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Hepatocellular Adenoma Immuno-Histochemistry

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Prof Andrew Clouston

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The A team

What are HCAs

- Benign lesions of the liver
- Barthelmes & Tait "Most important benign tumour of the liver
- First described by Edmondson 1958
- Linked by Baum to OCP in 1973
- Macroscopically
    - Palpable lesion
    - Range in colour from White-Yellow-Brown
    - Grow up to 30cm in diameter

What are HCAs

- Microscopically
- Lack normal hepatic parenchyma
- Tracts and hepatic veins are absent
- Subclassifed into 4 groups

1. HCA, inflammatory
2. HCA, HNF1 alpha inactivated
3. HCA, beta catenin activated
4. HCA, unclassified

Epidemiology

Who Classification of tumours of digestive system states:

- Incidence of HCA is 3-4 per 100 000 in Europe and North America
- Lower in Asia
- 85% cases occur in young women
- Rare in children, men and elderly

- At Envoi we have seen 121 HCAs from 99 patients

Etiology

- Major risk factor for HCA is exposure to oestrogenic and androgenic steroids
- 80% of young women with HCA have been on the contraceptive pill.
- Risk increases with duration of use
- Prevalence is declining with lower oestrogen pills being available
- Lesions usually shrink after stopping use of contraceptives and post menopause
- Most men have been users of anabolic steroids for body building

Etiology cont'd

- Non-hormonal risk factors:
- Glycogenosis type 1 (Von Gerke disease)
- Glycogenosis type 3 (Forbes disease)
- Galactosaemia
- Tyrosinaemia
- Familial polyposis coli
- Hepatic iron overload with β-thalassemia
- Obesity

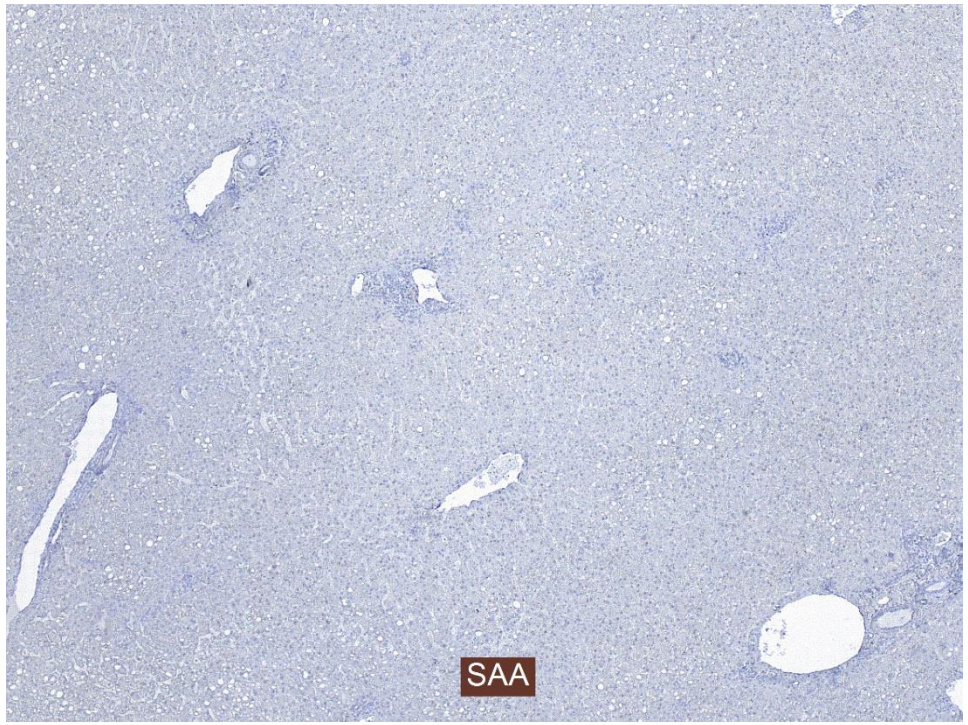
Clinical features

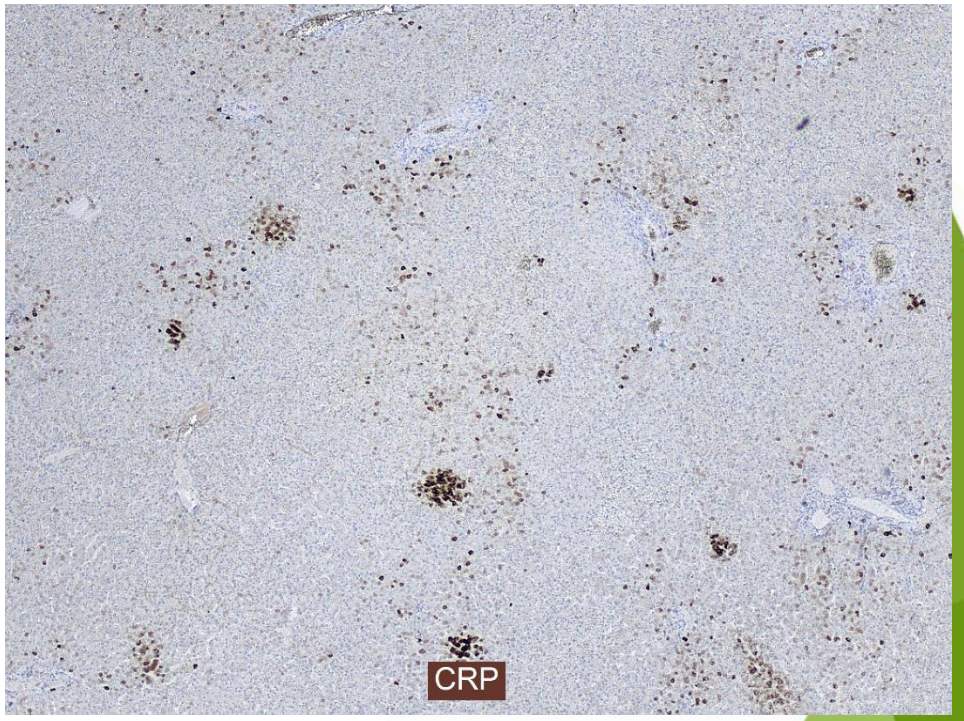
- Abdominal pain
- Abdominal mass
- Intraperitoneal haemorrhage (20-25% of cases have significant haemorrhage). Risk is higher when tumours >5cm
- Abnormal LFTs
- Incidental liver mass during radiology
- Can present as single or multiple lesions (>10 "adenomatosis")

Importance of classification

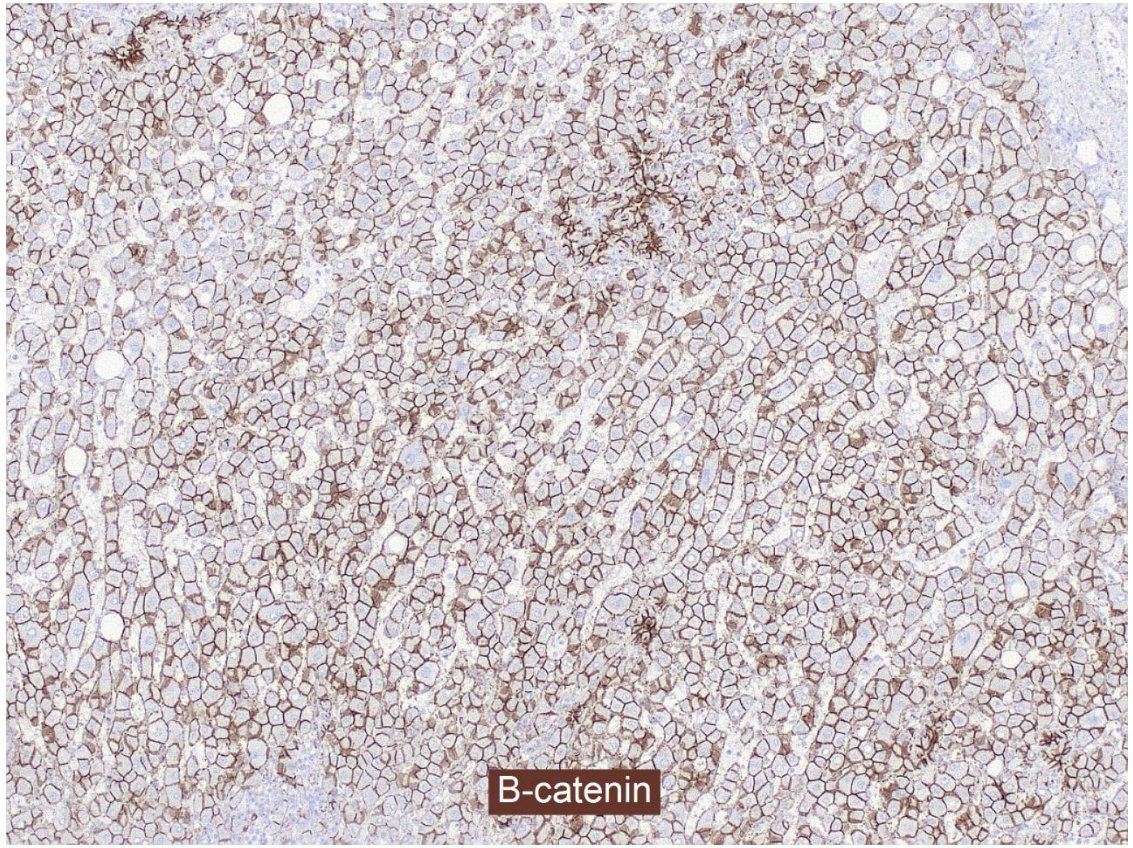
- Whilst benign there are a small proportion (4%) of HCAs which develop into HCCs
- Depending on HCA subtype the risk of transformation varies (typically increases in patients with glycogenosis or steroid use)
- Risk of Bleed
- Decision to operate

