

Hepatocellular Adenoma

Molecular pathology, morphology and clinical consequences

Benign hepatocytic
neoplasm

**Four molecularly defined
subtypes**

Hemorrhage and malignant
transformation risk

Dr Abu Suraih Sakhri

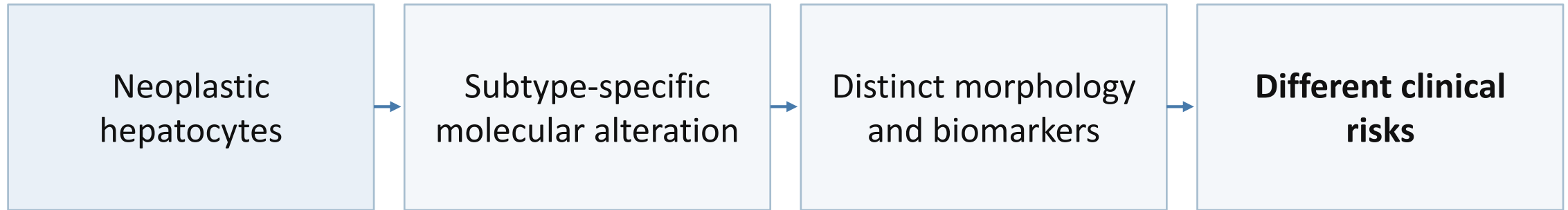
MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning goals

- Define hepatocellular adenoma and recognize its typical clinical context.
- Connect HNF1A, IL-6/JAK–STAT, Wnt/ β -catenin and GLI1 alterations to characteristic phenotypes.
- Interpret its gross, microscopic and immunophenotypic features.
- Distinguish clinically relevant subtypes and management risk factors.

The organizing principle: A benign but heterogeneous tumor



Adenoma is not a single biological risk category.

What makes this lesion an adenoma?

Identity

- Clonal, benign neoplasm of hepatocytes.
- Mass-forming lesion rather than a reactive hepatic nodule.
- Usually discrete within surrounding liver.

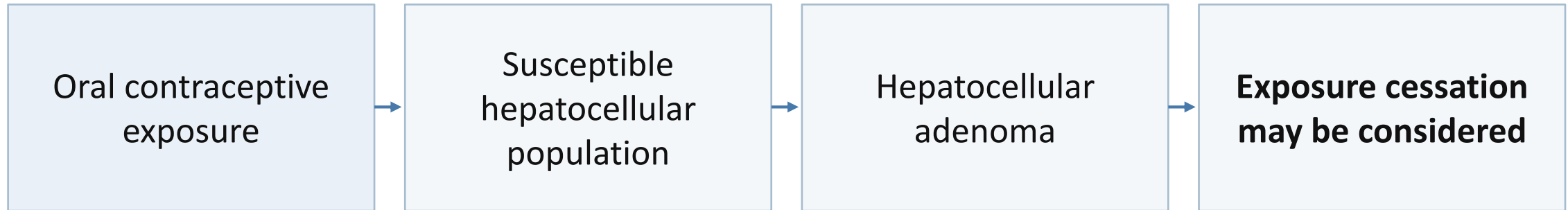
Consequences

- Can produce symptoms despite benign histology.
- Certain subtypes carry malignant transformation risk.
- Hemorrhage can be life-threatening.

A typical patient profile

- Hepatocellular adenoma most often occurs in young females.
- It is strongly linked with oral contraceptive exposure.
- Anabolic steroid exposure represents another important association.
- The prevalence pattern is changing with obesity and metabolic syndrome.

Exogenous hormone association



Exposure is a clinical association; Subtype-specific mutations define the lesions.

Anabolic steroids: Why the history matters

Epidemiologic link

- A recognized risk factor for hepatocellular adenoma.
- Particularly relevant to β -catenin–activated lesions.

Clinical evaluation

- Ask explicitly about anabolic steroid use.
- Exposure modification matters in selected low-risk lesions.
- Male sex is an independent surgical consideration.

Obesity and metabolic syndrome

- The reported rise in adenoma incidence is presumed to relate partly to increasing metabolic disease.
- Inflammatory adenoma is associated with obesity and metabolic syndrome.
- Metabolic association does not establish a molecular subtype by itself.
- Interpret epidemiologic context together with morphology and markers.

Solitary disease versus hepatic adenomatosis

Single lesion

- A discrete hepatic mass composed of neoplastic hepatocytes.
- May be found incidentally or following symptoms.

Multiple lesions

- Multiple adenomas can occur in familial or acquired settings.
- “Hepatic adenomatosis” denotes 10 or more tumors.
- The designation concerns multiplicity, not a fifth molecular subtype.

