HCC
The New Pathological Approach

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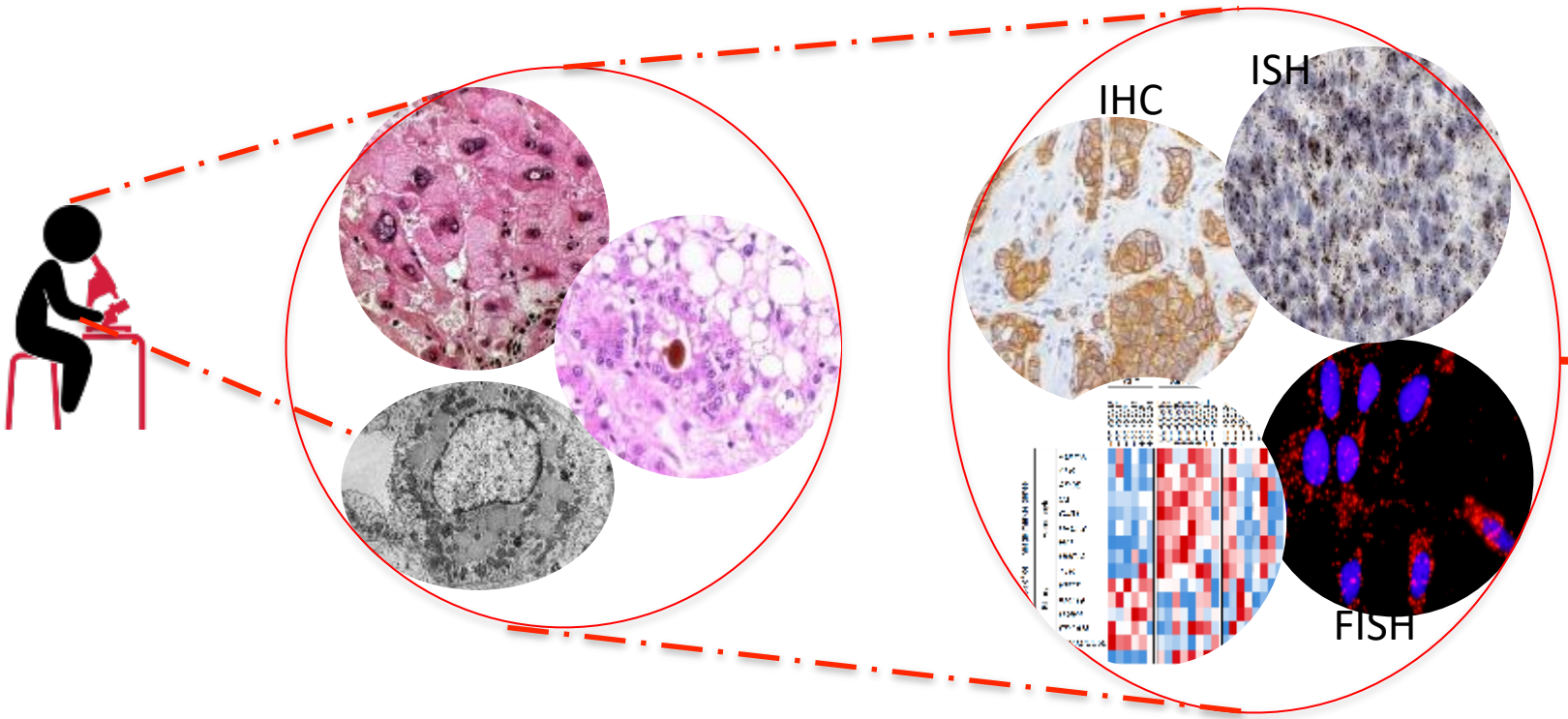
CRI CENTRE de RECHERCHE sur l'INFLAMMATION

