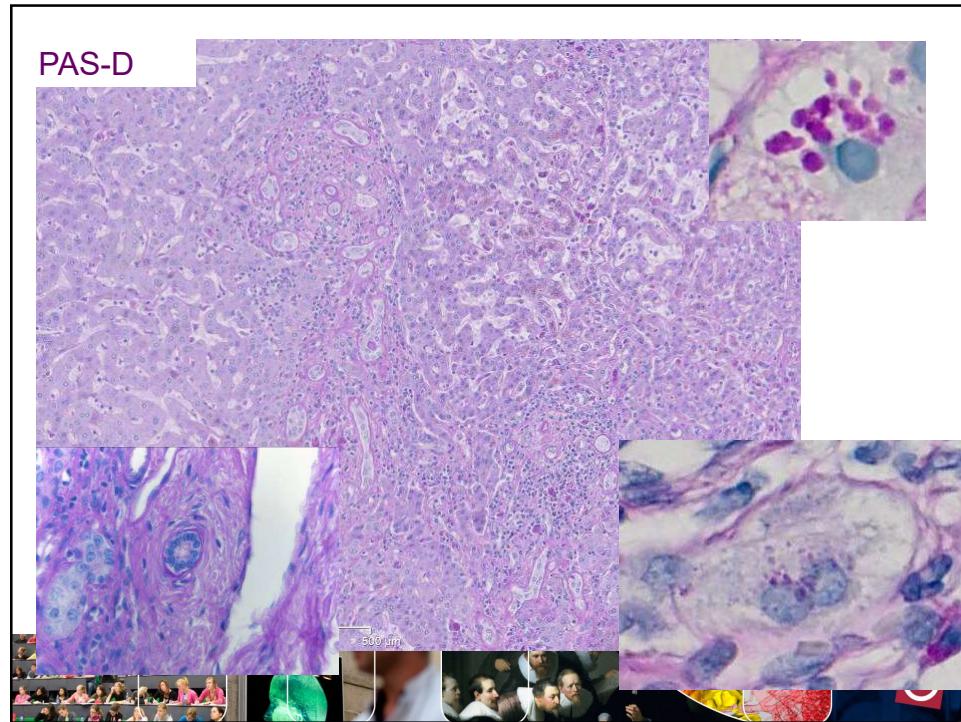


HE; hematoxylin eosin



PAS





Stainings

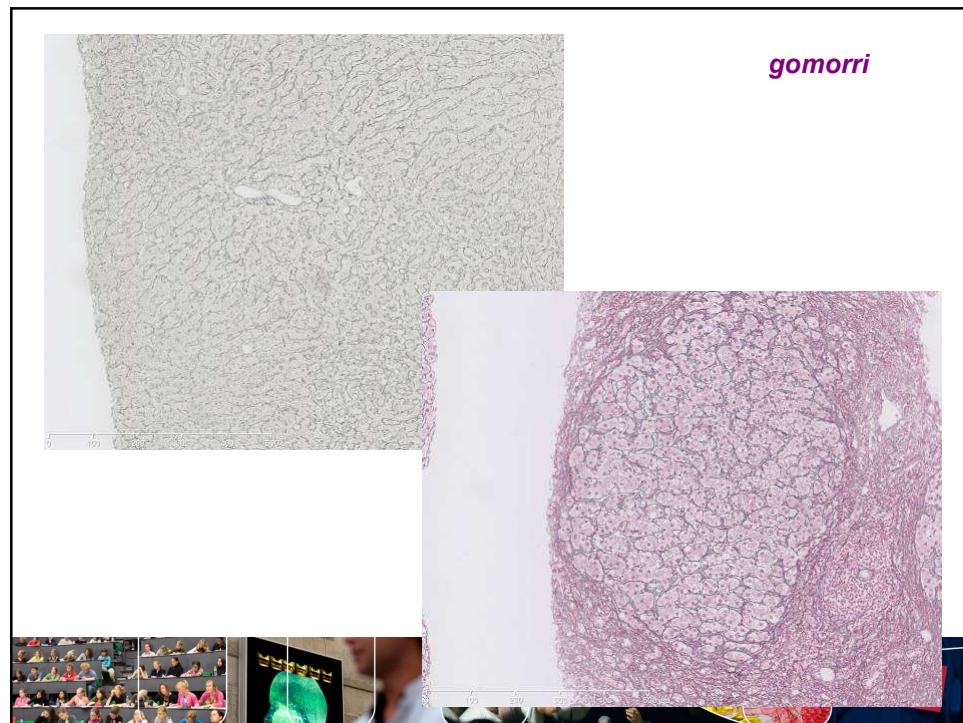
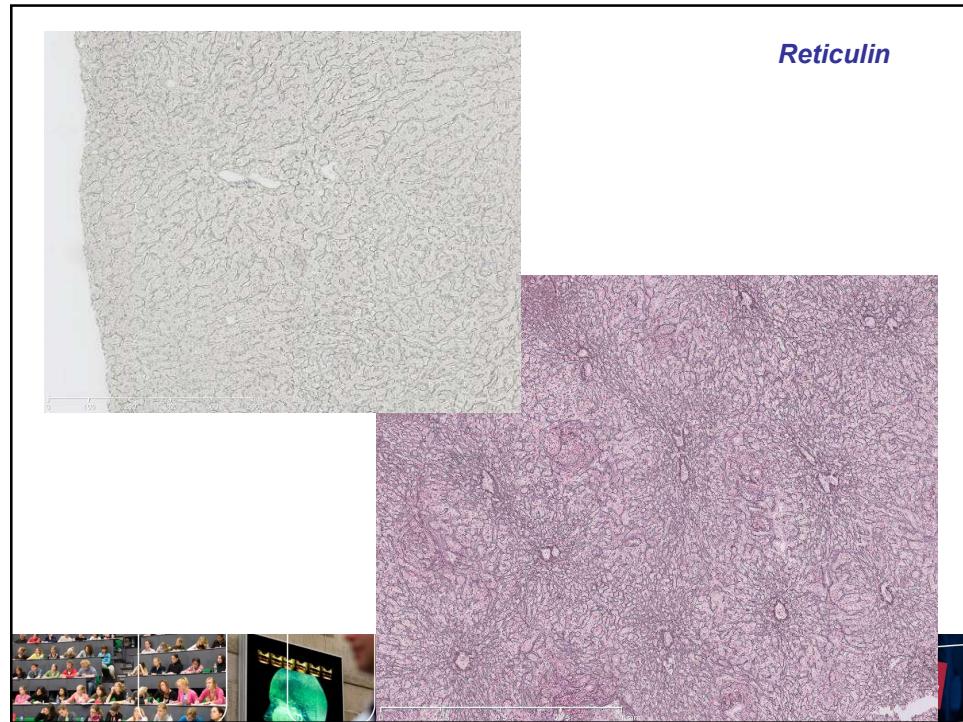
Reticulin structure of liver cell cords, subtle fibrosis