Why molecular classification is essential

- Four molecular subtypes are recognized in the source text.
- They have distinct mechanisms, morphologies and immunophenotypes.
- Frequency and sex distribution vary among subtypes.
- Hemorrhagic and malignant risks are not uniform.

Four molecular categories

Molecularly distinct hepatocellular neoplasms

HNF1 α -inactivated

HNF1A loss of function

Inflammatory

Gp130 / JAK–STAT

β -catenin–activated

Wnt pathway activation

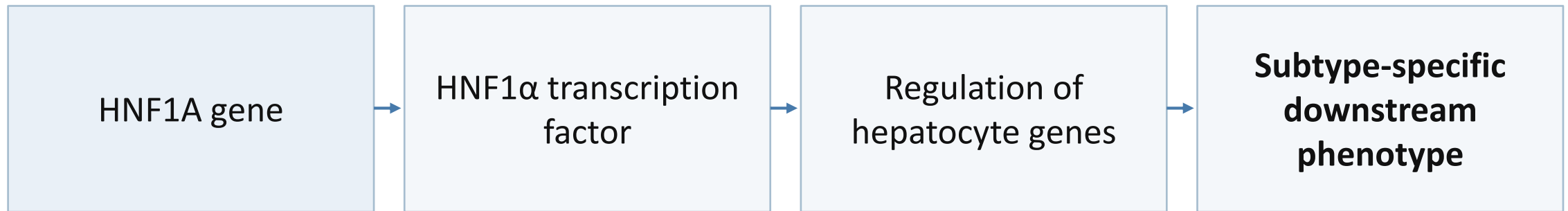
Sonic hedgehog

GLI1 fusion

Subtype prevalence and clinical associations

Molecular subtype	Source-reported frequency	Dominant clinical pattern
HNF1 α -inactivated	30–35%	Strong female predilection
Inflammatory	35–50%	Female; obesity / metabolic syndrome
β -catenin–activated	Not specified	Steroids; nearly 40% male
Sonic hedgehog	Not specified	Prominent hemorrhage propensity

HNF1A is a hepatocyte transcriptional regulator



Inactivation of the regulator affects multiple hepatocellular products.

HNF1 α -inactivated adenoma: Molecular lesion

- Loss-of-function mutations affect HNF1A.
- HNF1 α normally regulates numerous hepatocyte-expressed genes.
- The altered gene-regulatory program is reflected in characteristic steatosis and LFABP loss.
- This subtype has minimal malignant transformation risk.

Somatic and germline HNF1A alterations

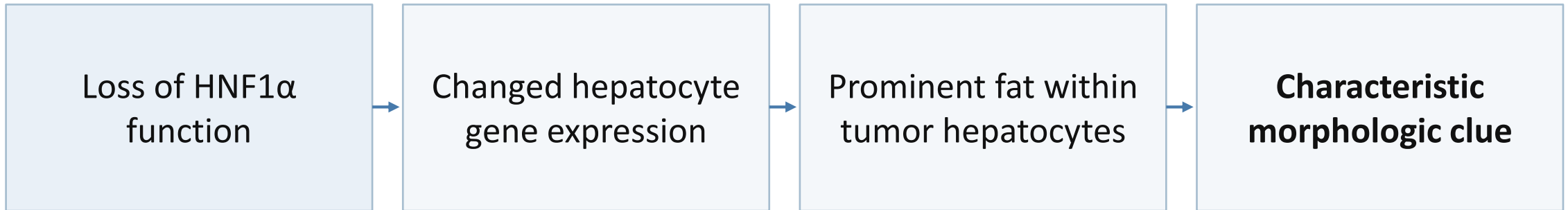
Hepatic tumor

- HNF1A loss of function defines the subtype.
- Most lesions are not identified solely from a germline history.

Inherited association

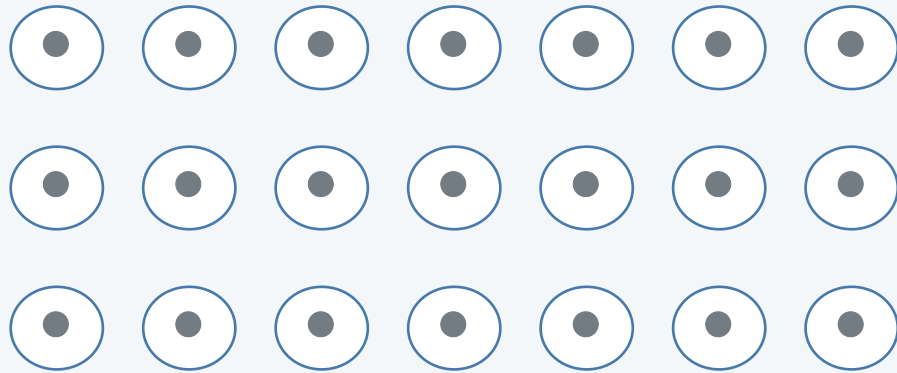
- Heterozygous germline HNF1A mutations cause autosomal dominant MODY type 3.
- They are associated with approximately 10% of HNF1 α -inactivated adenomas.