From Conventional Histology to Molecular Pathology

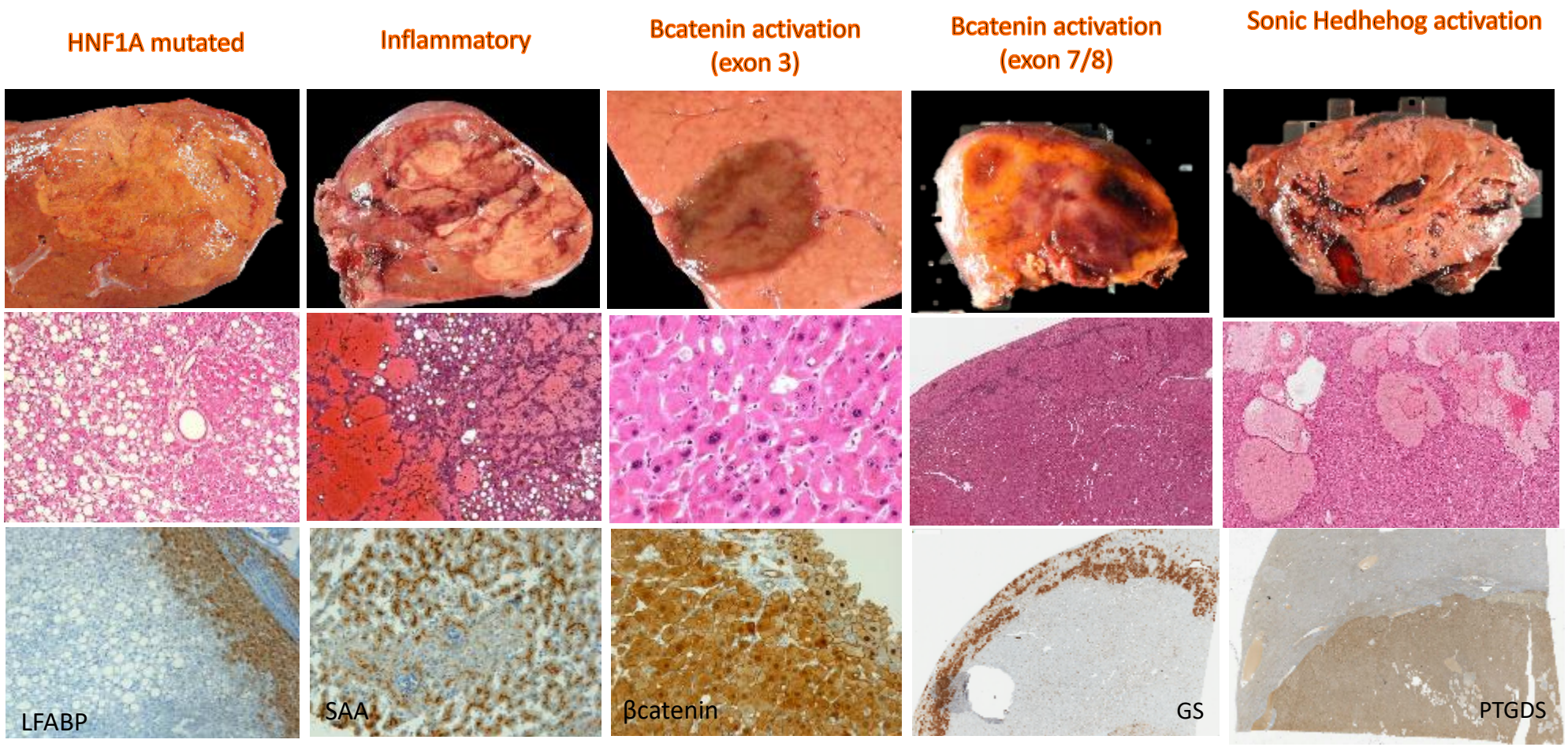


Molecular Pathology

👉 Routine pathological classification of tumor

👉 Provide prognostic and theranostic features for Precision Medicine

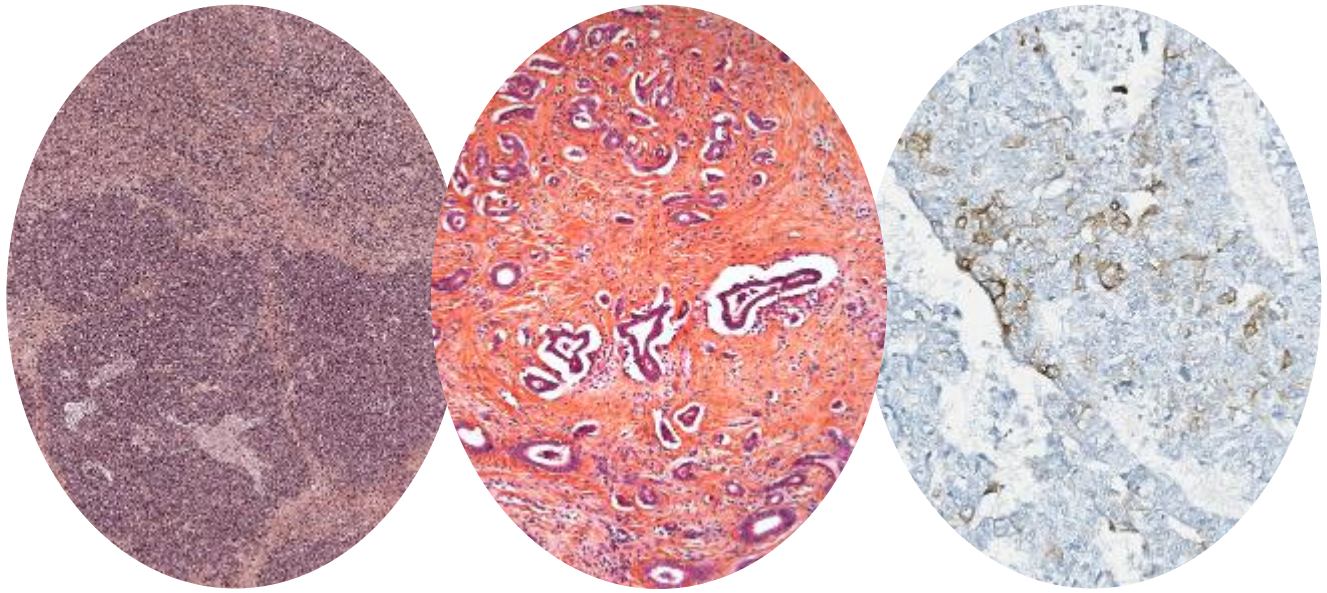
Pathomolecular Classification of Hepatocellular Adenomas



From 2006 to 2020

Molecular Pathology in HCC

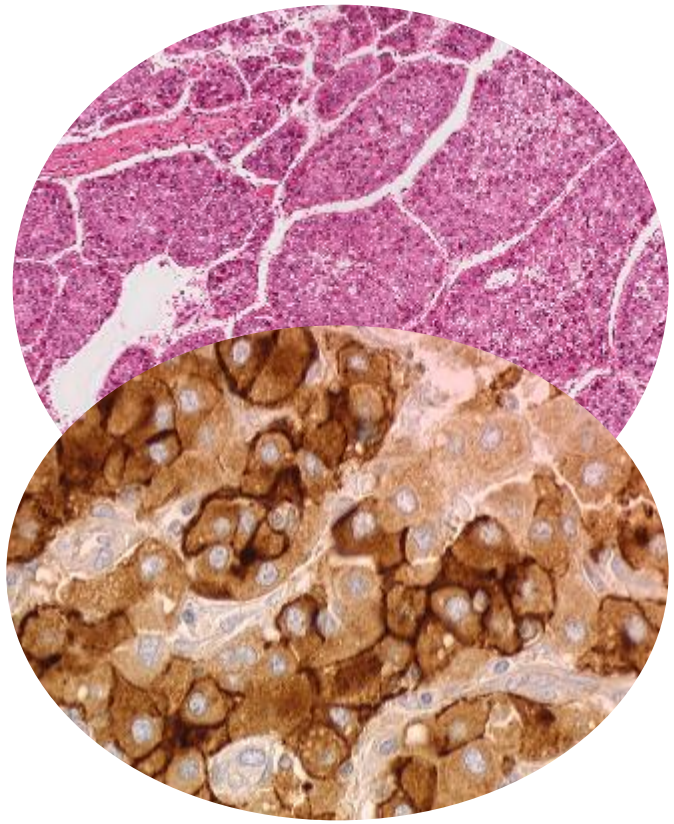
Intertumor heterogeneity &
Spatial Intratumor heterogeneity



➢ A key-issue in cancer medicine

- Impacts accurate diagnosis, prognosis and response to therapy
- Mostly explored at the genetic level by high-throughput NGS technologies
  - Using bulk tumor specimens
  - Ignoring cell heterogeneity and spatial organization
- The need to develop and use in situ approaches (Molecular Pathology)

Pathomolecular Classification of HCC



1. Diagnosis of early HCC (< 2 cm)

✓ Access to curative treatments

2. Exhaustive characterisation of HCC

✓ Improve patient management

1. DIAGNOSIS OF EARLY HCC (< 2 CM)

Hepatocellular nodules < 2 cm arising in cirrhosis
A wide spectrum of nodules (from regenerative to HCC)

Histological features

Cytologic features
- Small cell change
- Large cell change
- Clonelike foci (clear, fatty)

Architectural features
- Plate thickening ≥3 cells
- Increased cell density compared with surroundings
- Pseudoglands
- Nodule-in-nodule
- Portal tract
- Unpaired arteries and capillarized sinusoids[a]
- Stromal invasion[b]
- Reticulin framework

Immunophenotypical features

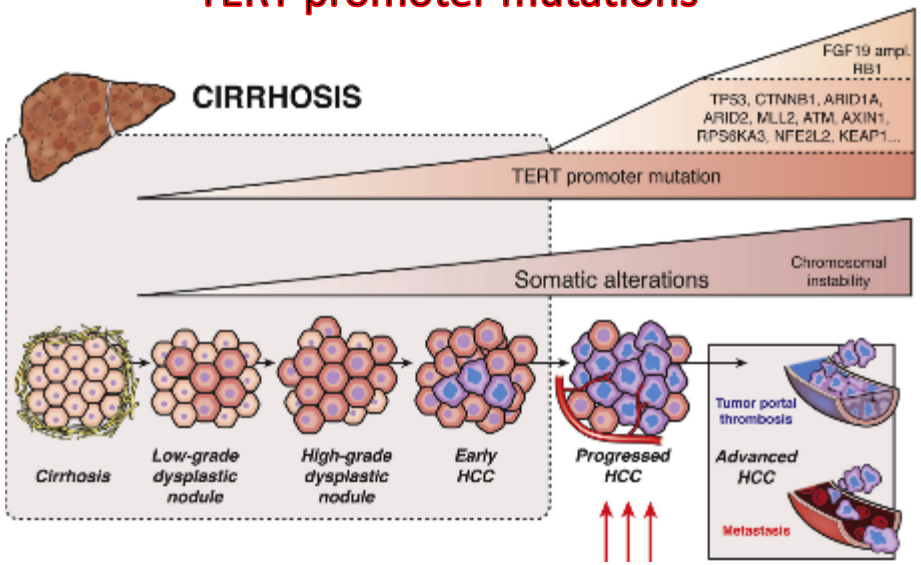
All 3 markers +ve (100% specificity, 72% sensitivity)

Accurate diagnosis of nodules < 2 cm remains challenging in some cases (biopsy specimen)

Park NY Arch Pathol Lab Med 2011, Di Tommaso L J Hepatol 2009, Tremosini S Gut 2012, Di Tommaso L Hepatology 2011