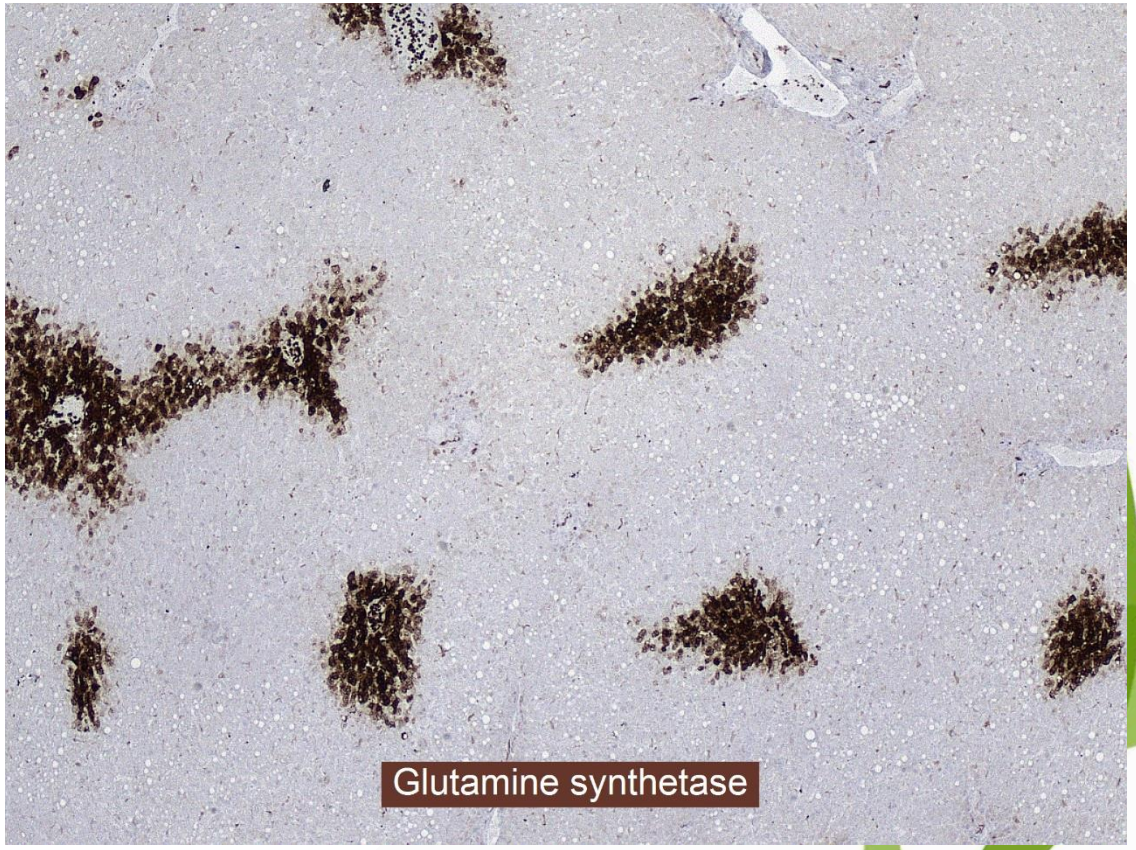
Microscopy Normal Liver



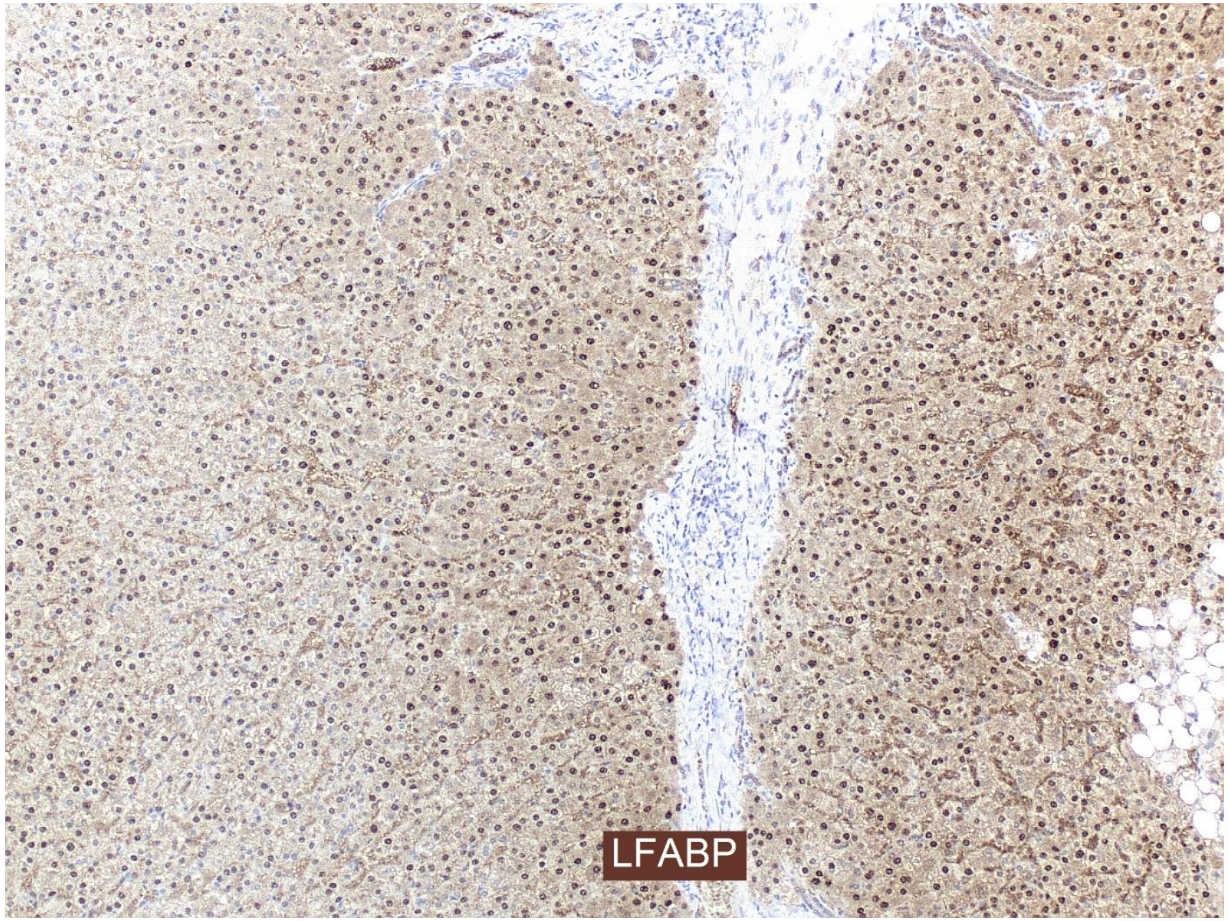


Microscopy Normal Liver Cont'd





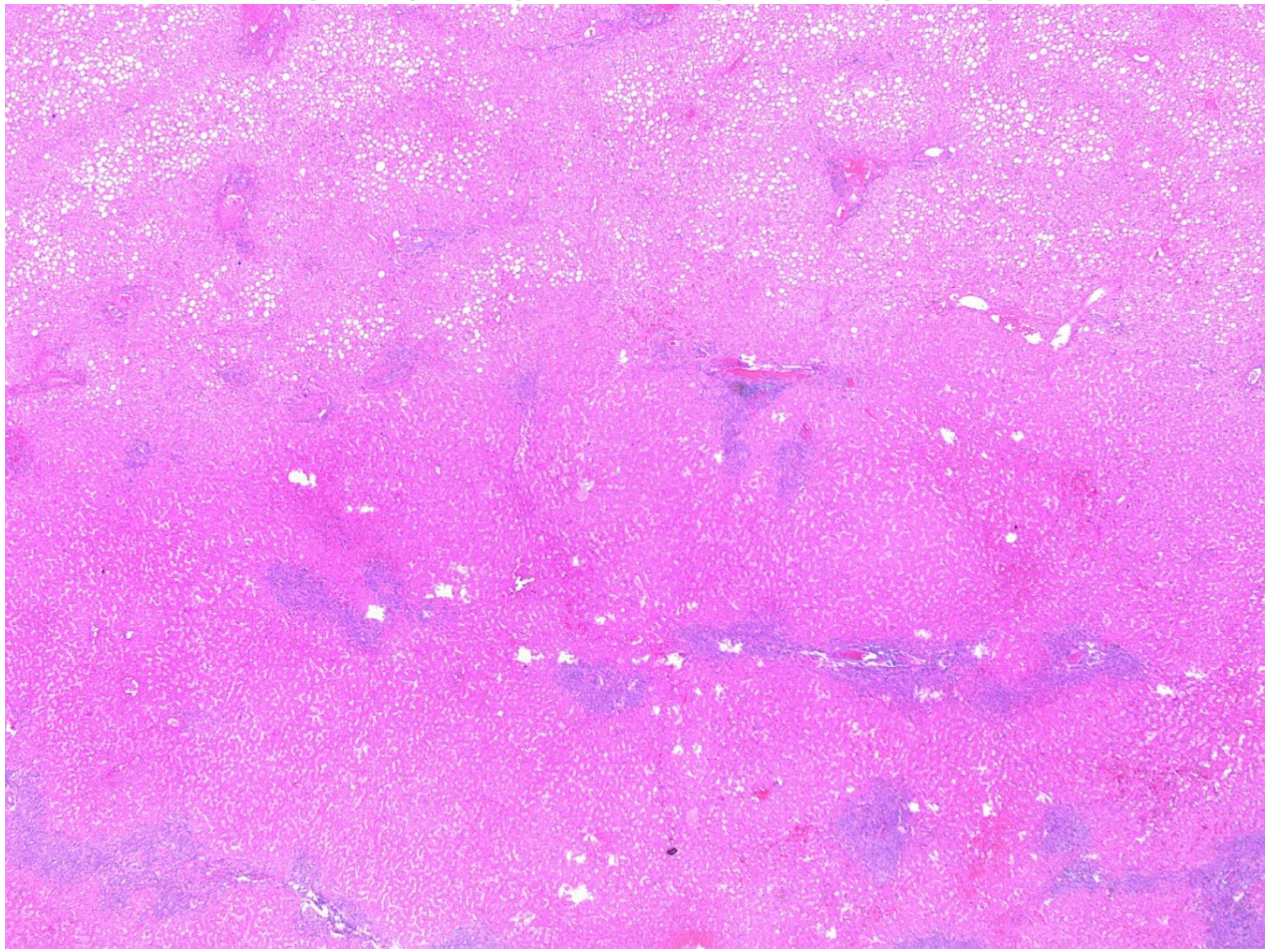
Microscopy Normal Liver Cont'd

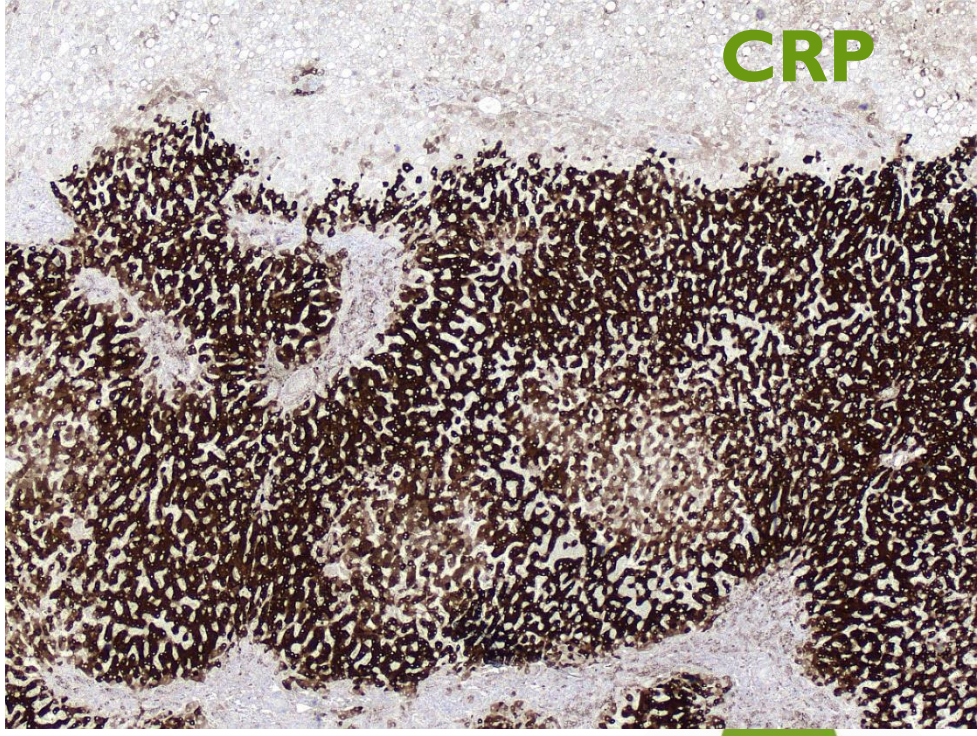


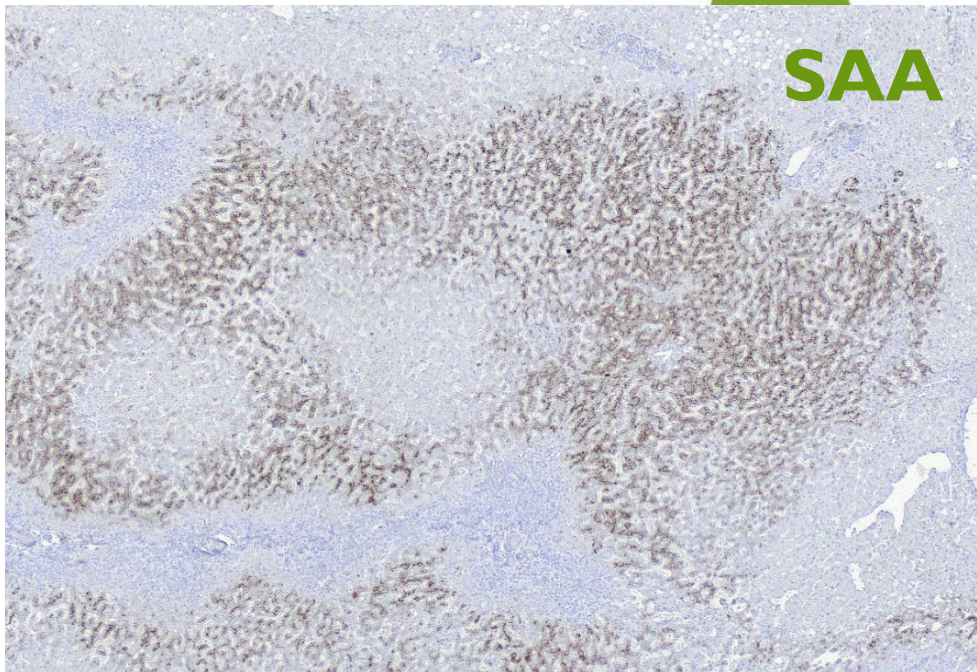
Inflammatory HCAs

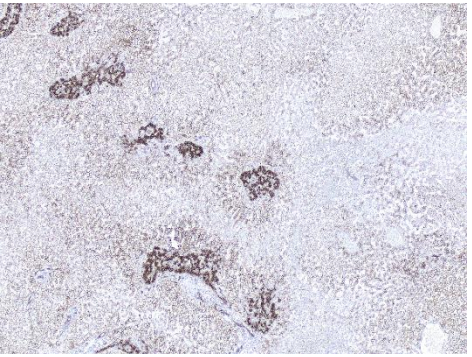
- Up to ½ of all HCA
- Due to mutation in JAK-STAT cell signalling pathway
- H&E – inflammation, bile ductular reaction, telangiectasia
- IHC – serum amyloid A and CRP are expressed