EVG/SR collagen deposition

CU/FE copper/iron

CK7 bile ducts, ductular reaction, CK7 expression on hepatocytes (~ biliary phenotype)





Collagen stainings

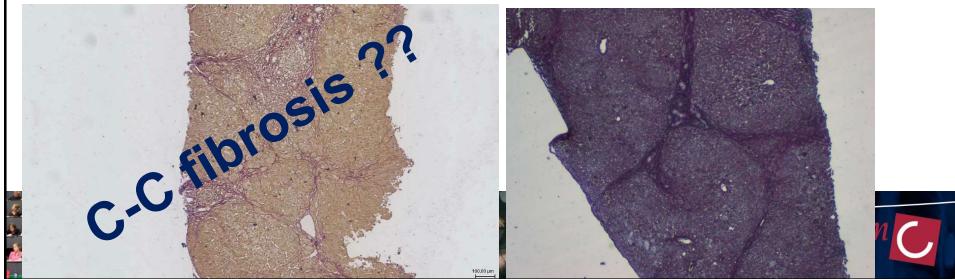
Patterns of necrosis and fibrosis

Confluent P-C necrosis : acute viral hepatitis and/or exacerbation of chronic hepatitis

Confluent P-P necrosis : chronic hepatitis and biliary tract disease

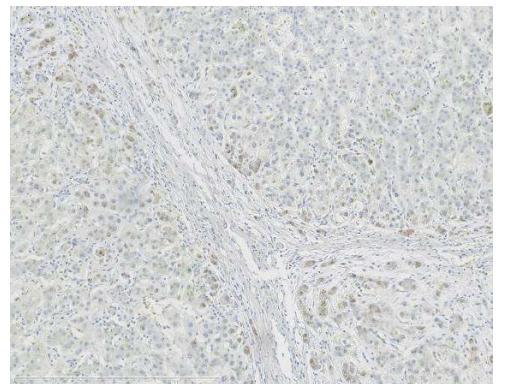
HCV: P-C; P-P

EHBDA: P-P

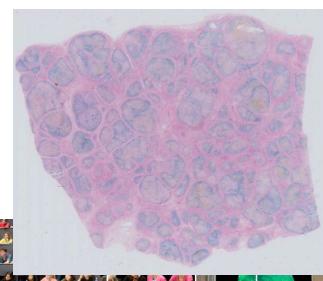


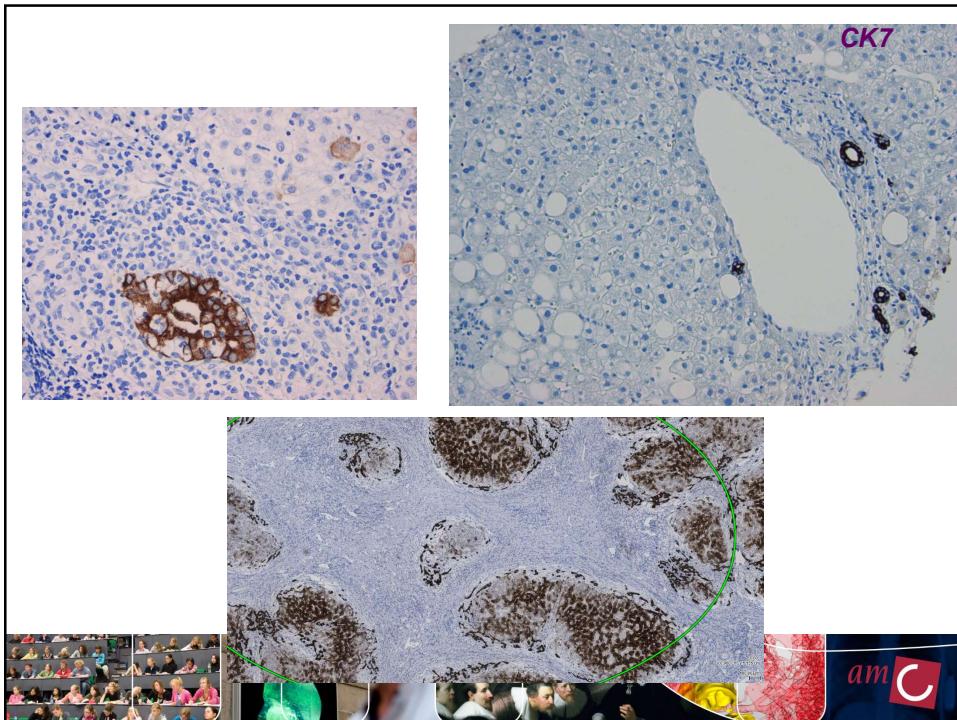
Copper

~ normally secreted in bile



Fe



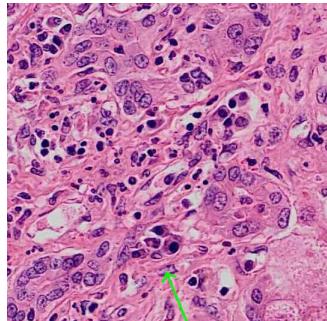


Liver diseases

Diagnostic clues

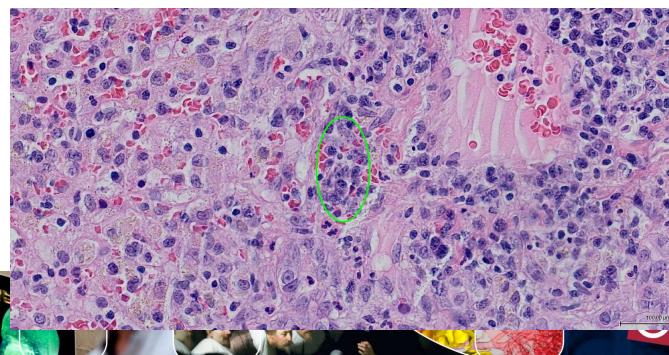
Inflammatory cells





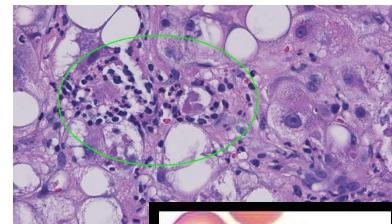
2 verschillende patiënten met acute hepatitis:

- A. 2 x AIH
- B. 1 x AIH, 1 x AIH-like drug reaction
- C. 1 x AIH, 1 x virale hepatitis

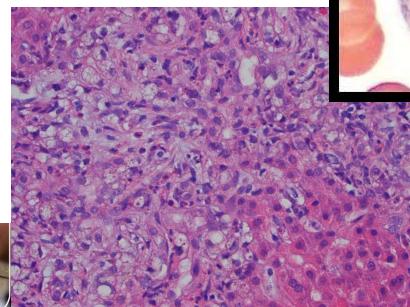


Polymorphs/neutrophils:

Steatohepatitis
Ductular reaction
Drugs



Microabcesses ~ CMV
Perfusion damage
Surgical necrosis



Eosinophilic granulocytes:

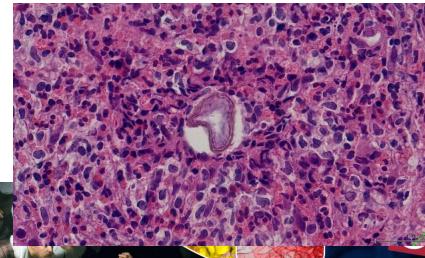
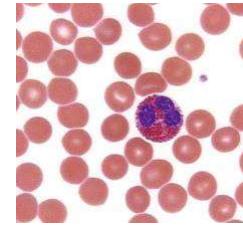
Parasites

Drugs

Primary biliary cholangitis (PBC)/AIH

IgG4 disease

Cellular rejection



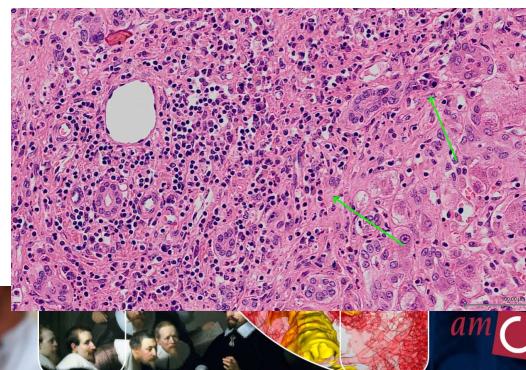
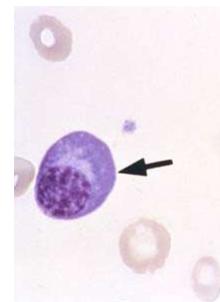
Plasma cells:

Auto Immune Hepatitis (AIH)

Viral hepatitis

PBC