Need for Additional Tissue Biomarkers

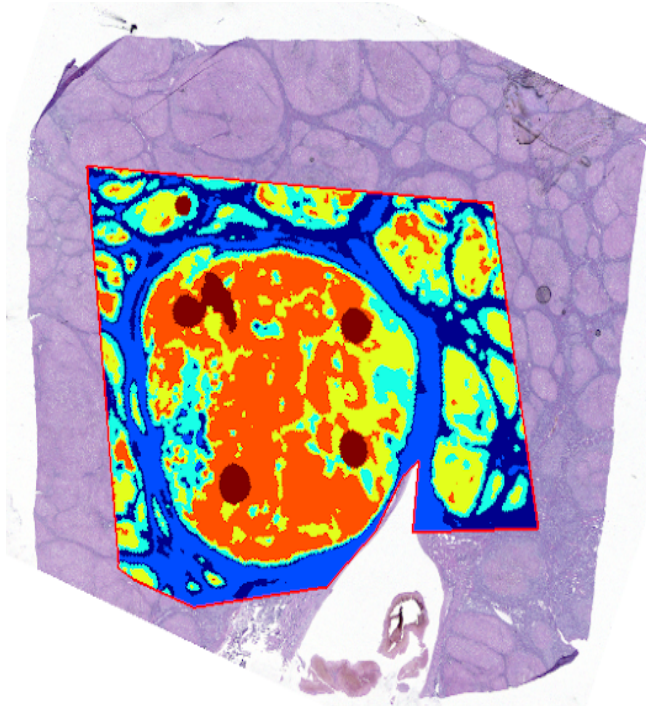
TERT promoter mutations



- Main mechanism of telomerase reactivation
- A prerequisite for malignant transformation
- The most frequent mutations in liver carcinogenesis
  - Increasing rate from cirrhosis (0%), LGDN (6%), HGDN (19%) to eHCC (61%)

Nault JC Hepatology 2014; Zucman-Rossi J Gastroenterology 2015

Surrogate tissue biomarkers of TERT promoter mutations in nodules < 2 cm using MALDI imaging (global in situ proteomic approach)



➢ 11 protein peaks correlated with TERT promoter mutations

S Paisley (manuscript in prep.)

2. EXHAUSTIVE CHARACTERISATION OF HCC

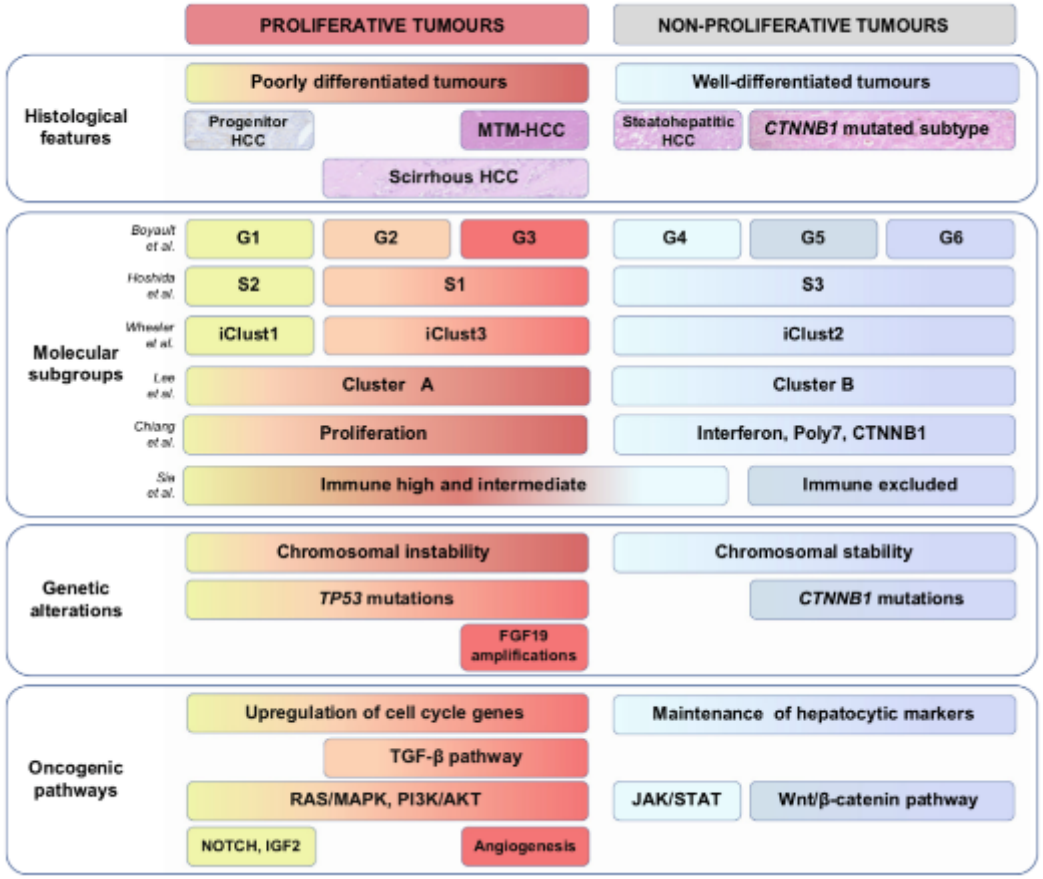
HCC : A Wide Spectrum of Tumors

WHO classification of tumours of the liver and intrahepatic bile ducts

Malignant hepatocellular tumours and precursors

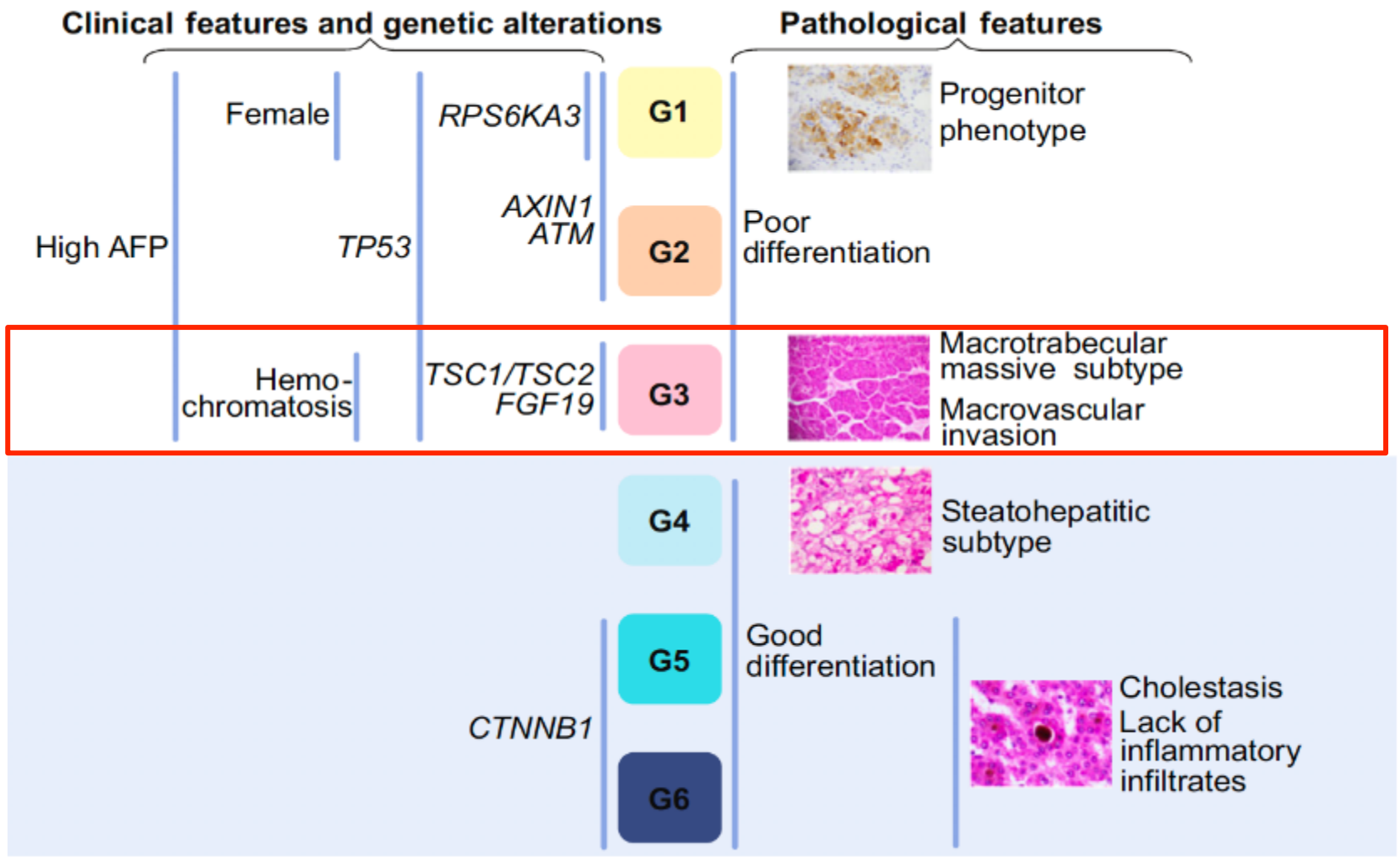
8170/3 Hepatocellular carcinoma NOS
8171/3 Hepatocellular carcinoma, fibrolamellar
8172/3 Hepatocellular carcinoma, scirrhous
8174/3 Hepatocellular carcinoma, clear cell type
Hepatocellular carcinoma, steatohepatitic
Hepatocellular carcinoma, macrotrabecular massive
Hepatocellular carcinoma, chromophobe
Hepatocellular carcinoma, neutrophil-rich
Hepatocellular carcinoma, lymphocyte-rich
8970/3 Hepatoblastoma NOS