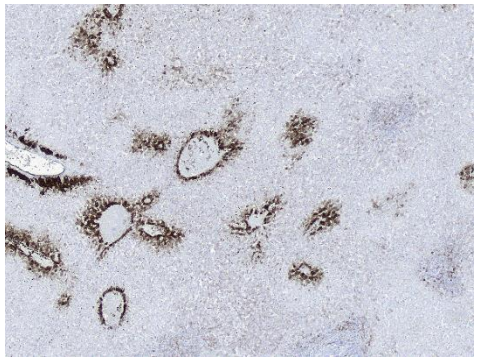
Benign hepatocytes arranged in regular plates





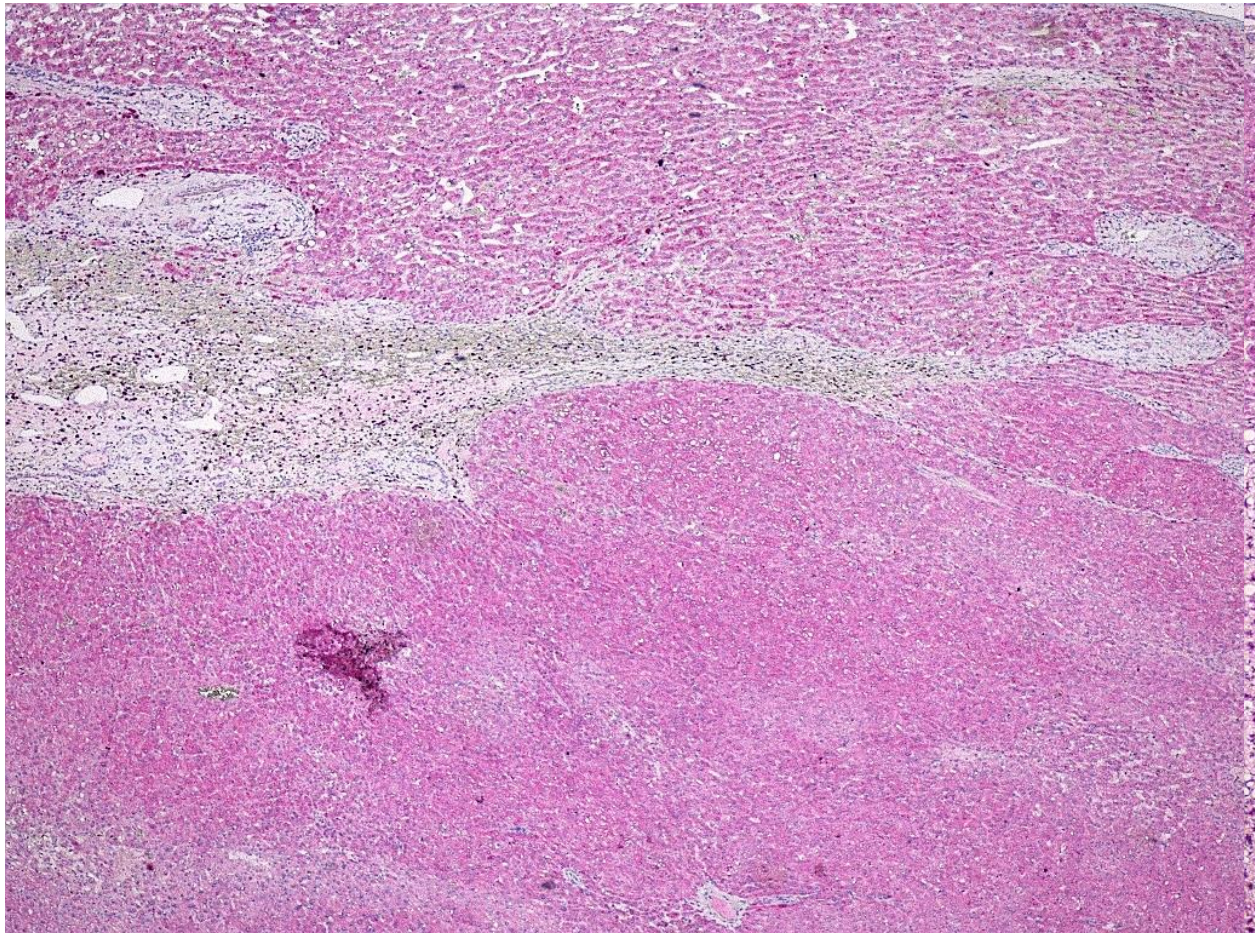


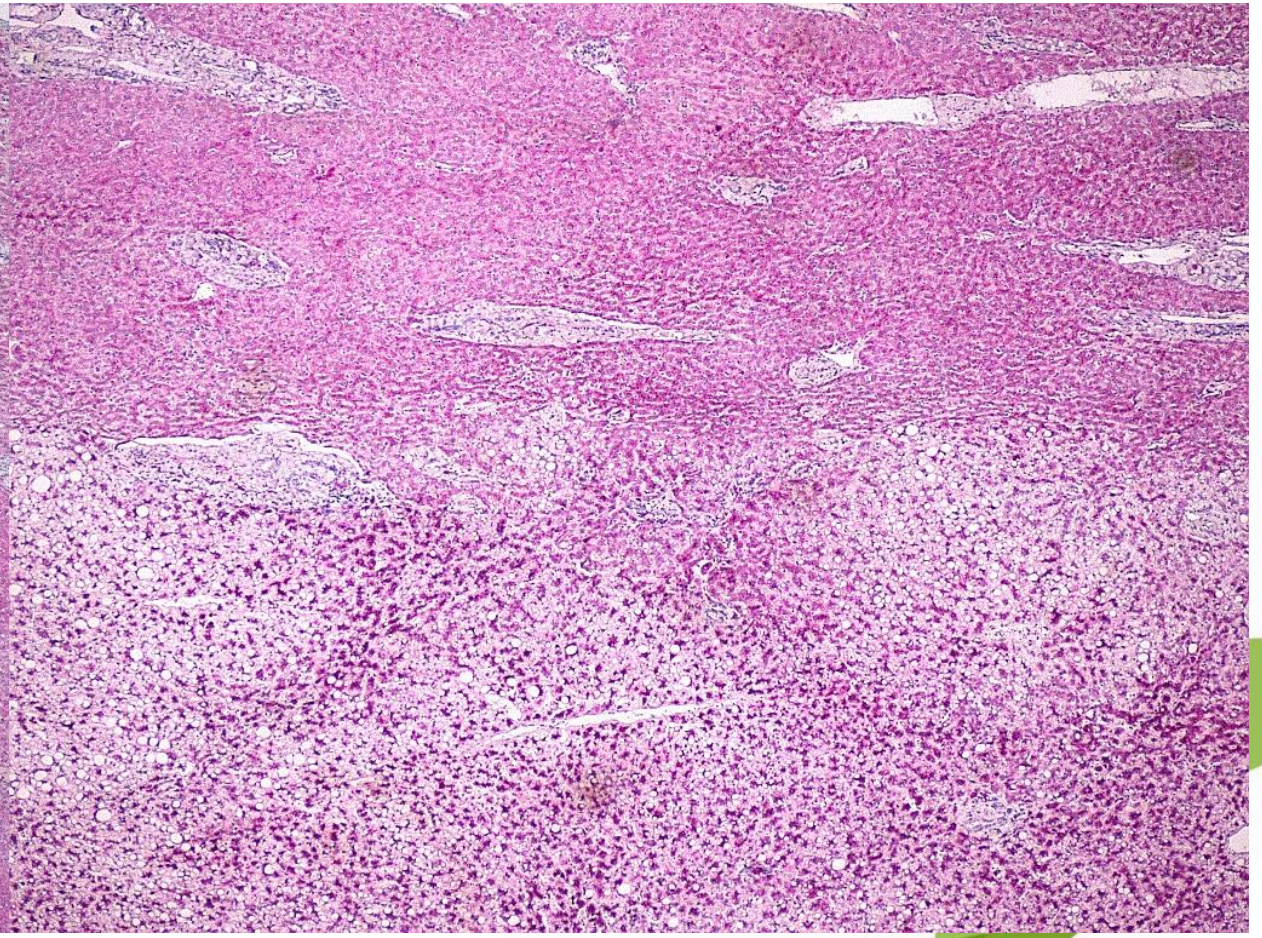




SAA Alk-Phos Chromogen

Normal Liver

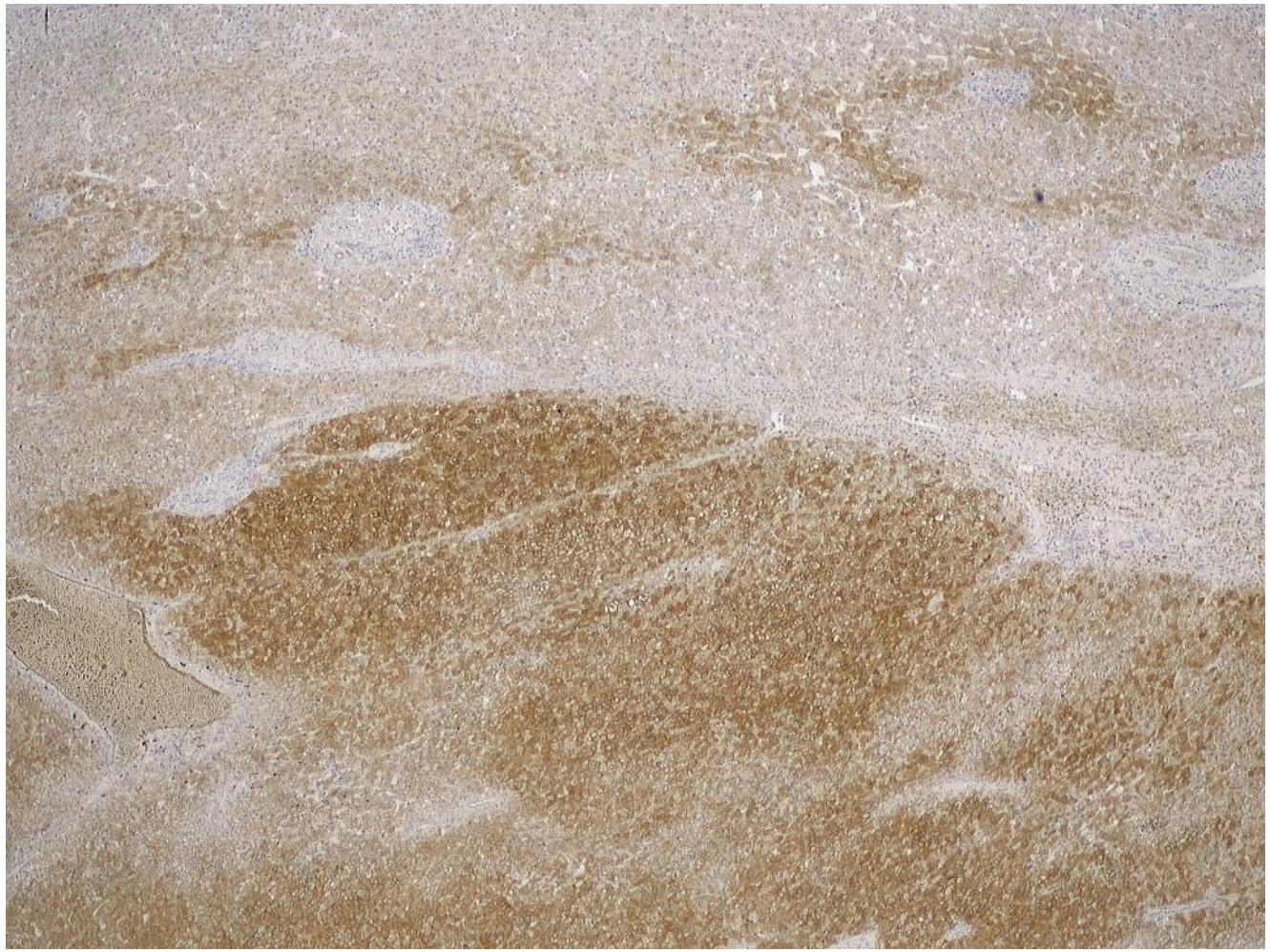




Adenoma

Repeated with DAB

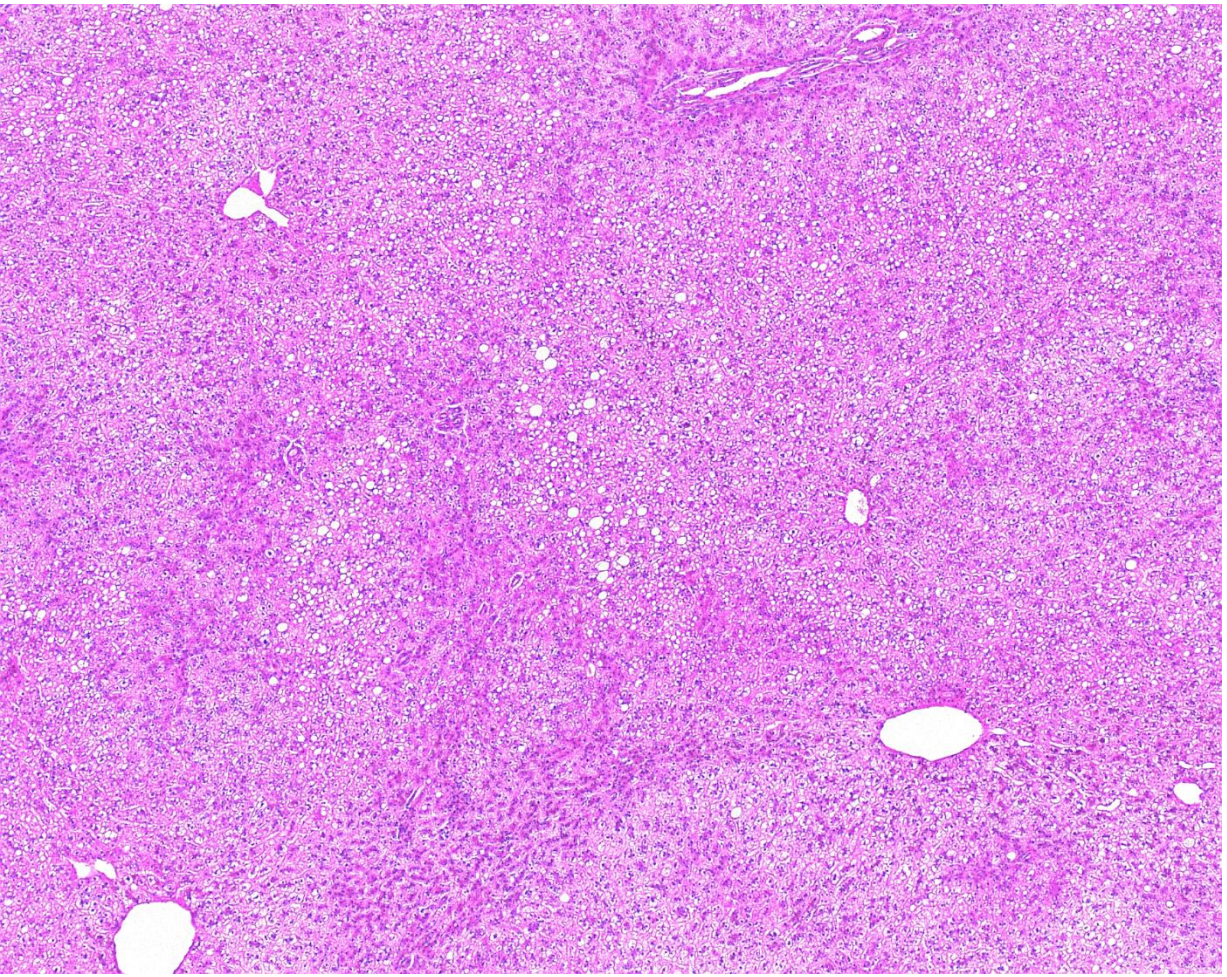
Normal Liver



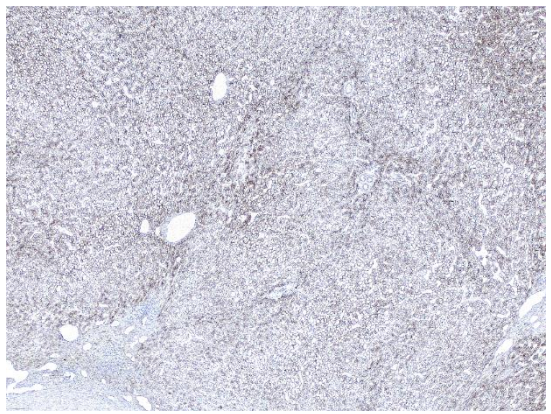
Adenoma

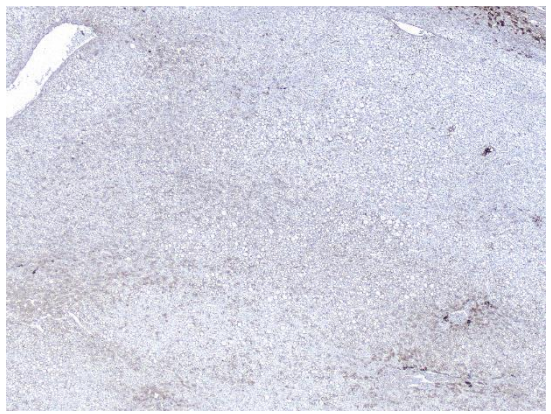