Drugs



Lymphoid aggregates:

Hepatitis C (or B)

PBC

AIH

Lymphoma

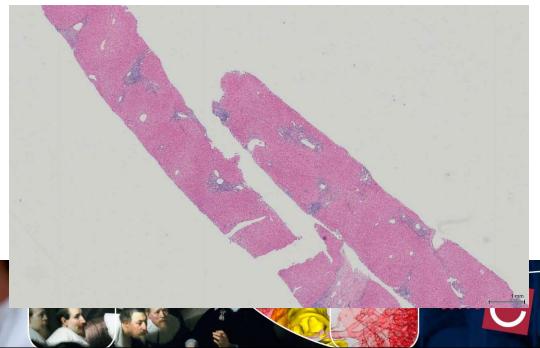
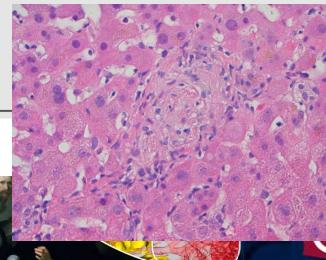


Table 2 Granuloma etiologies and characteristics.

Granuloma etiologies	Granuloma characteristics
Autoimmune	
Sarcoid	Noncaseating epithelioid granulomas
Primary biliary cirrhosis	Noncaseating granulomas near portal triads
Infectious	
<i>Mycobacterium tuberculosis</i>	AFB inside epithelioid granulomas and giant cells often with ring of lymphocytes and histiocytes
<i>M avium intracellulare</i>	Aggregates of foamy macrophages in parenchyma and portal tracts with +AFB stain
<i>M leprae</i>	Foamy histiocytes in portal tracts and lobules with multiple AFB found
Brucella	Noncaseating granulomas
Rickettsia	Fibrin ring surrounding vesicle of fat
Francisella	Suppurative microabscesses with surrounding macrophages
Listeria	Microabscesses with small granulomas
<i>Bartonella henselae</i>	Stellate abscesses with three distinct zones
<i>Tropheryma whipplei</i>	Epithelioid granulomas
Histoplasma	Macrophages and lymphocytes with histoplasma and epithelioid cells in center
Schistosoma	Eosinophils with fibrosis and collagen deposition in peri-portal and peri-sinusoidal areas often with egg at the center
Leishmania	Fibrin ring or epithelioid granulomas
Hepatitis C	Epithelioid granulomas
Drugs and Chemicals	Granulomas with eosinophils
Malignancy	Non-necrotic granulomas