WHO (5th edition, 2019)



From Calderaro J J Hep 2020

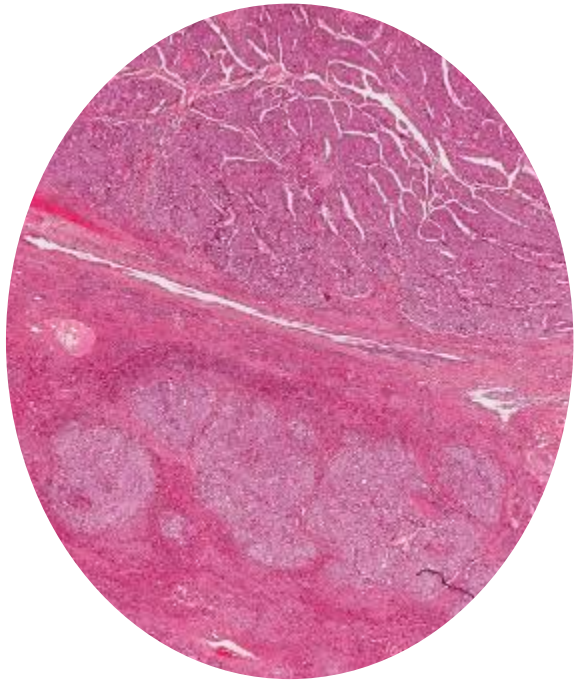
Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification☆



Calderaro J J Hepatol 2017

Macrotrabecular-Massive HCC (MTM-HCC, G3)

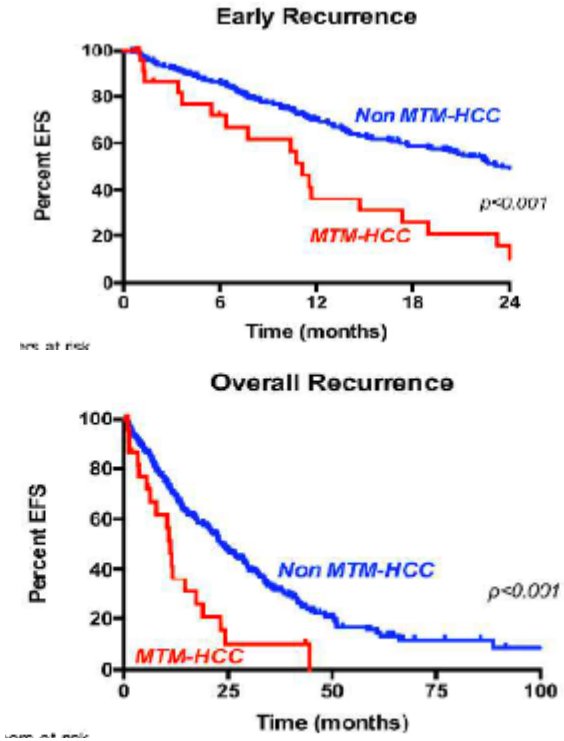
TP53 mutations



➢ Molecular features

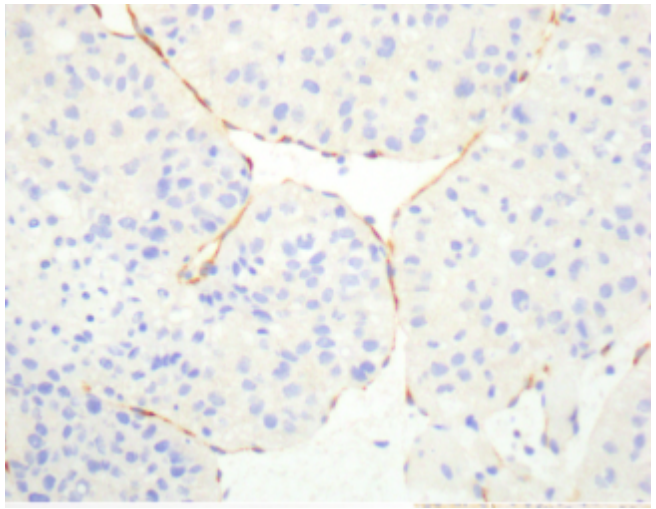
- PI3K/AKT pathway activation
- Increased cell proliferation
- EMT activation
- Angiogenesis activation

➢ Prognostic impact
284 HCC (Biopsy pre-RFA)