HCA, HNF1-alpha inactivated

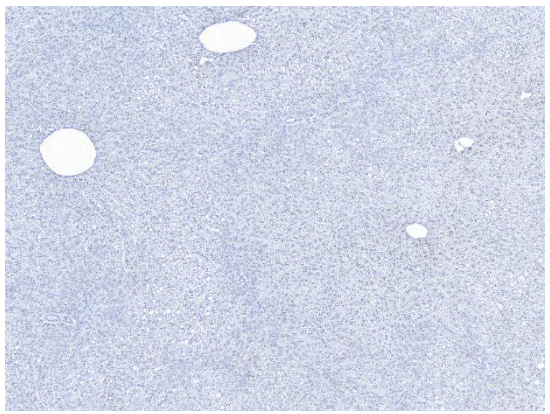
- 1/3 of all HCA
- Due to inactivation of HNF1α
- Fatty acid production, steatosis
- Loss of LFABP staining



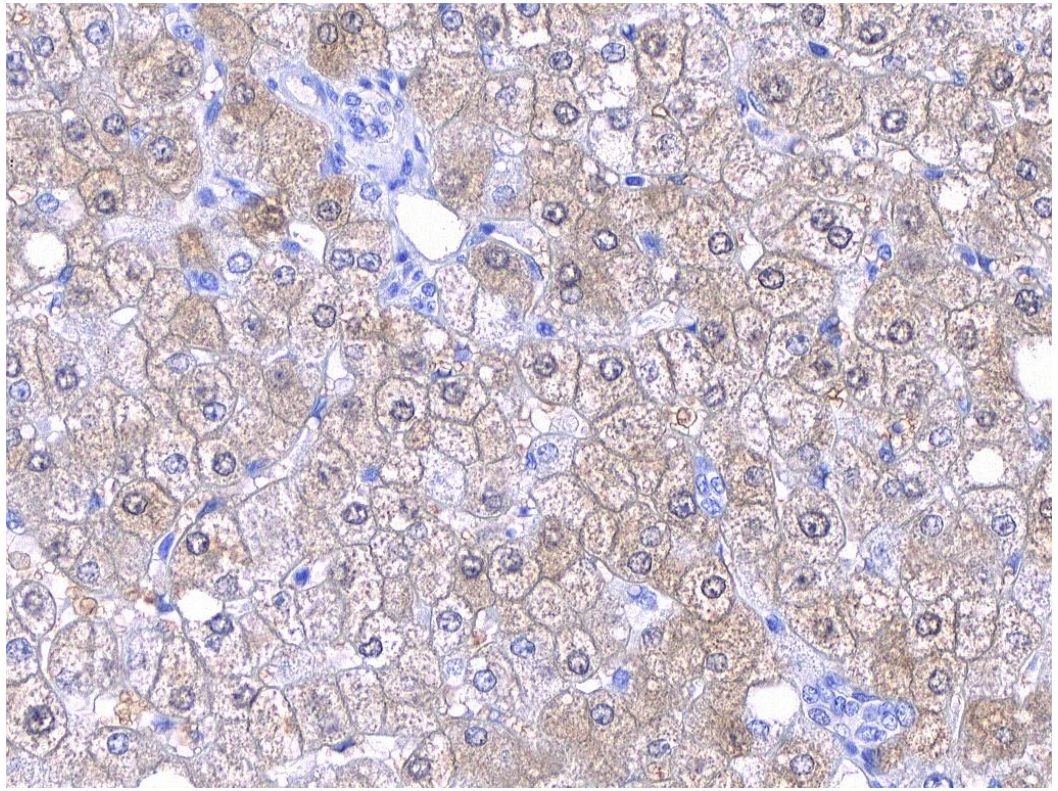

LFABP

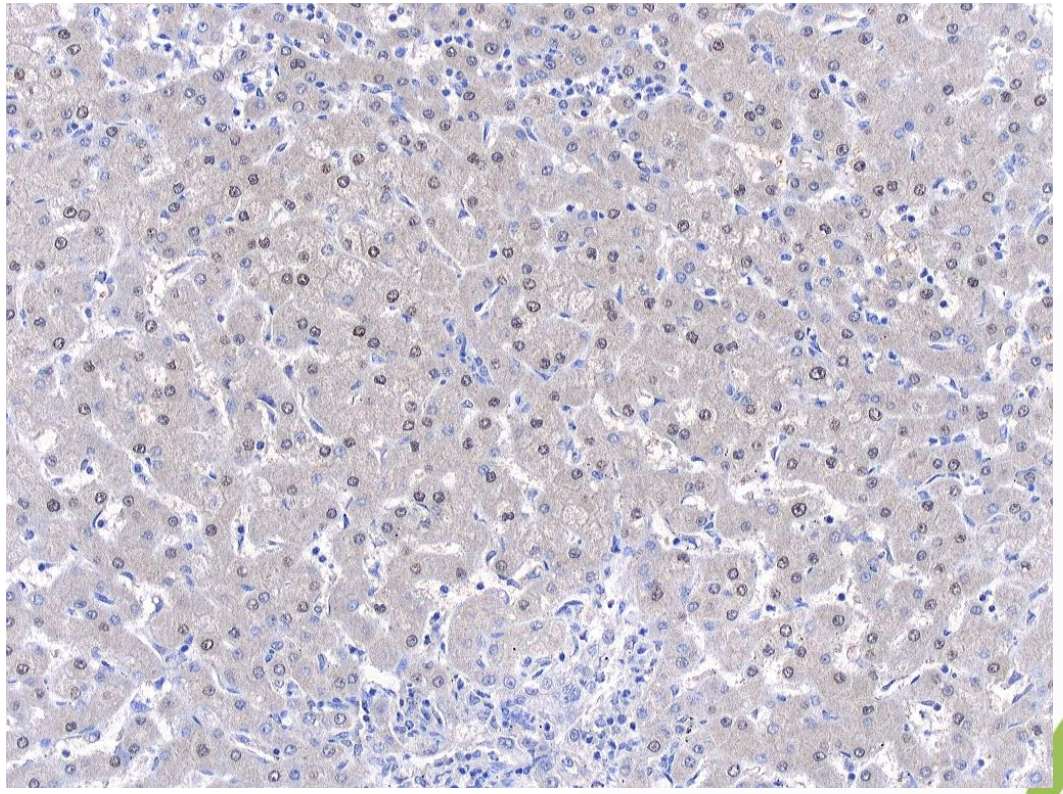






Weaker LFABP Staining





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Unfortunately, ab7807 is no longer available and has now been removed from our product list.