Drug-induced hepatitis

Table 2 Overview of drug-induced liver injury patterns

Histological pattern	Differential diagnosis	Common drugs involved
Acute hepatitis and cholestatic hepatitis	Viral hepatitis, autoimmune hepatitis, Wilson disease, idiopathic	See table 3
Acute liver failure		
Necrosis with marked inflammation	Autoimmune hepatitis, viral hepatitis, Wilson disease	Isoniazid, monoamine oxidase inhibitors, anticonvulsants (phenytoin, valproate), antimicrobials (sulfonamides, cotrimoxazole, ketoconazole)
Necrosis with little or no inflammation	Herpes simplex or adenoviral hepatitis, Wilson disease, malignant infiltration	Acetaminophen, cocaine, MDMA (ecstasy), carbon tetrachloride
Microvesicular steatosis with little or no inflammation	Acute alcohol intoxication, Reye syndrome, fatty liver of pregnancy	Tetracycline, nucleoside analogues
Chronic hepatitis		
Autoimmune marker-negative	Autoimmune hepatitis, chronic viral hepatitis, Wilson disease	Lisinopril, sulfonamides, trazodone, uracil, tegafur, tamoxifen, methotrexate
Drug-induced autoimmune hepatitis	Autoimmune hepatitis	Minoxycline, nitrofurantoin, methyldopa, clometacin
Cholestasis		
Bland cholestasis	Sepsis, cardiac failure, shock, large duct obstruction, benign intrahepatic cholestasis, intrahepatic cholestasis of pregnancy	Anabolic/androgenic steroids, oestrogenic steroids, NSAIDs (nimesulide, piroxicam)
Cholestatic hepatitis (cholangiolitic or hypersensitivity cholestasis)	Viral hepatitis, large duct obstruction	Chlorpromazine, clarithromycin
Granulomatous hepatitis	Infections, sarcoidosis, primary biliary cirrhosis, talc, metal toxicity	Isoniazid, interferon, phenytoin, allopurinol (also see box 2)
Steatohepatitis		
Macrovesicular steatosis	Diabetes, obesity, Wilson disease, hepatitis C	Alcohol, steroids, total parenteral nutrition, gold, chlorinated hydrocarbons, chemotherapeutic agents (5-fluorouracil)
Microvesicular steatosis	Fatty liver of pregnancy, carnitine deficiency, Reye syndrome (See macrovesicular steatosis differential)	Cocaine, tetracycline, valproic acid, zidovudine
Steatohepatitis		Amitriptadine, chemotherapeutic agents (irinotecan), perhexiline
Vascular abnormalities		
Sinusoidal obstruction syndrome	Myelosuppression, venous outflow obstruction, right heart disease	Doxorubicin, pyrrolidine alkaloids, chemotherapy for ALL

ALL, acute lymphoblastic leukaemia; MDMA, 3,4-methylenedioxymethylamphetamine; NSAID, non-steroidal anti-inflammatory drug.

482

J Clin Pathol 2009;62:481–492. doi:10.1136/jcp.2008.058248



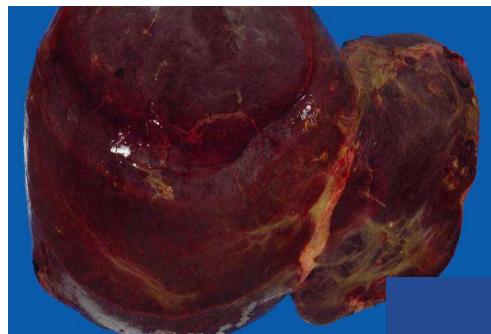
Drug-induced hepatitis

Altijd in de DD!!!



Hepatitis

Acute vs chronic

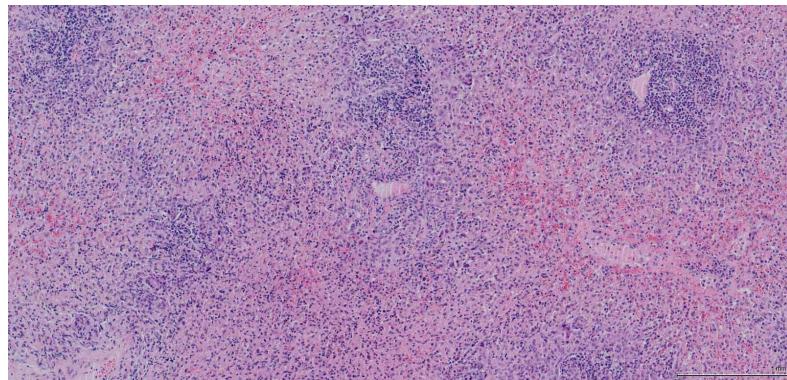


acute

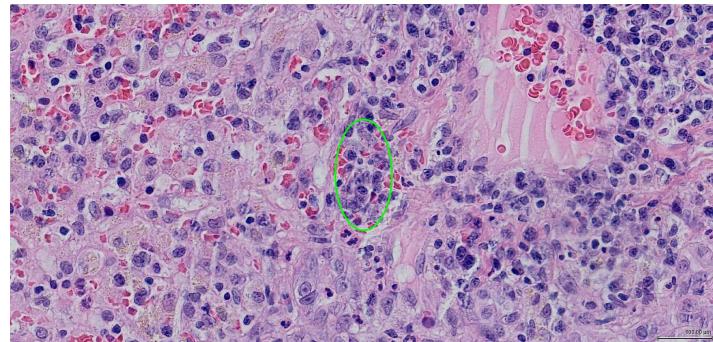


chronic

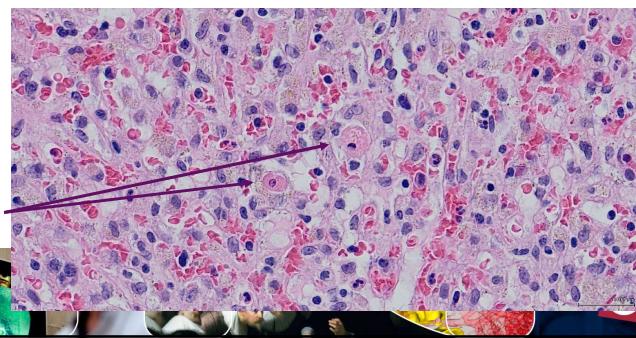


Acute HBV

HbS en HbC (-)