The HNF1 α –steatosis relationship

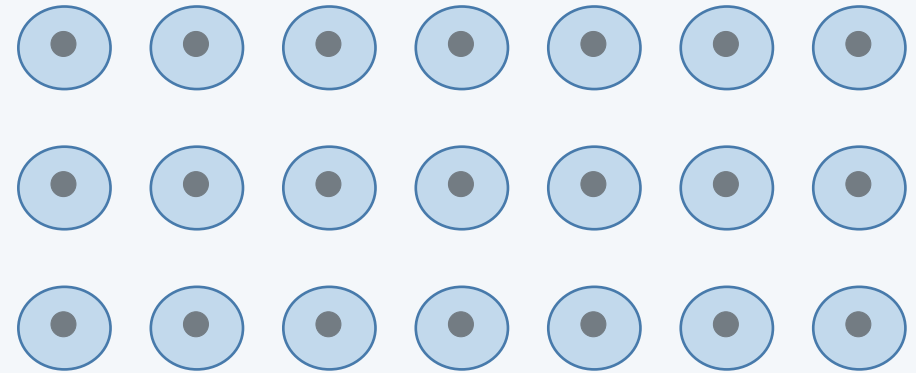


Steatosis is a characteristic association, not proof of genotype in isolation.

Interpreting LFABP immunostaining



Tumor hepatocytes
LFABP expression lost



Adjacent normal hepatocytes
LFABP expression preserved

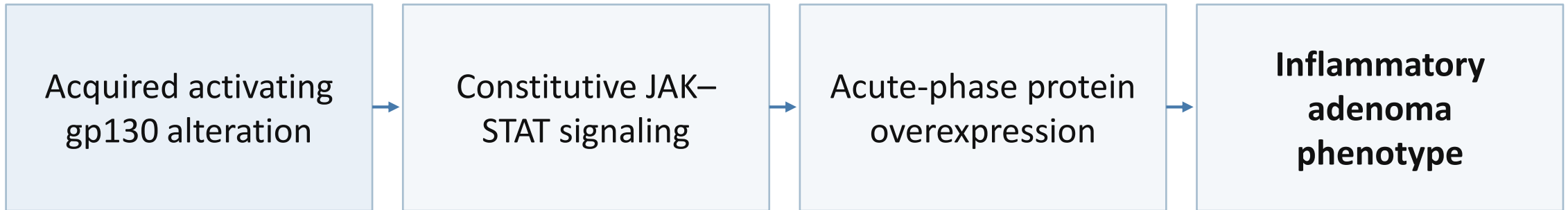
Schematic — not a tissue specimen

Internal positive control in adjacent liver makes loss in the tumor interpretable.

HNF1 α -inactivated tumors: Clinicopathologic signature

- Constitute approximately one-third of hepatocellular adenomas.
- Strong female predominance is typical.
- Intratumoral steatosis and LFABP loss support subtype assignment.
- Malignant transformation risk is characterized as minimal.

Inflammatory adenoma: Pathway driver

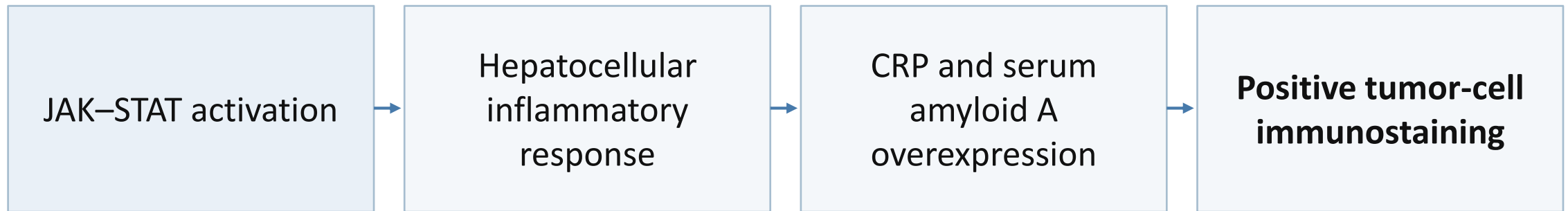


Gp130 is a coreceptor in the IL-6 signaling system.