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Please let me know if you would like to order the alternative product ab76812 or cancel the order.

I apologize for the inconvenience and look forward to hearing from you.

Best regards,
Panda

Panda Hung
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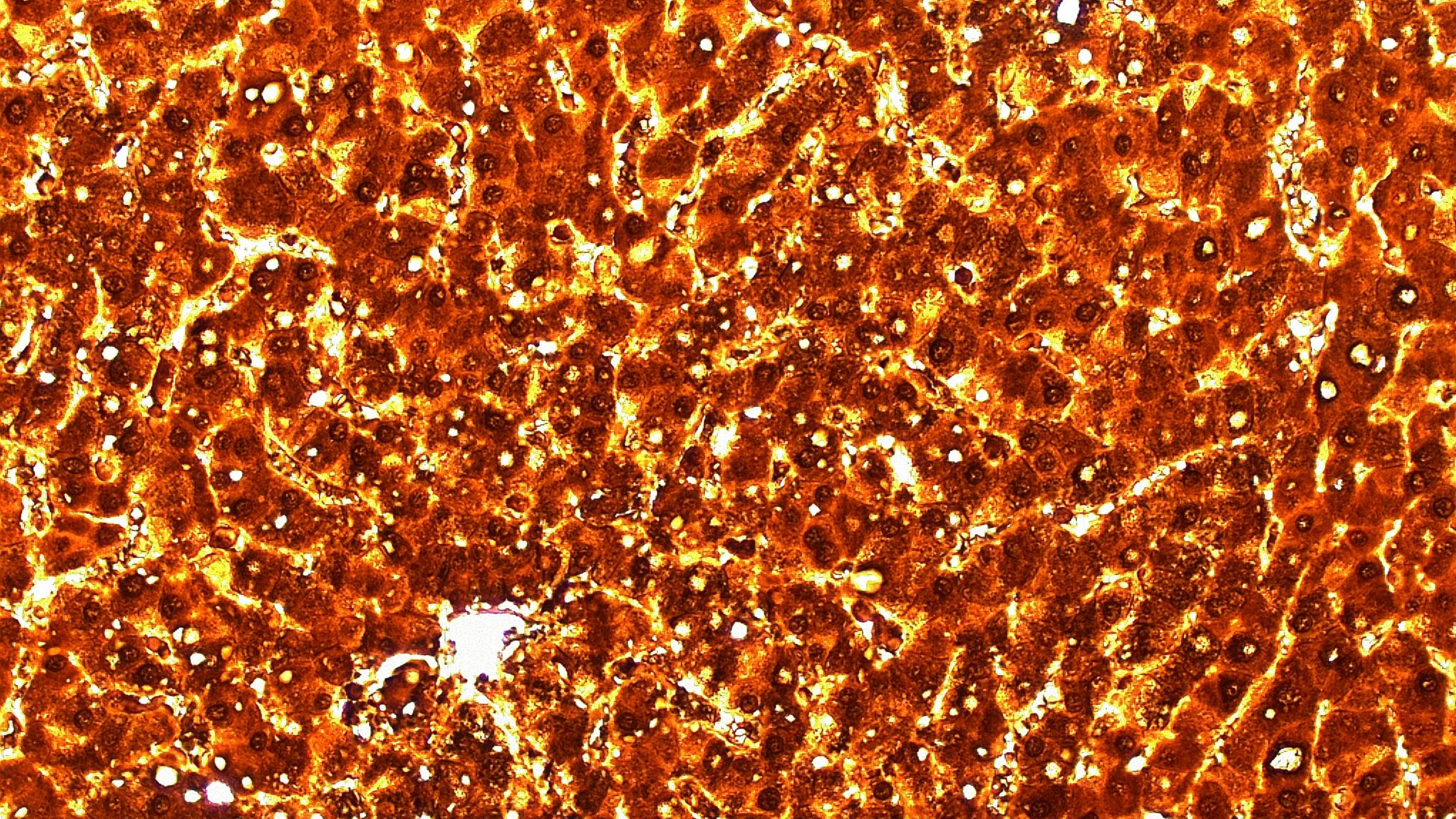

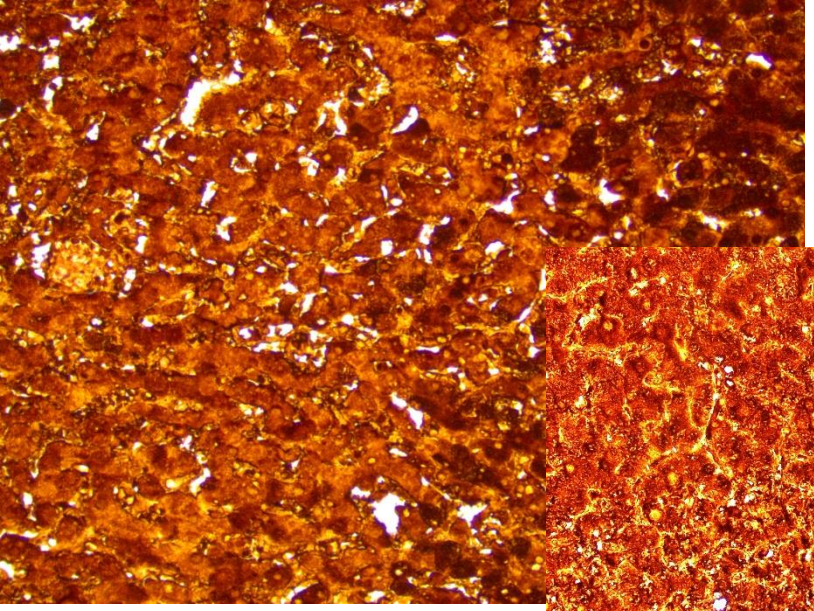

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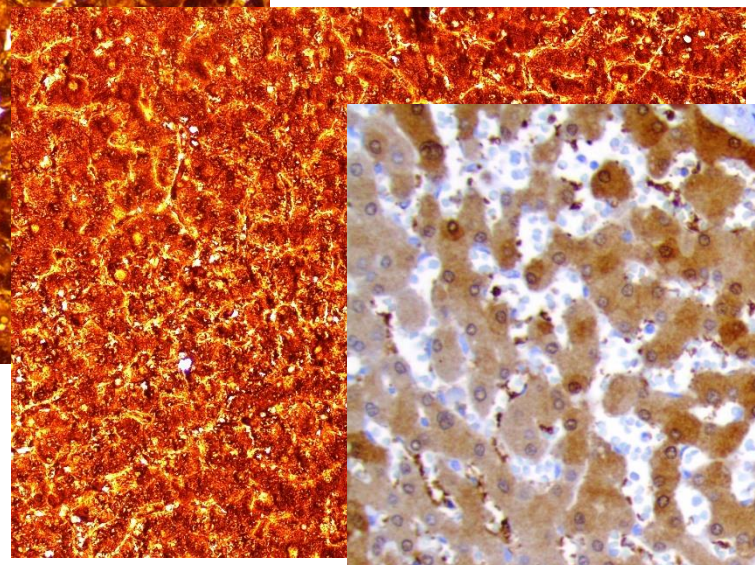

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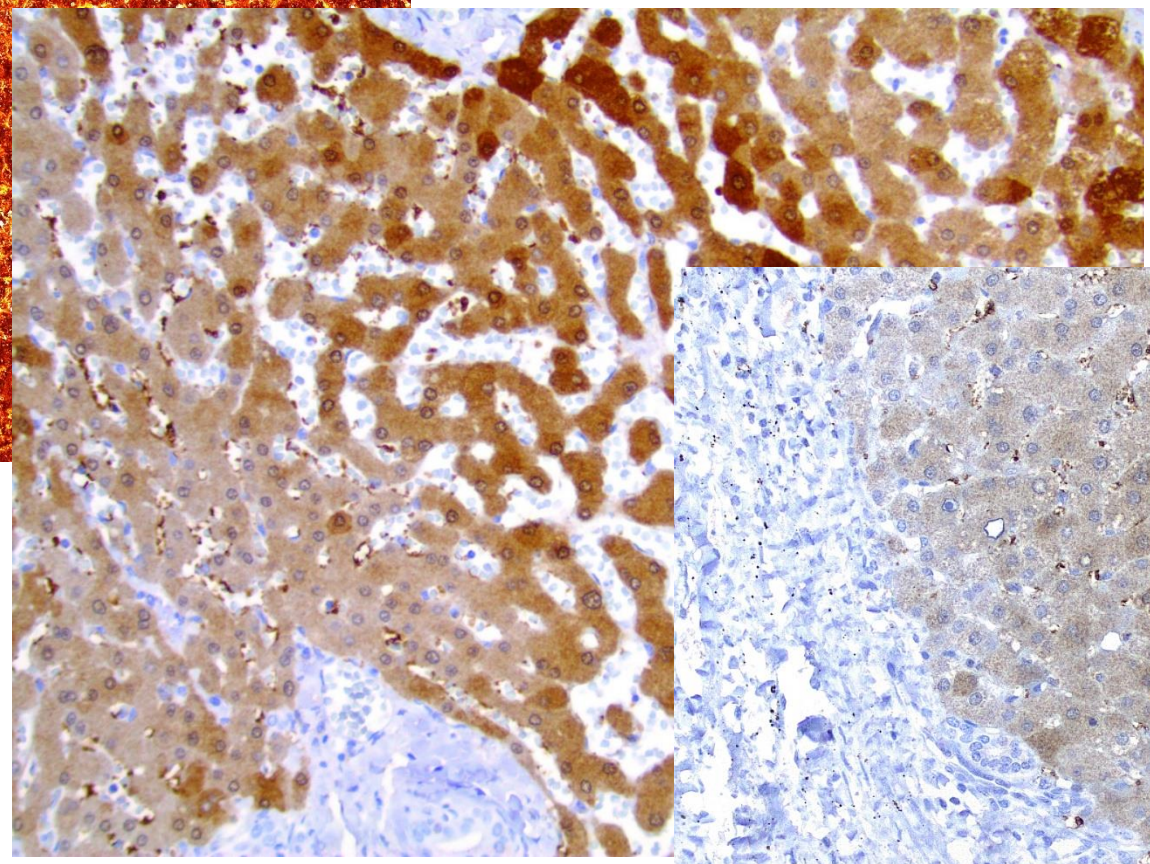