Ziol M Hepatology 2017

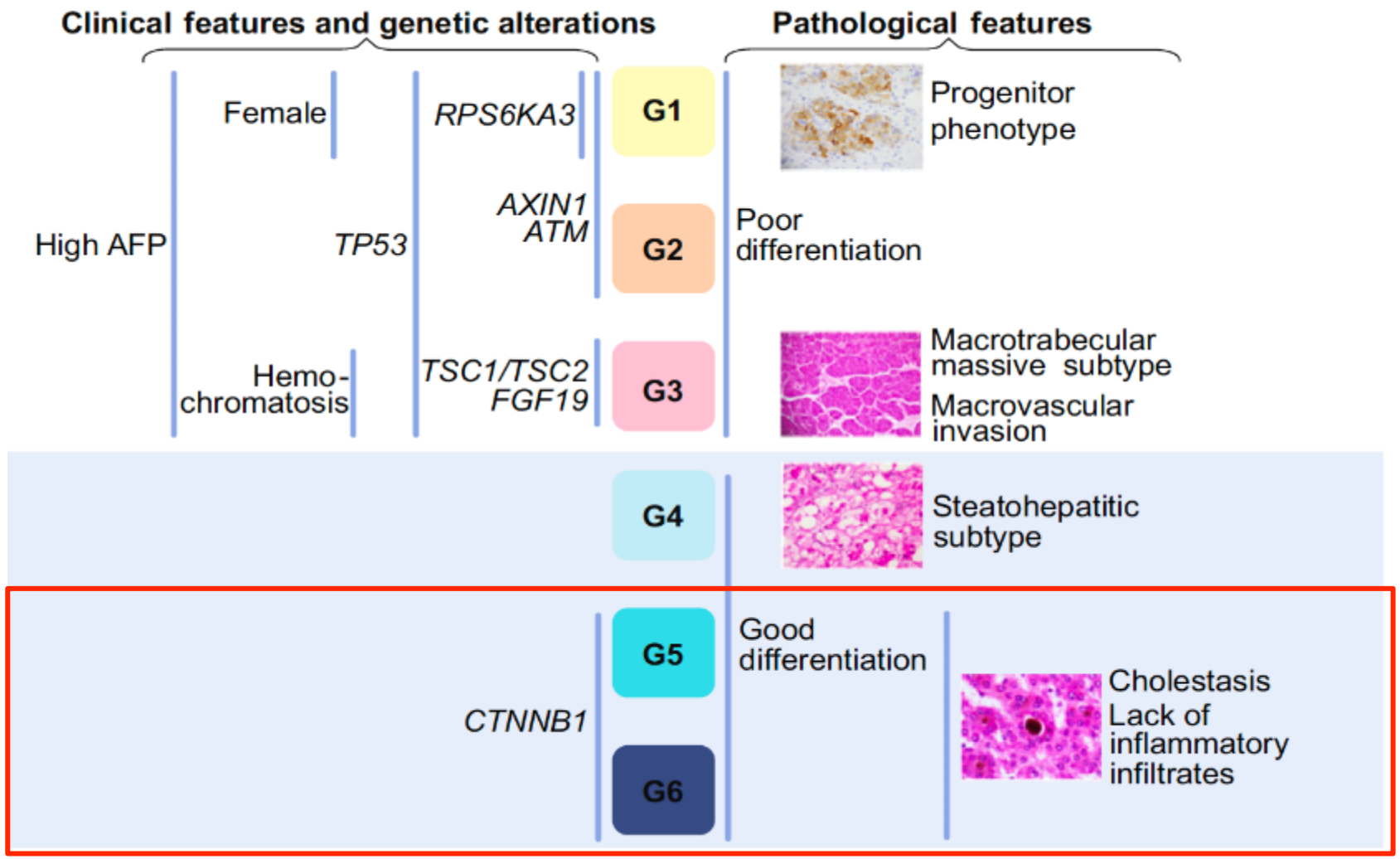
ESM-1
A good surrogate marker of MTM-HCC



Sst 93%, Spe 91%, Kappa 0.77

Calderaro J Clin Cancer Res 2019

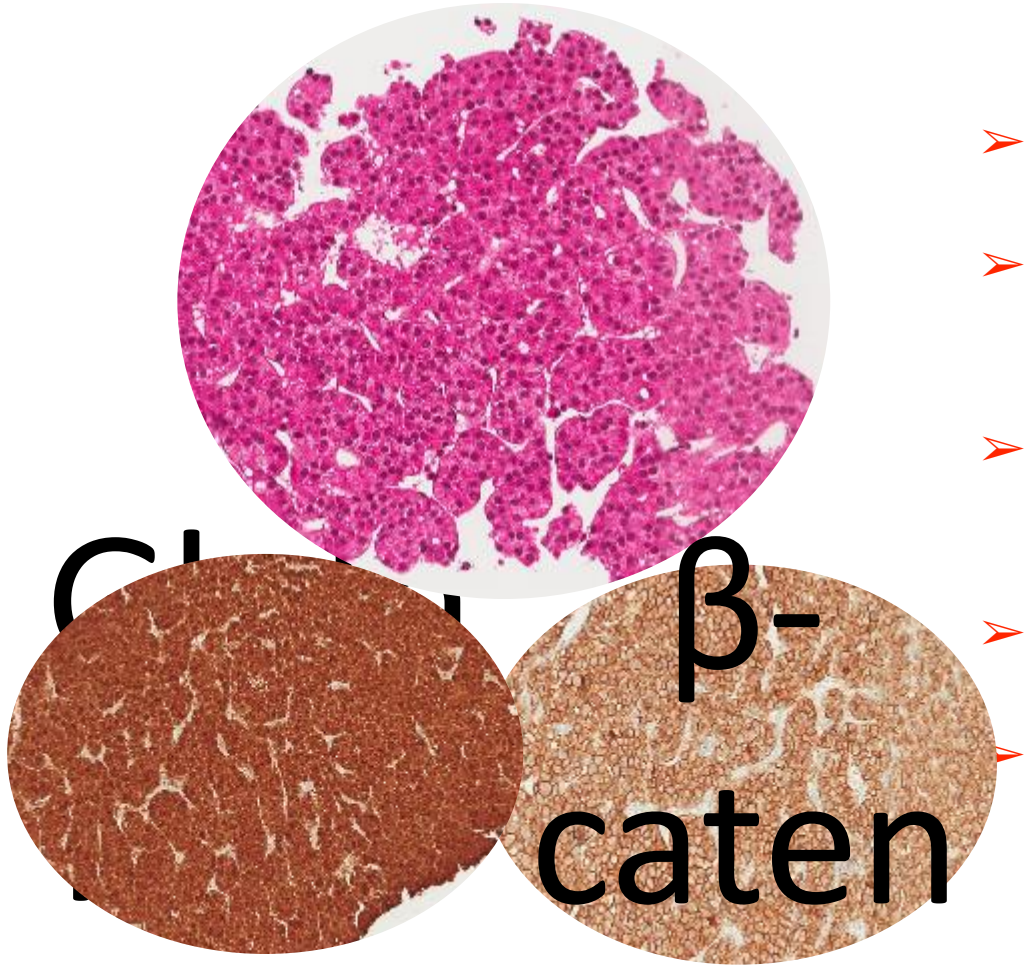
Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification☆



Calderaro J J Hepatol 2017

Well-differentiated Cholestatic HCC (G5-G6)

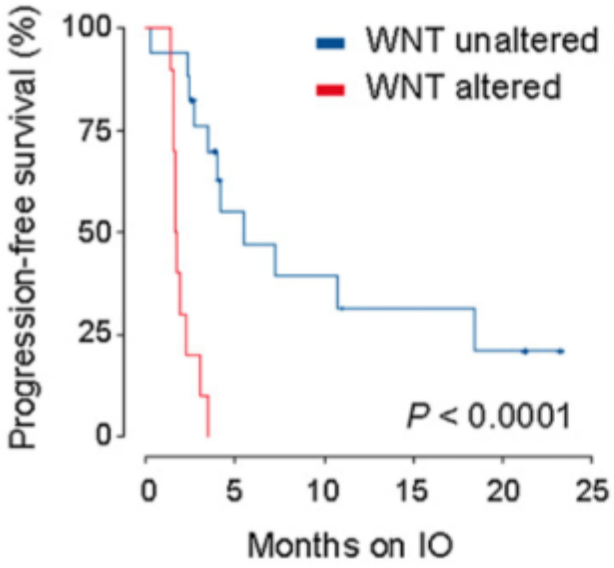
CTNNB1 mutations (exon 3)