Gp130 and IL-6 signaling: Key distinction

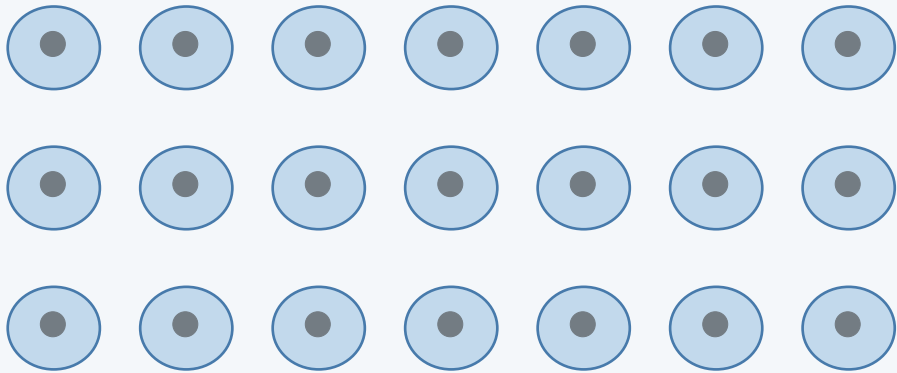
- Inflammatory adenomas are linked to acquired activating mutations in gp130.
- Gp130 functions as a coreceptor for interleukin-6.
- Constitutive signaling activates the downstream JAK–STAT pathway.
- The molecular effect explains increased expression of acute-phase proteins.

Why CRP and serum amyloid A are elevated

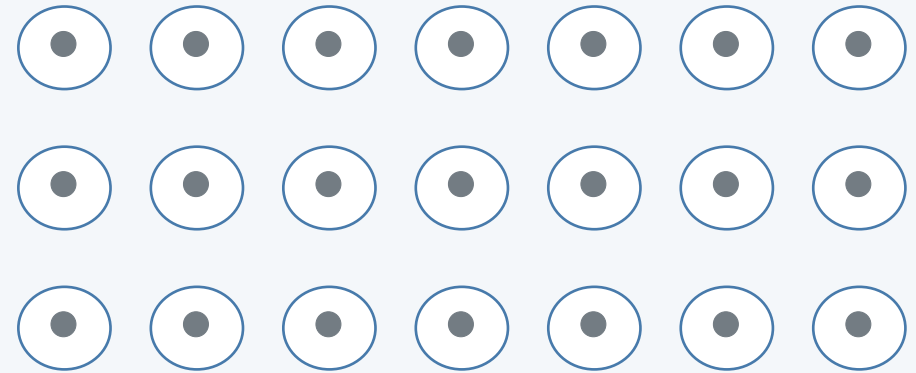


These proteins are phenotypic markers of pathway activation.

Inflammatory immunophenotype



Tumor hepatocytes
CRP / SAA overexpressed



Surrounding hepatocytes
Variable and generally lower expression

Schematic — not a tissue specimen

The positive tumor-cell signal can support subtype classification when interpreted with morphology.

Inflammatory adenoma: Morphologic features

- Sinusoidal dilatation is characteristic.
- Fibrous septa may be present within the lesion.
- A ductular reaction can occur.
- The latter two features can mimic focal nodular hyperplasia.

Inflammatory adenoma: Clinical setting

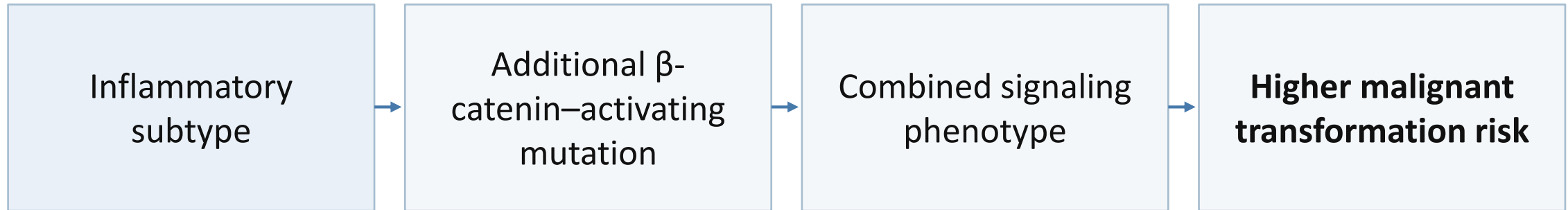
Common context

- Women predominate.
- Obesity and metabolic syndrome are associated.
- Accounts for 35–50% of cases.