Councilman
bodies



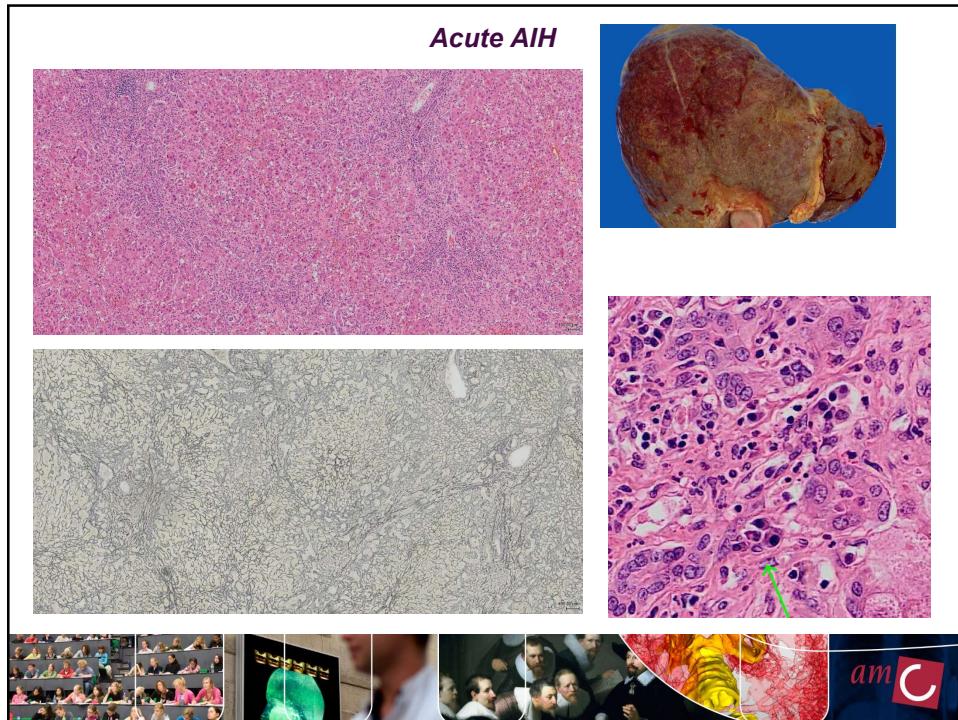


Table 2. Simplified Diagnostic Criteria for the Diagnosis of AIH

Parameter	Discriminator	Score
ANA or SMA +	$\geq 1:40$	+1
ANA or SMA +	$\geq 1:80$ or	+2
LKM +	$\geq 1:40$ or	+2
SLA	Positive	+2
IgG Level	$>$ Upper limit of normal	+1
	$>1.1 \times$ Upper limit of normal	+2
Liver Histology	Compatible with AIH	+1
	Typical of AIH	+2
Absence of Viral Hepatitis	No	0
	Yes	+2

Adapted from Hennes et al.⁸

≥ 6 points: Probable AIH

≥ 7 points: Definite AIH

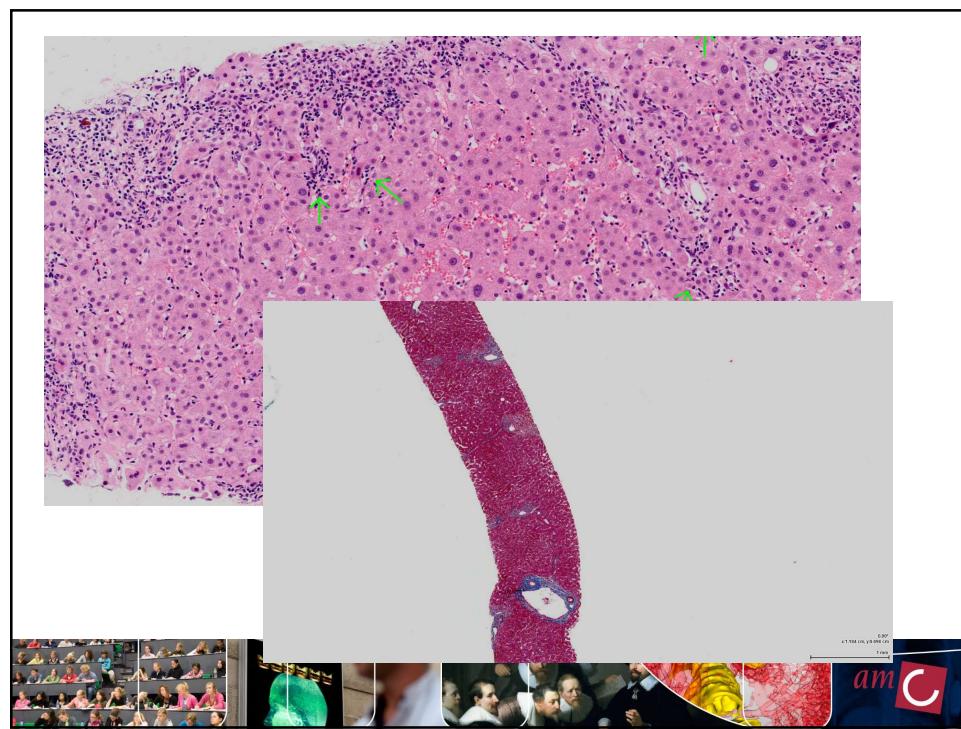
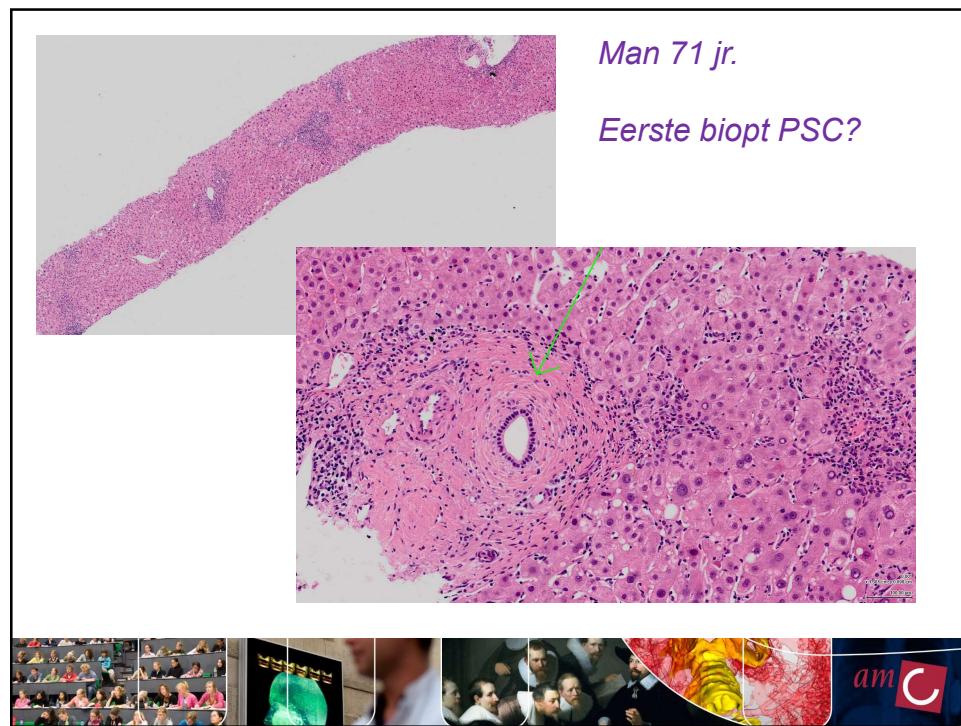
Yeoman AD, Westbrook RH, Al-Chalabi T, Carey I, Heaton ND, Portmann BC, Heneghan MA. Diagnostic value and utility of the simplified International Autoimmune Hepatitis Group (IAIHG) criteria in acute and chronic liver disease. Hepatology. 2009 Aug;50(2):538-45.