Molecular features

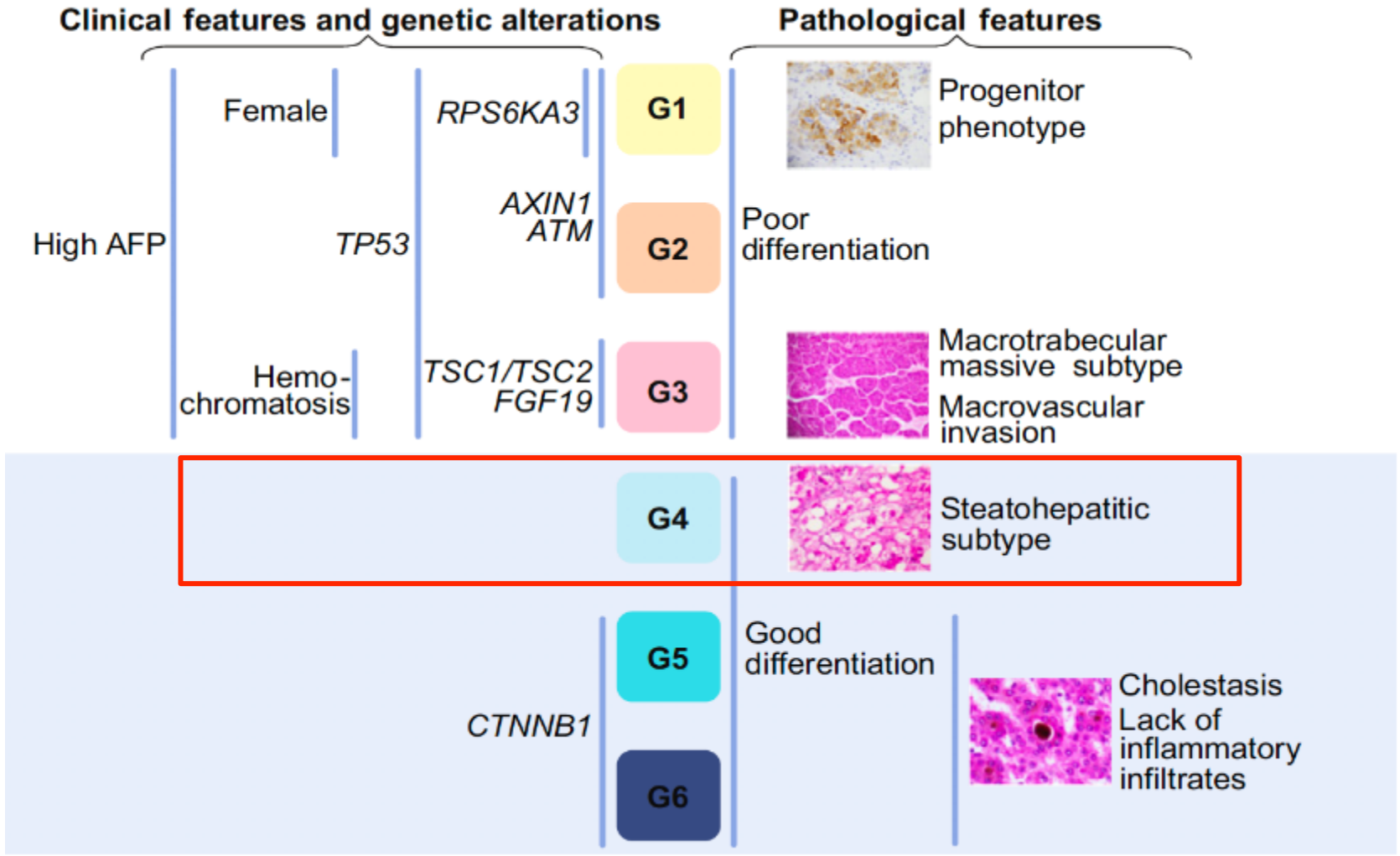
- B-catenin pathway activation
- IL6/ JAK/STAT pathway downregulation
- Maintenance of hepatocellular differentiation & function
- Low proliferation
- Dysregulated expression of bile salt transporters

Clinical implication (HCC patients with immune checkpoint inhibitors)



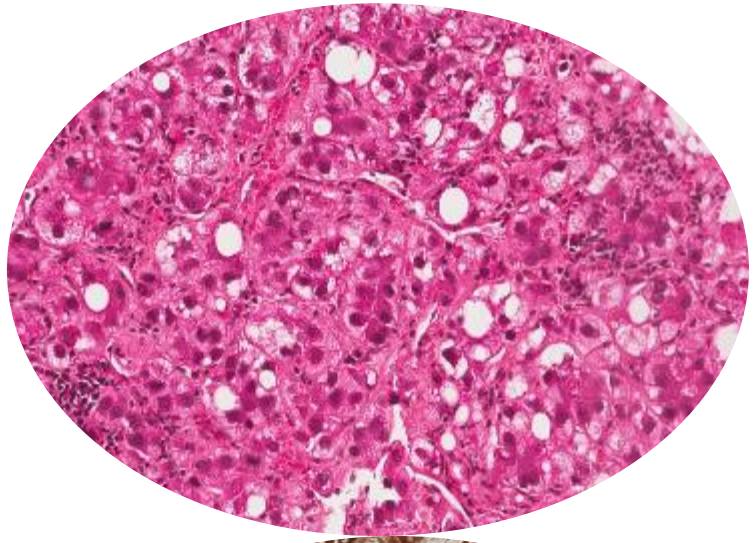
Harding J J Clin Cancer Res 2018

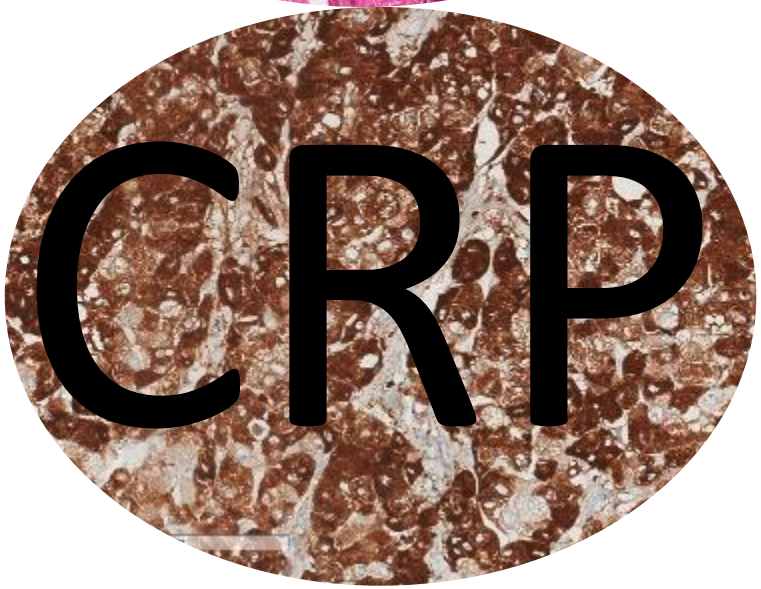
Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumour classification☆



Calderaro J J Hepatol 2017

Steatohepatitic HCC (G4)