Risk nuance

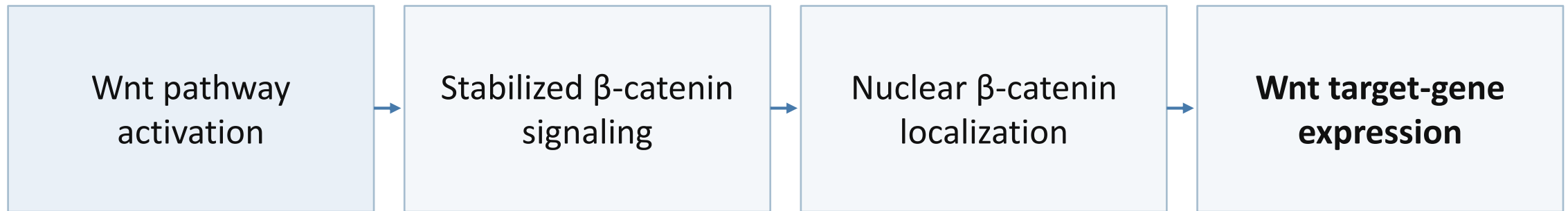
- A subset additionally harbors β -catenin activation.
- Overlap may increase malignant transformation risk.
- A purely inflammatory label should not hide β -catenin-associated risk.

Inflammatory/ β -catenin overlap



Source reports β -catenin activation in about 10% of inflammatory adenomas.

Wnt/ β -catenin pathway context



Schematic sequence shows the causal relationship stated by the source.

β -catenin–activated adenoma: Affected genes

- CTNNB1 encodes β -catenin and may harbor activating mutations.
- Other alterations can affect Wnt regulatory components such as APC or AXIN2.
- Constitutive signaling can produce nuclear β -catenin accumulation.
- The precise CTNNB1 exon is important for risk stratification.

CTNNB1 exon 3 versus exons 7–8

Exon 3

- High-level β -catenin activation.
- High risk of malignant transformation into HCC.
- Greater concern when atypical morphology coexists.

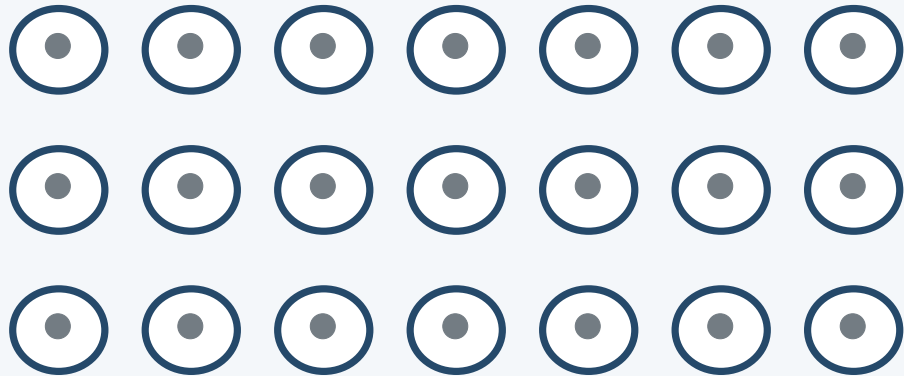
Exons 7 or 8

- Lower-level β -catenin activation.
- Low association with HCC in the source.
- Not biologically interchangeable with exon 3.

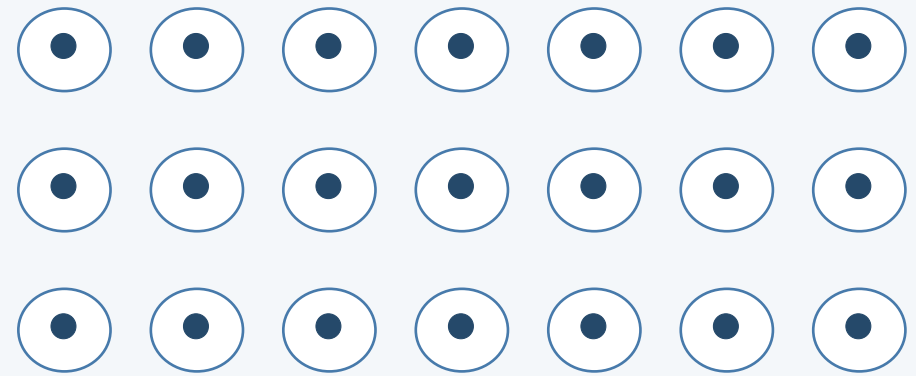
Why “ β -catenin positive” is not enough

- Normal β -catenin is associated with cell membranes.
- Pathway activation may shift the staining pattern toward nuclei.
- Strong nuclear localization is reported in β -catenin–mutated adenomas.
- Staining and exon-specific genotype must be distinguished.

Nuclear β -catenin: Conceptual immunostain



Resting localization
Predominantly membranous signal



Activated pathway
Tumor-cell nuclear signal

Schematic — not a tissue specimen

A change in subcellular compartment supports pathway activation; This is a schematic, not a photomicrograph.