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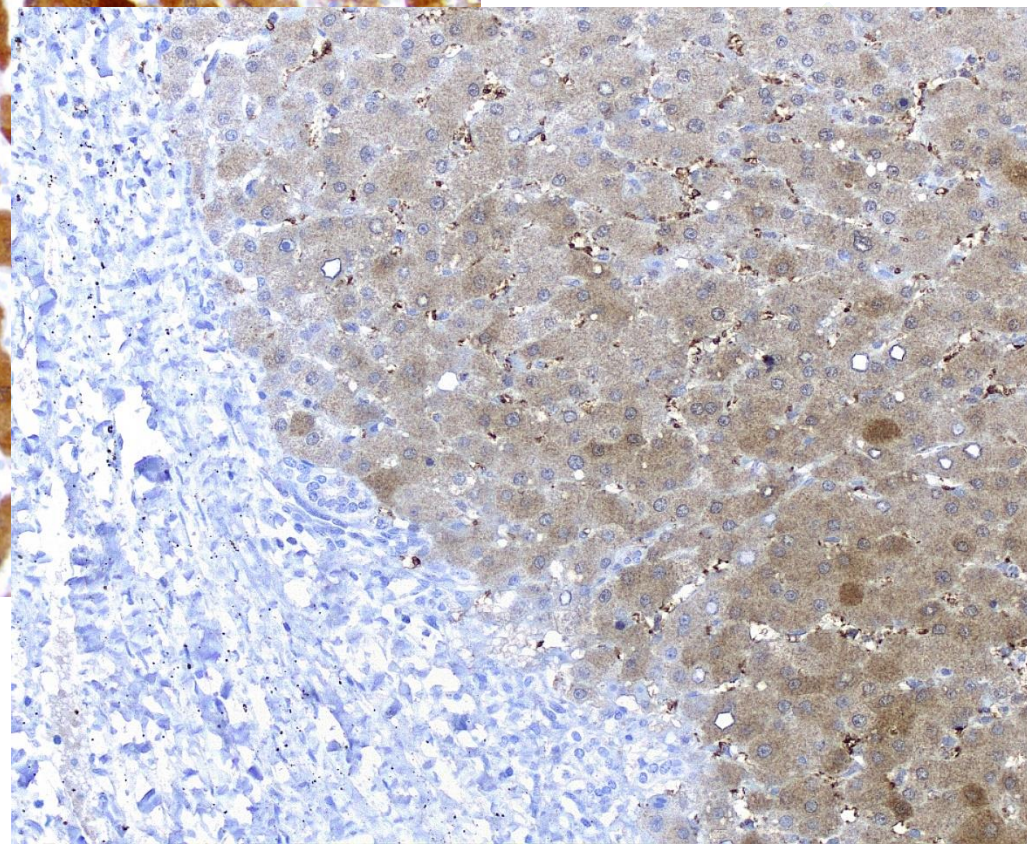

1:3200

HCA, beta catenin activated

- 10-15% of HCA
- 4% risk of malignant transformation
- Can show cholestasis and architectural and cytologic atypia
- Mutation in gene for b-catenin – WNT pathway activation
- Nuclear staining for B-catenin and diffuse staining for glutamine synthetase

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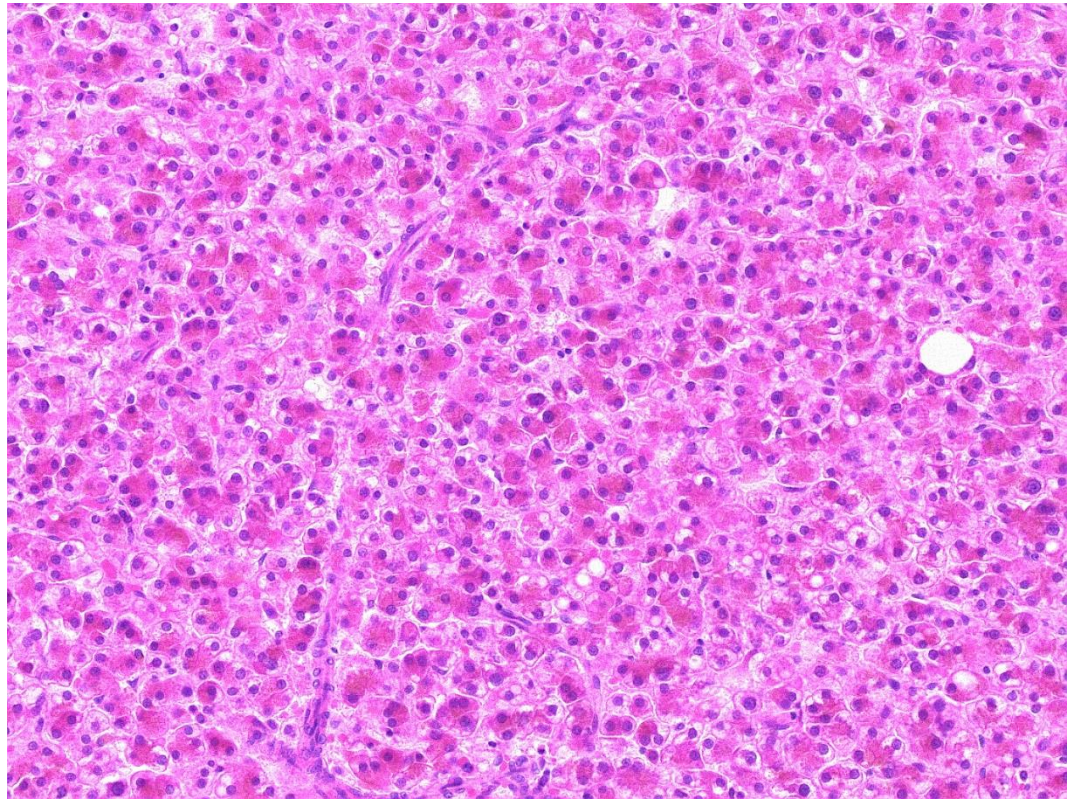
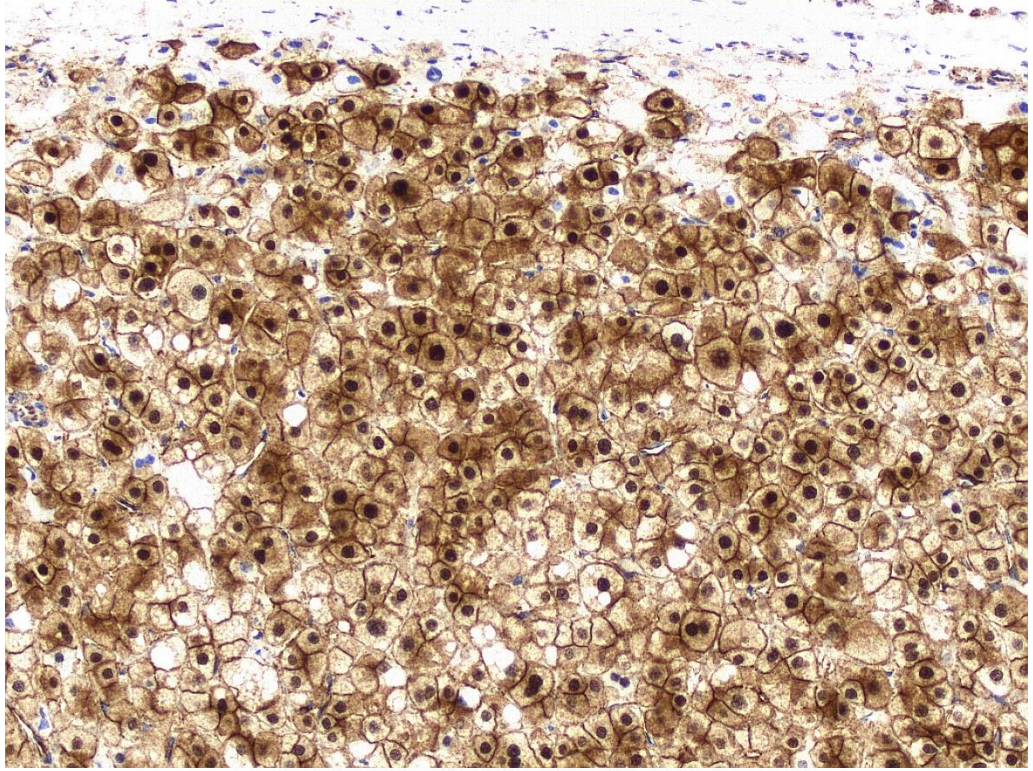
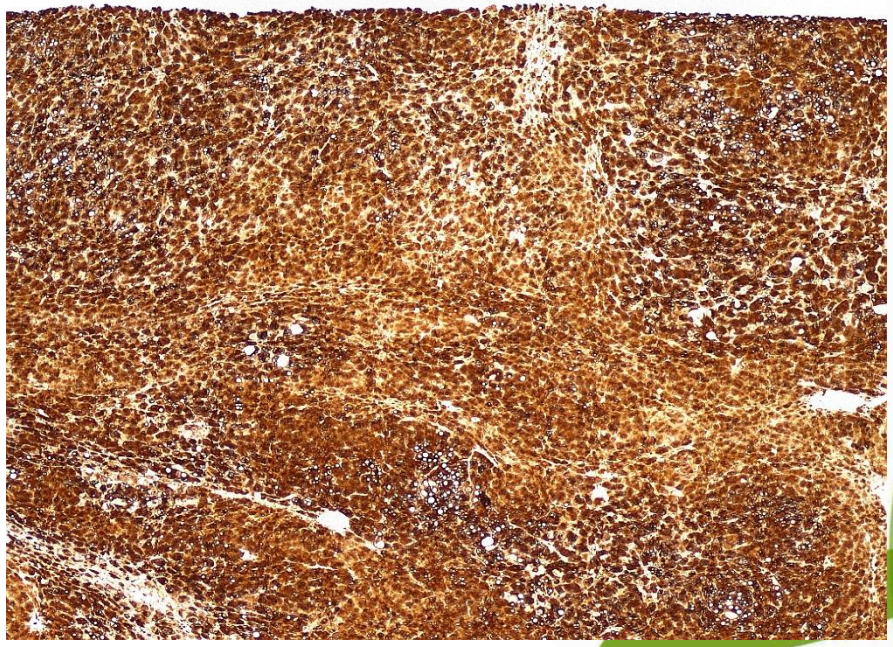


B-catenin



Glutamine synthetase



Well differentiated HCC

- Well differentiated HCC can be difficult to differentiate from a dysplastic nodule or HCA
- Accuracy improves when 2 of these 3 are positive
  - HSP70
  - Glypican 3
  - Beta catenin