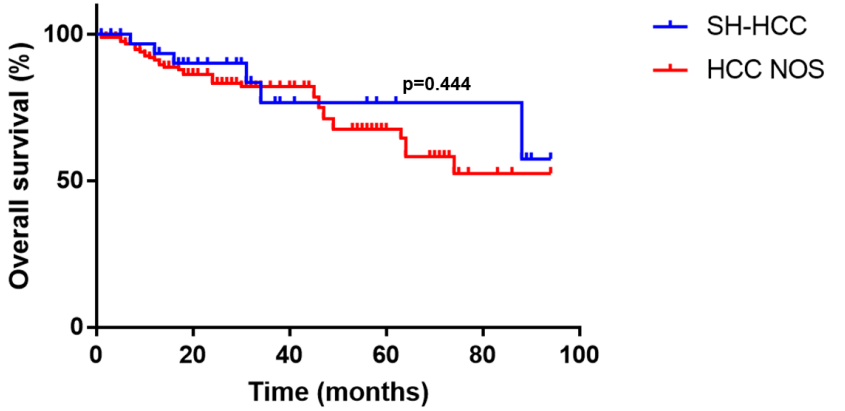


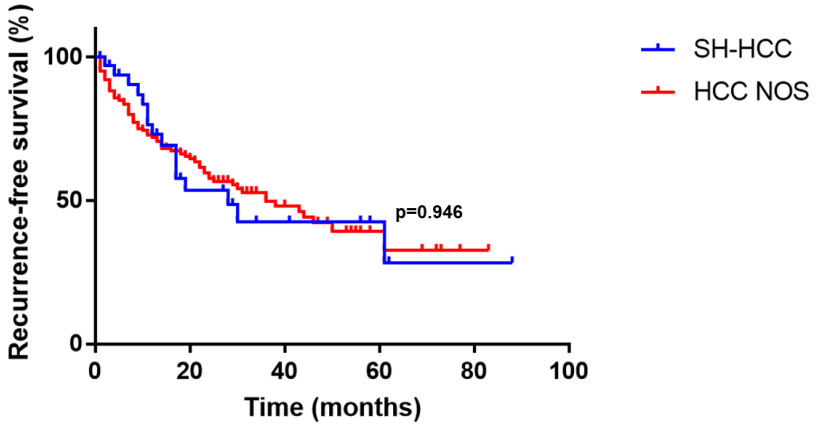
➢ Molecular features

- No specific genetic abnormalities
- Lack of Wnt/β-catenin pathway activation
- Activation of IL6/JAK/STAT pathway

➢ Less agressive phenotype (microvascular invasion, satellite nodules)

Beaujon experience
298 HCC (39 SH-HCC)

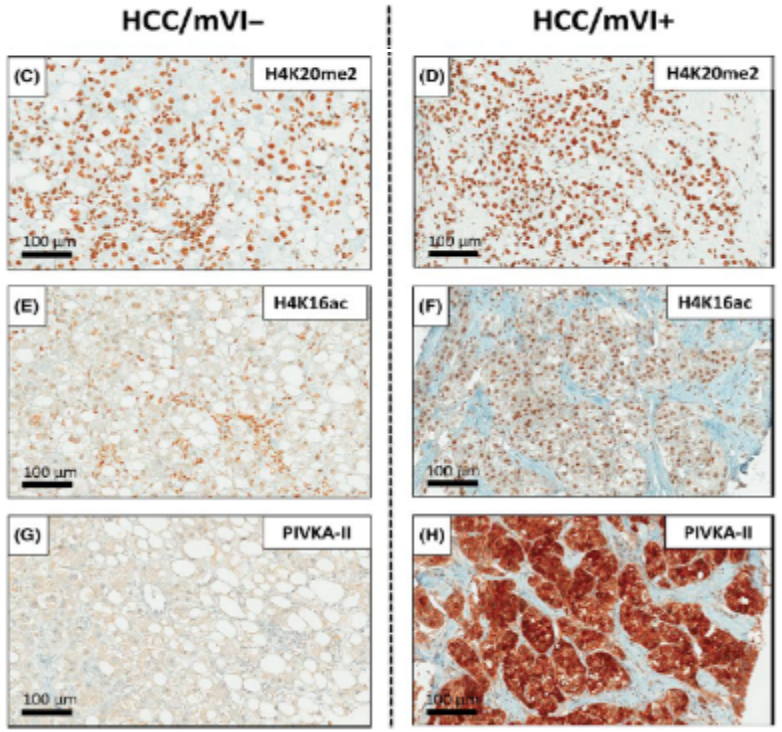




A Beaufrère (manuscript in prep.)

Surrogate Markers of Prognosis
In progress (need validation)

Contribution of virtual biopsy to the screening of microvascular invasion in hepatocellular carcinoma: A pilot study

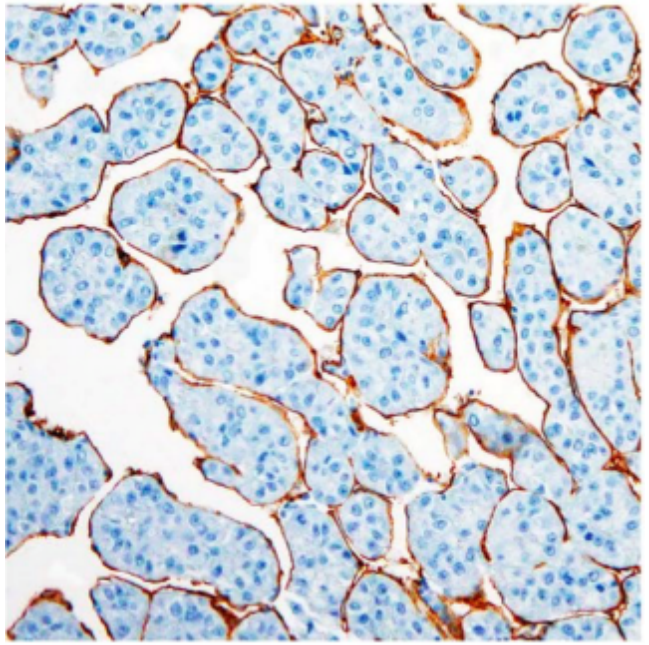


- At least 2 +ve markers: sst 72 %, spe 64%
- 3 +ve markers: sst 36%, Spe 90%

Poté N et al Hepatology 2013, J Hepatol 2015 & Liver Int 2017

Vessels Encapsulating Tumor Clusters (VETC) Is a Powerful Predictor of Aggressive Hepatocellular Carcinoma

CD34 (>55% of tumor area)



- Correlated with AFP, tumor size, MTM-HCC, microvascular invasion

Renne SL Hepatology 2020

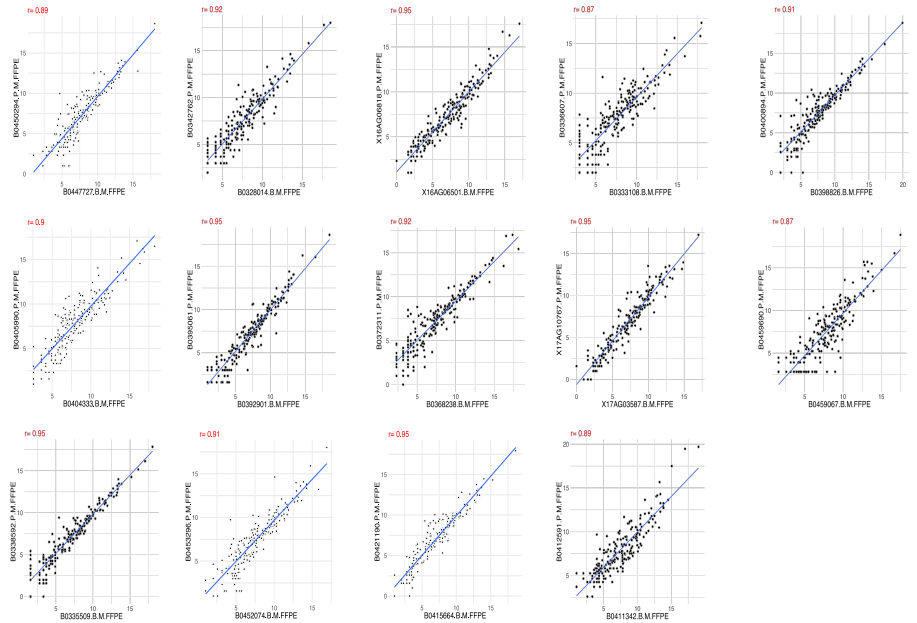
Performance of Tumor Biopsy

- Sampling variability : a major issue
  - Biopsy may miss Intratumor heterogeneity
    - Present in 2/3 of HCC (morphological & molecular levels) *
    - More frequent in larger tumors
  - Adapt the procedure according to the HCC macroscopic features (imaging) ?