β -catenin activation and atypical morphology

- Cytologic or architectural atypia may occur within the adenoma.
- Areas of overt hepatocellular carcinoma can be present.
- An atypical focus therefore warrants attention to malignant transformation.
- Risk assessment cannot rely on overall benign designation alone.

β -catenin subtype: Clinical associations

Hormonal exposure

- Anabolic steroid use is a known risk factor.
- Exposure history supports clinicopathologic interpretation.

Sex distribution

- Nearly 40% of β -catenin–activated adenomas occur in males.
- Male sex carries a separate resection recommendation.

Sonic hedgehog adenoma: Genetic mechanism



The source identifies a fusion-driven signaling mechanism.

Why sonic hedgehog adenoma matters

- A recently characterized hepatocellular adenoma subtype.
- GLI1 fusion genes activate the sonic hedgehog pathway.
- Its standout reported clinical phenotype is hemorrhage.
- Biological risk is not captured by malignant transformation alone.

Molecular lesions and their phenotypic readouts

Subtype	Driver / pathway	Feature that helps recognition
HNF1 α -inactivated	HNF1A loss	Steatosis; LFABP loss
Inflammatory	gp130 $\rightarrow$ JAK–STAT	CRP / SAA upregulation
β -catenin–activated	CTNNB1 / Wnt	Nuclear β -catenin; atypia
Sonic hedgehog	GLI1 fusion	High hemorrhage propensity