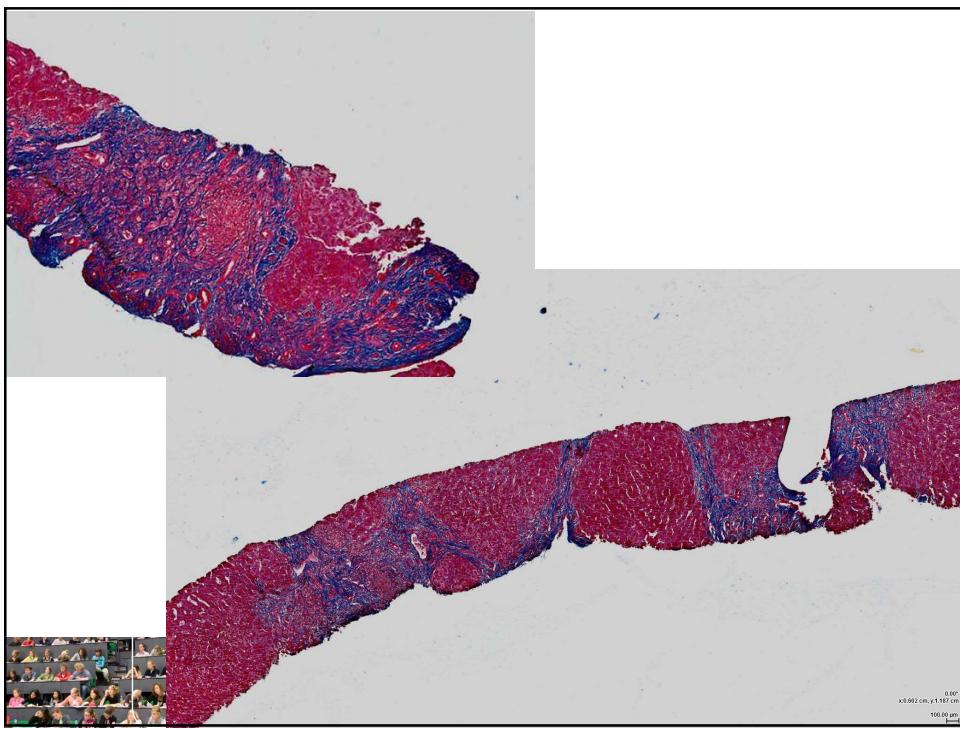
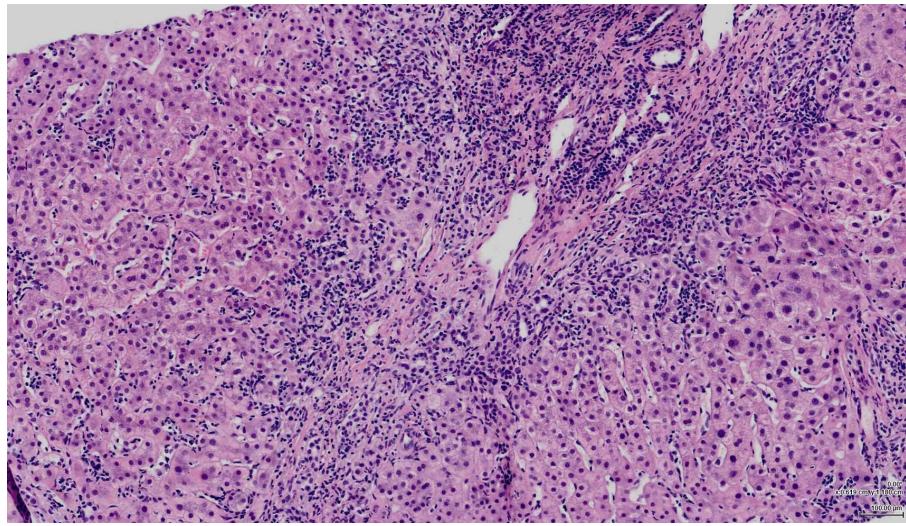