- Expertise of pathologist
  - Usefulness of panel of immunomarkers
    - Diagnosis and prognosis
  - Analysis of non tumoral liver

* Friemel J et al Clin Cancer Res 2014

Gene expression signature (Nanostring®, 200 genes)
Correlation between 12-paired surgical and biopsy specimens [0.97 (0.87-0.95)]



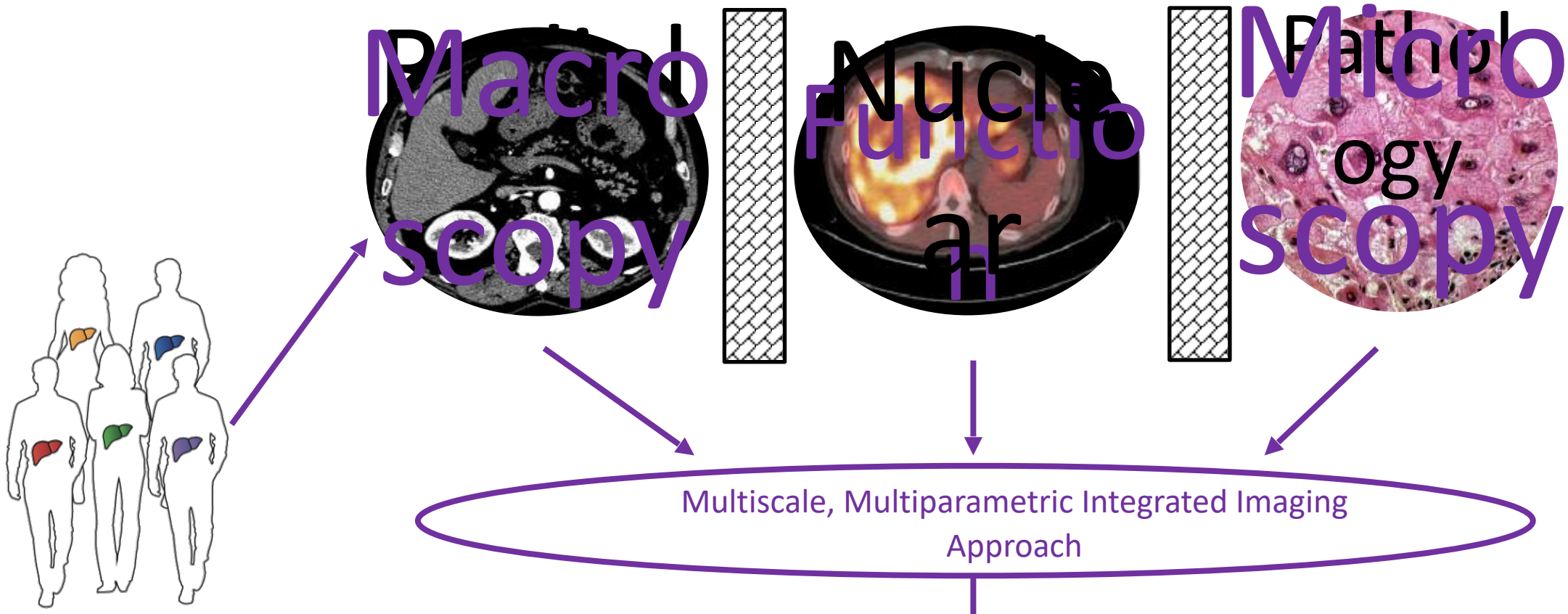
Beaufrère A, submitted
(collab. J Zucman-Rossi lab)

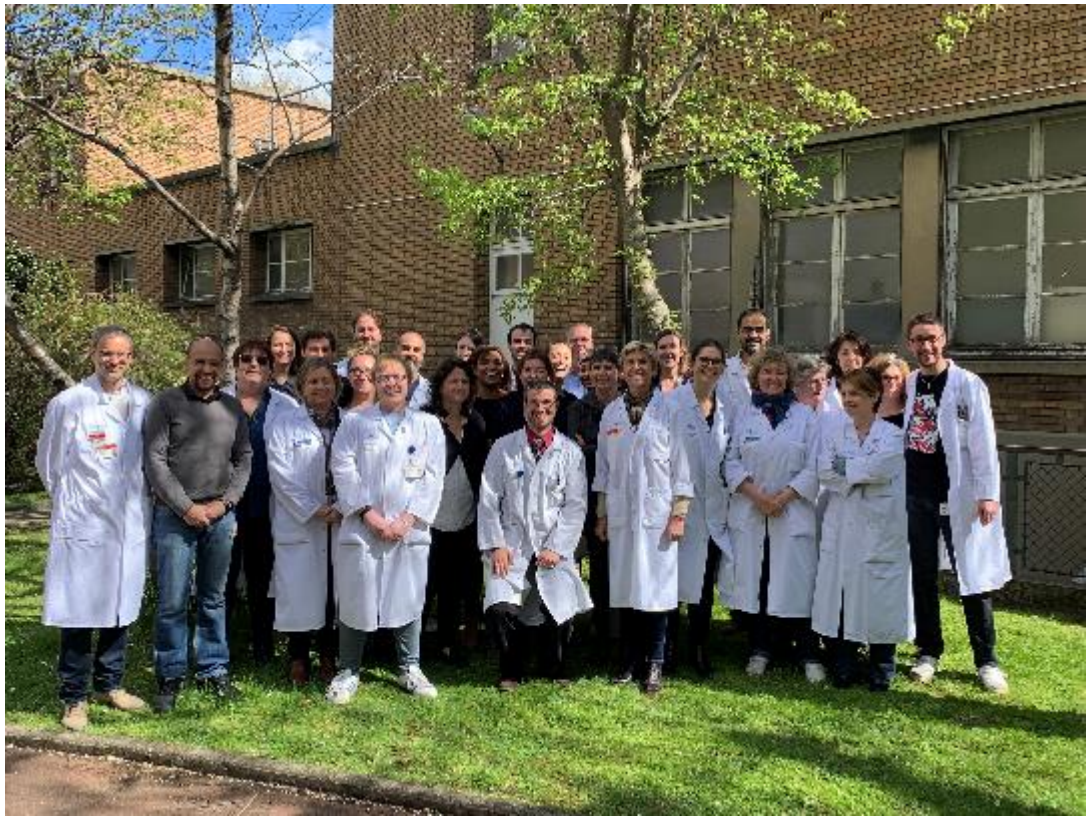
Conclusions
Pathomolecular Classification of HCC

➢ From Classical histology to Molecular pathology

- Provides an exhaustive characterisation of HCC, including prognostic features
  - Already applied for subtyping Hepatocellular adenomas
- Several tissue biomarkers available, some of them needed to be independently validated
- Relevant approach for considering intratumoral heterogeneity
- **Towards IMAGOMICS**

Multiscale Optimized Strategy for Artificial Intelligence-based Imaging Biomarkers in Digestive Cancer





Inserm U 1149 / CRI

From inflammation to cancer in digestive diseases »

V Paradis

- A Couvelard, N Guedj, J Cros, V Rebours, A Beaufrère
- A Hammoutène (Post-doc)
- F Cauchy, S Frendi, E Gigante, L de Mestier (Doc)
- M Tabard (M2)
- S Laouirem, C de Flori, H Cazier, M Albuquerque (IE)

Beaujon hospital

- Pathology (V Paradis)
- Surgery (O Soubrane)
- Oncology (M Bouattour)
- Radiology (V Vilgrain)
- Hepatology (F Durand)

CONTRE LE CANCER LA LIGUE pour la vie

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unity Addressing Unmet Needs through Innovation In hepaTology and gastroenterologY

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