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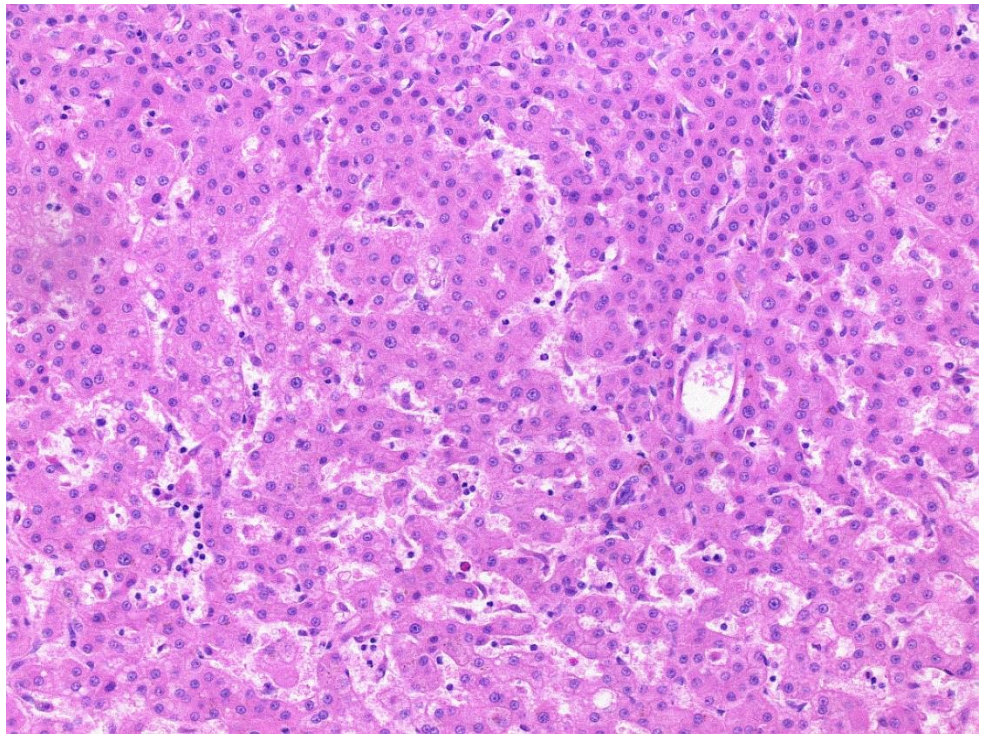
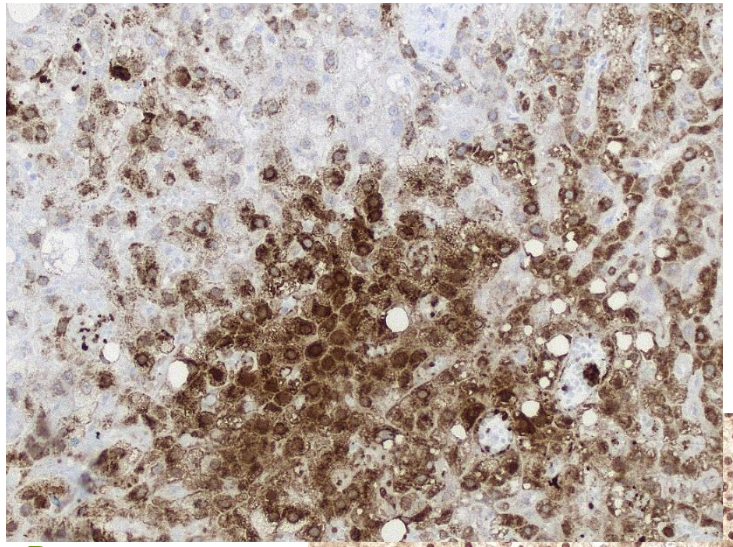
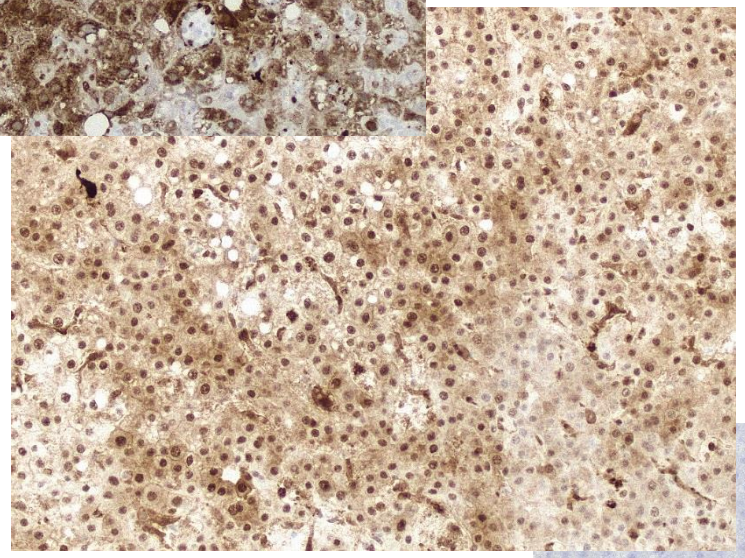
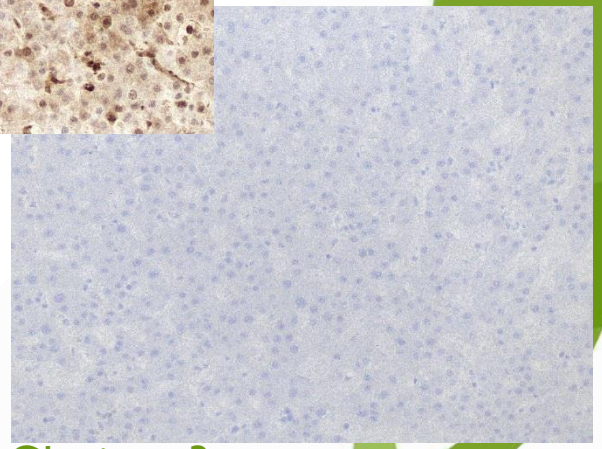




B-catenin



HSP70



Glypican 3

HCA, unclassified

- Up to 10% of cases
- No known mutation or morphologic pattern
- No abnormal IHC staining

Markers of hepatocellular differentiation

- Poorly differentiated HCC can be difficult to distinguish from other poorly differentiated malignancies – melanoma, carcinoma
- New markers have been developed to identify tumours with hepatocellular differentiation
  - Arginase-1
  - HepPar1
  - Glypican3

- CD10, pCEA, AFP

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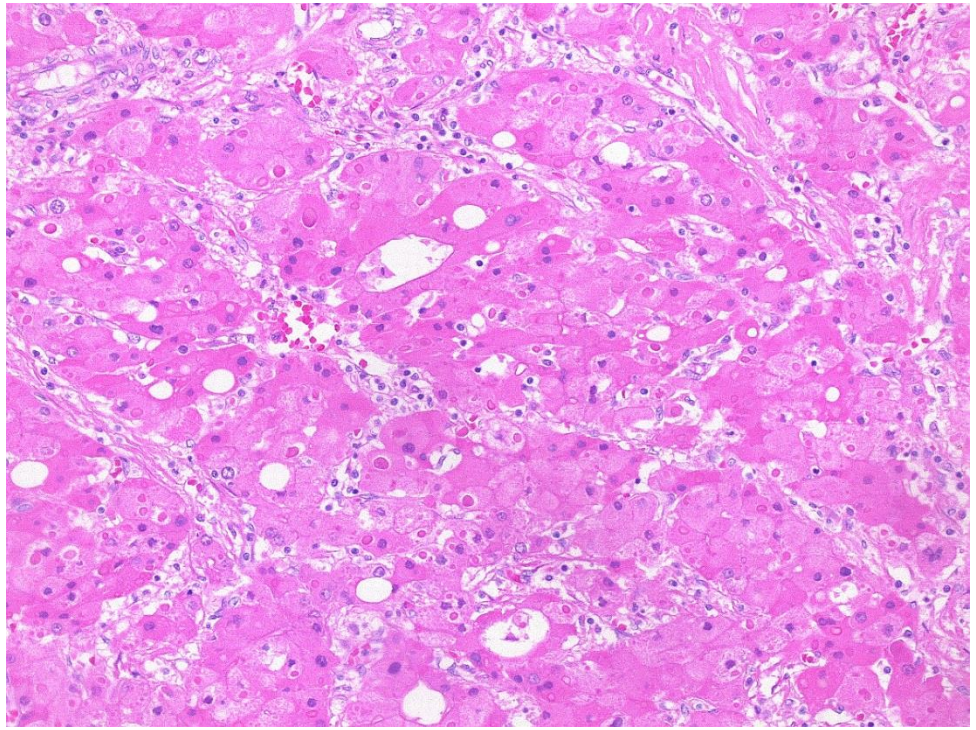
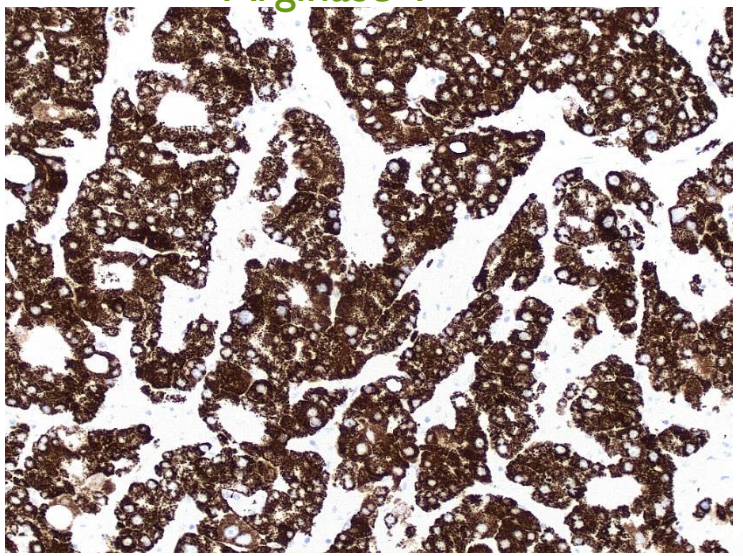
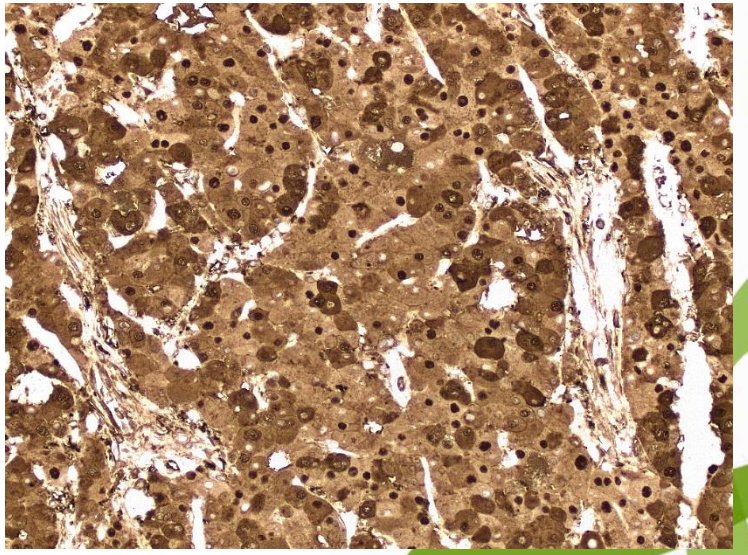
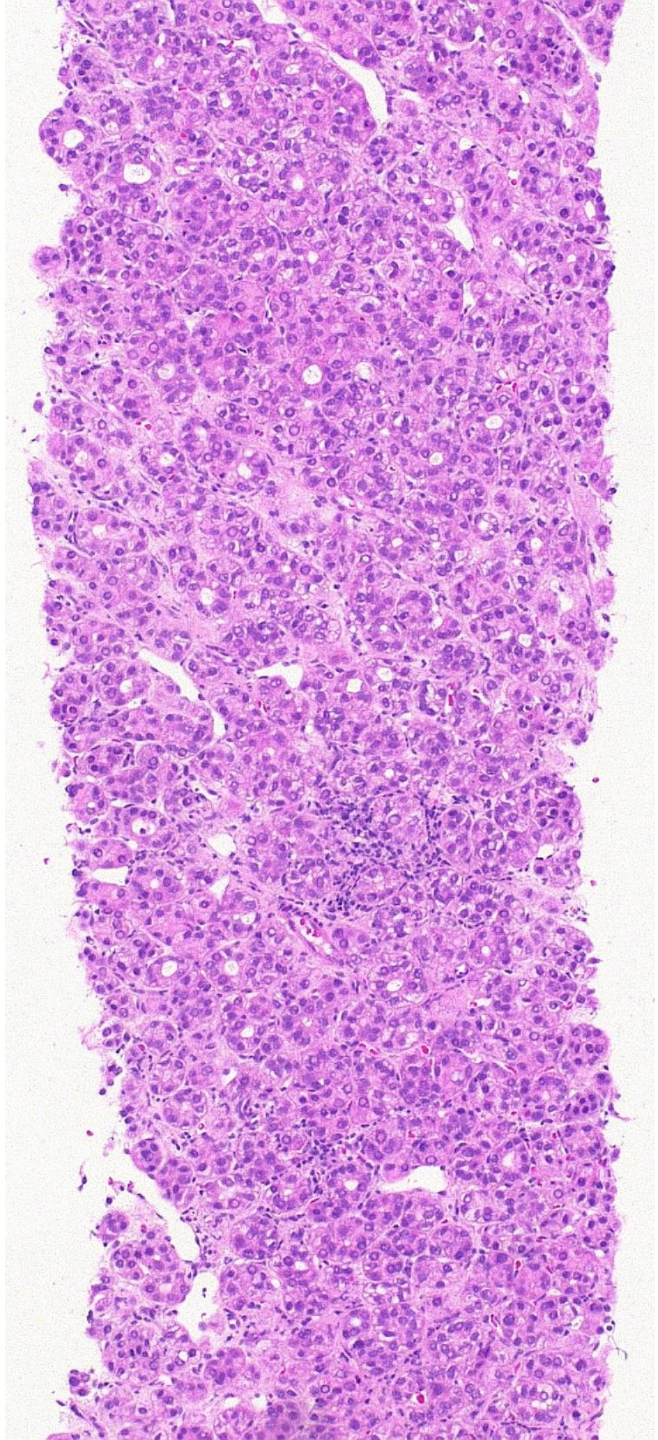