AUTOIMMUNE, CHOLESTATIC AND BILIARY DISEASE		
The Use of Liver Biopsy Evaluation in Discrimination of Idiopathic Autoimmune Hepatitis Versus Drug-Induced Liver Injury		
Ayako Suzuki, ¹ Elizabeth M. Brunt, ² David E. Kleiner, ³ Rosa Miquel, ⁴ Thomas C. Smyrk, ⁵ Raul J. Andrade, ^{6,7} M. Isabel Lucena, ^{7,8} Agustin Castilla, ⁹ Keith Lindor, ¹⁰ and Einar Björnsson ¹¹		
HEPATOLOGY 2011;54:931-939		
Table 6. Histologic Features Favoring AIH Versus DILI		
	Favoring	
Histologic Features	AIH	DILI
Severe portal inflammation (\geq grade 2)	*	
Prominent intra-acinar lymphocytes		*h
Prominent intra-acinar eosinophils	*	
Cholestasis canalicular		*h, *c
Prominent portal plasma cells	*	
Rosette formation	*	
Any levels of fibrosis (\geq grade 1)	*	
Prominent port neutrophils		*c
Hepatocellular cholestasis		*c
Severer focal necrosis (\geq grade 4)	*	

*h, DILI (HC); *c, DILI (CS). Abbreviations: AIH, autoimmune hepatitis; DILI, drug-induced liver injury; HC, hepatocellular injury; CS, cholestatic/mixed injury.



8 years later



Chronic hepatitis

➤ *6 months*

Inflammation and scarring

(grading and staging)



Grading and staging

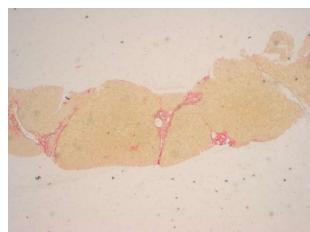
Chronic (viral) hepatitis: Metavir (F1-F4), Ishak (F1-F6)

NASH: Kleiner-Brunt, SAF score

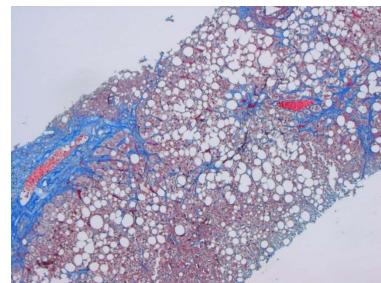
Biliary disease (PBC): Ludwig staging system,
Nakanuma



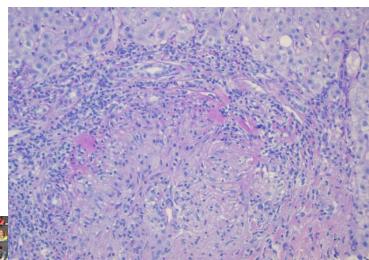
Grading and staging



HBV: Metavir F2, Ishak F3



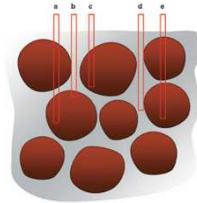
NASH, Brunt F2



PBC, Ludwig stadium 2



Attention



Patchy distribution of some diseases
adequate biopsy

Interobservability
double reading, consensus
validation ~ clinical relevancy



CIRROSE

René Laënnec (1781-1826) in "De l'auscultation médiate ou Traité du Diagnostic des Maladies des Poumons et du Coeur" (1819).

"Le foie réduit au tiers de son volume se trouvait caché dans la région qu'il occupe; incisé, il paraissait entièrement composé d'une multitude de grains de la grosseur d'un grain de chênevis ou de millet, de couleur jaune ou jaune roux."



Cirrhosis histology and Laennec staging system correlate with high portal pressure

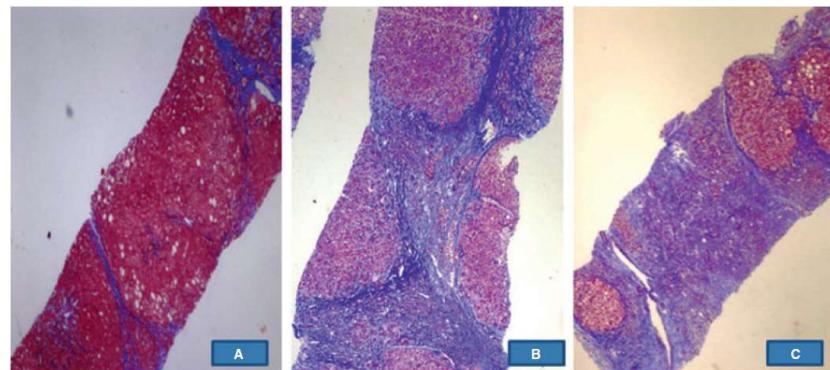
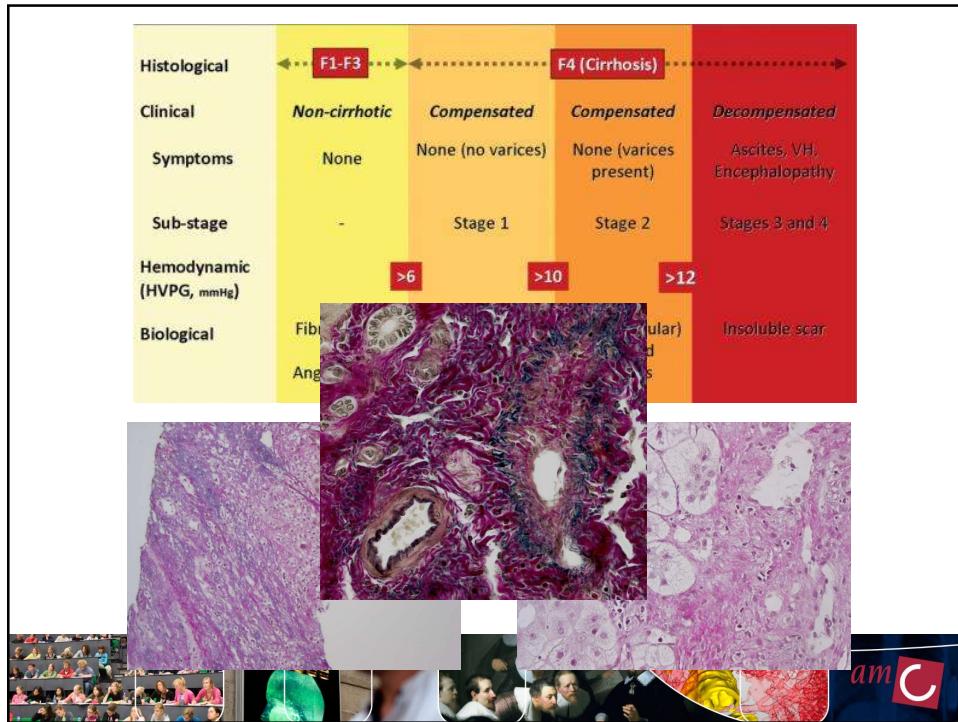