Do not equate subtype frequency with risk

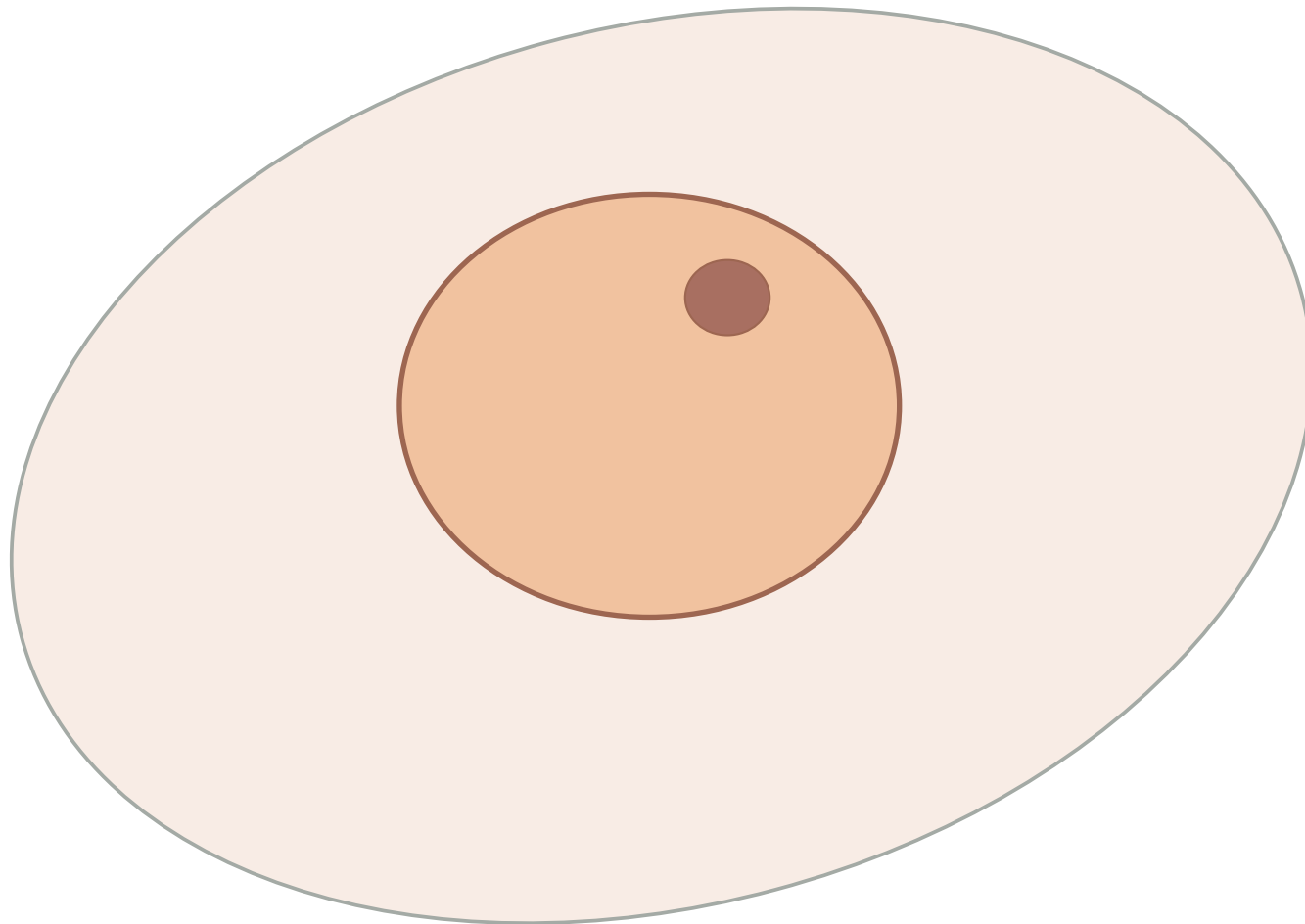
More frequent categories

- Inflammatory and HNF1 α -inactivated lesions comprise substantial proportions.
- Their biology and clinical risks differ.

Risk-enriched categories

- Exon 3 β -catenin activation is linked to high malignant risk.
- Sonic hedgehog activation is linked to bleeding.
- Inflammatory + β -catenin overlap deserves separate attention.

Gross morphology: The discrete hepatic mass



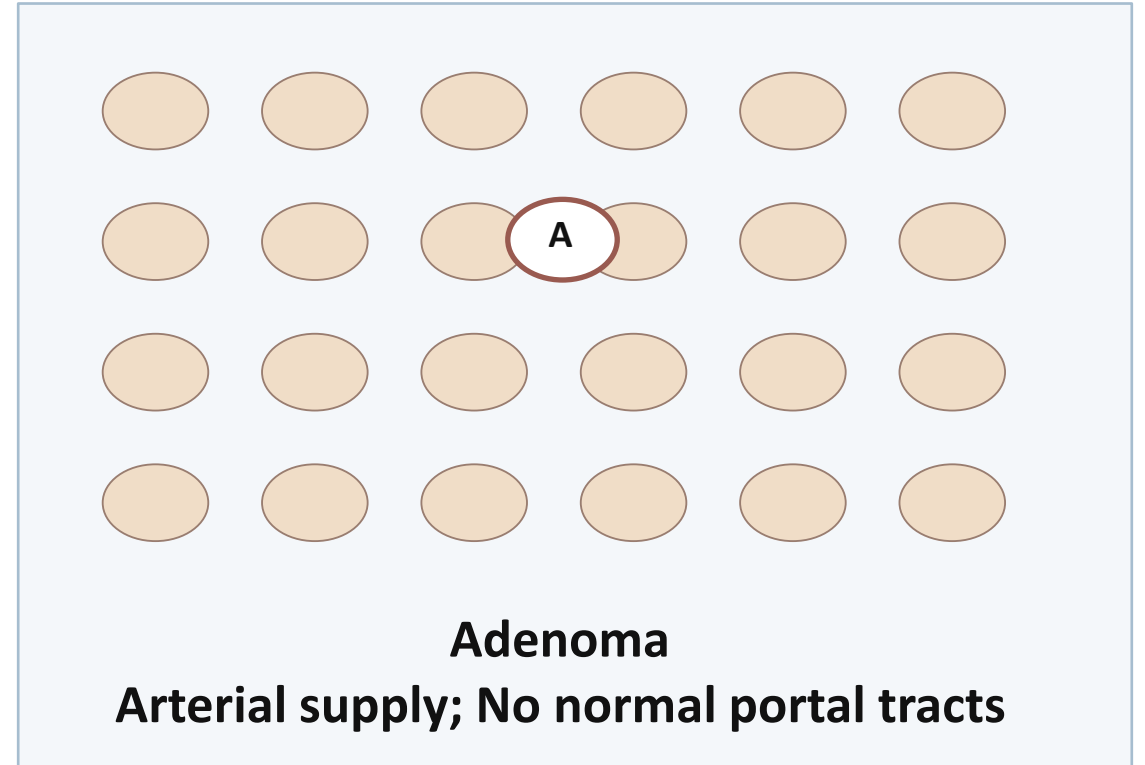
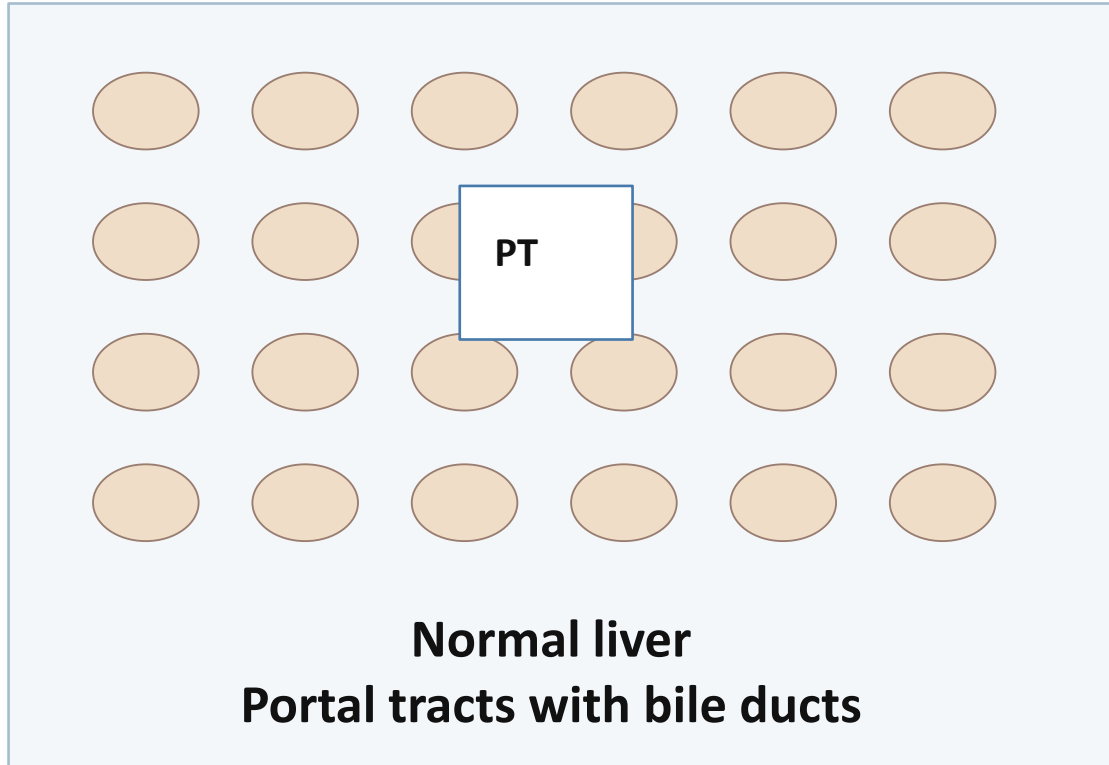
Schematic gross cross-section