Arginase-1

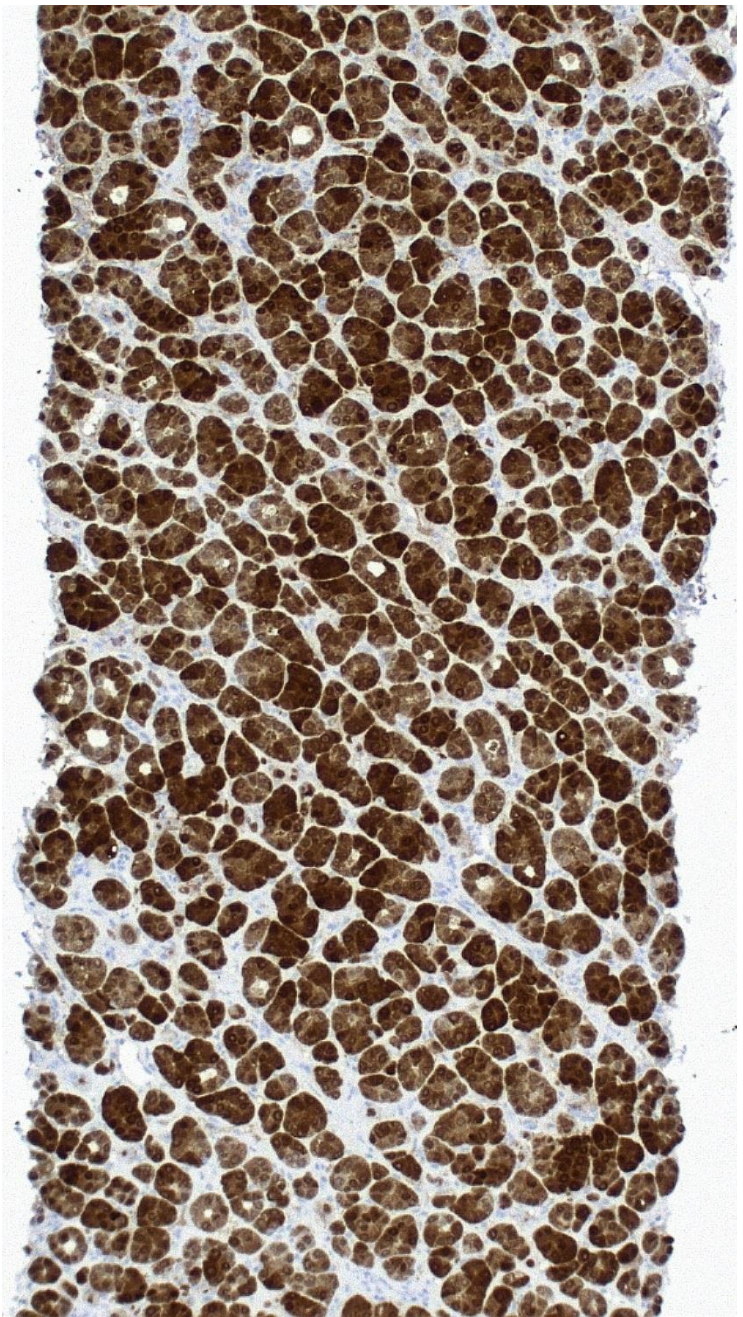


HepPar1

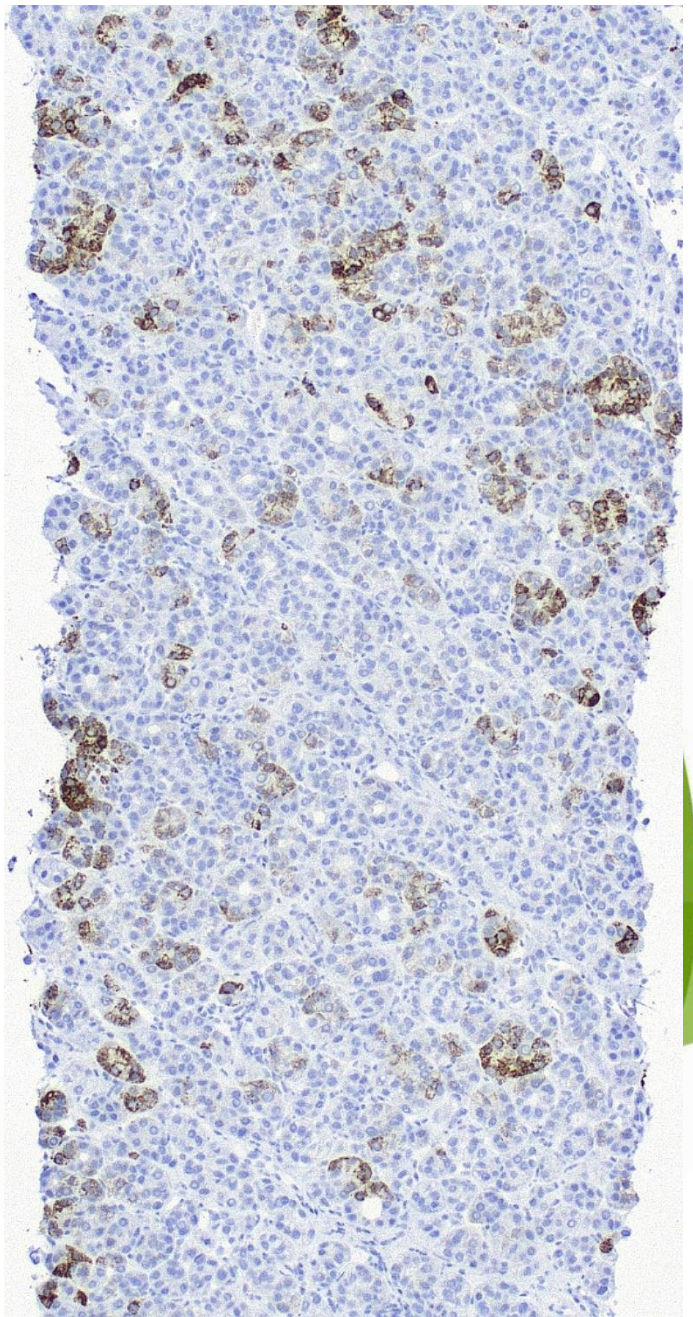


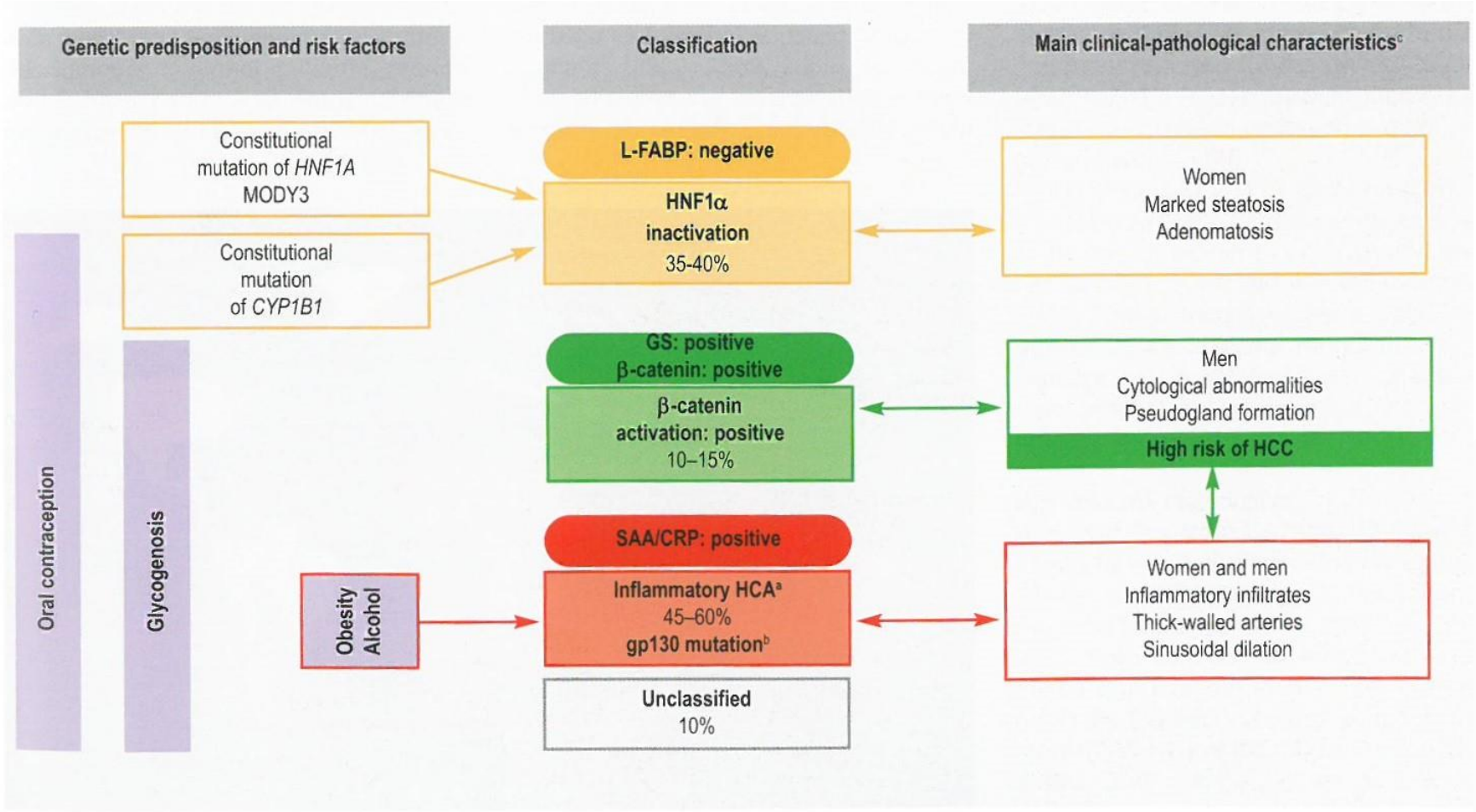


Arginase-1



HepPar 1




Genetic predisposition and risk factors
Classification
Main clinical-pathological characteristics[c]
Constitutional mutation of *HNF1A* MODY3
Constitutional mutation of *CYP1B1*
Oral contraception
Glycogenosis
Obesity
Alcohol
L-FABP: negative
HNF1α inactivation 35-40%
Women
Marked steatosis
Adenomatosis
GS: positive
β-catenin: positive
β-catenin activation: positive 10–15%
Men
Cytological abnormalities
Pseudogland formation
High risk of HCC
SAA/CRP: positive
Inflammatory HCA[a] 45–60% gp130 mutation[b]
Women and men
Inflammatory infiltrates
Thick-walled arteries
Sinusoidal dilation
Unclassified 10%

	HCA	HCC	FNH
B-Catenin	+ Should be Nuclear, but only rarely seen.		
Glutamine Synthetasae	+		
CRP/AA	+		Geographical Pattern
LFABP	Loss of Staining		
Glypican-3		+	
HSP70		+	
Hep-Par1		+ (Poorly Differentiated)	
Arginase1		+ (Poorly Differentiated)	
Reticulin		Loss of reticulin architecture.	
CD34		Increased. Vascularisation of the sinuses.	

Marker	Clone	Pre-treatment	Dilution	Supplier
LFABP	2G4	DAKO TRS High pH	1:3200	Abcam
Glutamine Synthetase	6/Glutamine Synthetase	DAKO TRS High pH	1:1000	Becton Dickinson
Amyloid-A	MC1	DAKO TRS High pH	RTU	Agilent
C-Reactive Protein	Y284	DAKO TRS High pH	1:1500	Abcam
β-Catenin	β-catenin-1	DAKO TRS High pH	RTU	Agilent
Arginase 1	SP156	DAKO TRS High pH	1:3000	Cell Marque
Hep-Par 1	OCH1E5	DAKO TRS High pH	RTU	Agilent
Glypican 3	1G12	DAKO TRS High pH	1:100	Cell Marque

Future Work

- Ass-1
- Initially used to try to classify unclassified HCA
- Shows strong link to risk of bleed 67.4%
- Also shown in some of the classified HCAs
- Tumours showed activation of Sonic Hedgehog Pathway

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Many thanks to Dr Greg Miller

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