Figure 1. A-C, Laennec stages of cirrhosis: 4A (showing visible nodules with thin fibrous septa), 4B (showing three broad fibrous septa), and 4C (showing very broad septa with more than half of the biopsy comprising micronodules).

Histopathology, April 2013





Juni 2016

REVIEW

Role of aetiology in the progression, regression, and parenchymal remodelling of liver disease: implications for liver biopsy interpretation

Alberto Quaglia,¹ Venancio A Alves,² Charles Balabaud,³ Prihi S Bhathal,⁴ Paulette Bioulac-Sage,⁵ James M Crawford,⁶ Amar P Dhillon,⁷ Linda Ferrell,⁸ Maria Guido,⁹ Prodromos Hytiroglou,¹⁰ Yasuni Nakanuma,¹¹ Valerie Paradis,¹² Dale C Snover,¹³ Neil D Theise,¹⁴ Swan N Thung,¹⁵ Wilson M S Tsui,¹⁶ Dirk J van Leeuwen^{17,18}
The International Liver Pathology Study Group

Conclusion

New concepts on the reversibility of the pathological changes in advanced chronic liver diseases are having a major impact on patient management and, in turn, on the role of the liver pathologist, which evolves from the traditional grading and staging task to a more sophisticated investigation of tissue biology dynamics, gauging of disease severity, progression or regression, hepatic regeneration and functional recovery. The chronological and topographical variability of the disease process depends very much upon the underlying aetiology and needs to be taken into account, particularly when interpreting liver biopsy



Liver biopsy

Exclusion of concomitant disease

For diagnosis and/or confirmation of (suspected) disease

Confirmation of tumor and tumor type

Grading and staging of disease, taking into account specific patterns of damage

Morphological classification of cirrhosis based on quantitative/morphometric methods able to provide more precise prognostic information?



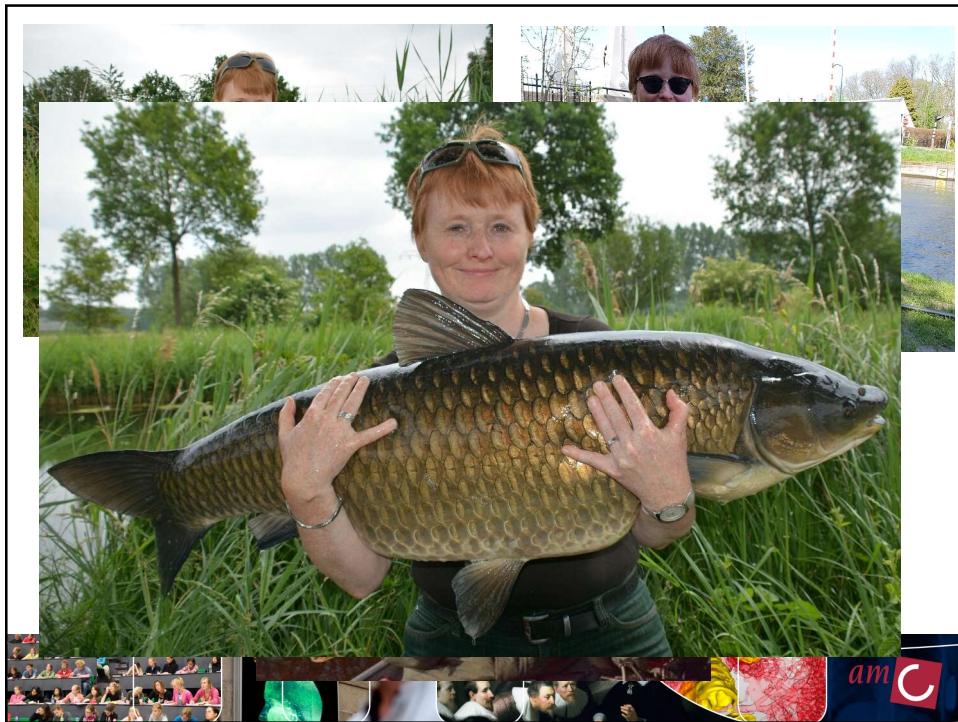
Aanvraag leverbiopt

GARBAGE IN.....

GARBAGE OUT!!!!

Overige bijzonderheden
Vraagstelling /DD





Interpretation liver biopsy

It takes two to tango..

A colorful illustration of a man and a woman dancing the tango. The man is in a dark suit and the woman is in a red dress, both in mid-dance. The background is composed of warm orange and red brushstrokes.

www.leverpathologie.nl

At the bottom of the slide is a decorative footer bar featuring various small images and the text "amC".