- The neoplasm forms a distinct mass.
- Hemorrhage may change its gross appearance.
- Gross inspection cannot specify every molecular subtype.

Microscopic architecture: Thin hepatocyte plates

- Neoplastic hepatocytes form one- to two-cell-thick plates.
- Overall architecture may resemble benign hepatic tissue.
- The lesion has a distinctive vascular and portal-tract organization.
- Architecture must be interpreted along with the clinical and molecular context.

Schematic: Normal liver versus adenoma



PT = portal tract | A = artery | Schematic — not a photomicrograph

The comparison depicts a diagnostic organizational difference, not actual histologic tissue.

The arterial supply is a structural clue

- Large arteries may course through scant fibrous stroma.
- The lesion lacks normal portal tracts.
- The arrangement differs from ordinary hepatic lobular anatomy.
- An isolated artery is not sufficient by itself for definitive classification.

What is absent within the adenoma?

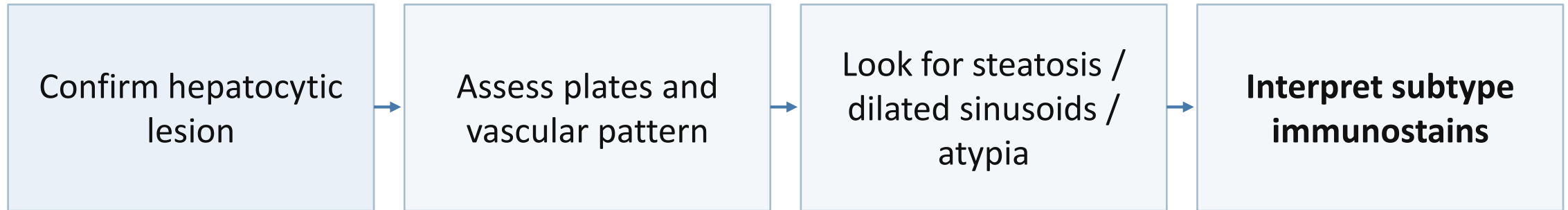
Present / typical

- Neoplastic hepatocyte plates.
- Arterial blood supply.
- Limited interstitial fibrous stroma.

Absent / expected

- Normal portal tracts.
- Interlobular bile ducts as components of portal tracts.
- Ordinary portal–lobular organization.

A morphology-first review sequence



A diagnostic reading sequence inferred from source morphology and markers.

Steatosis points toward HNF1 α inactivation

- HNF1 α -mutated adenomas commonly contain conspicuous lipid.
- The fat resides in the neoplastic hepatocytes.
- Loss of LFABP strengthens the subtype interpretation.
- Steatosis alone is not a complete molecular diagnosis.

Sinusoidal dilatation points toward inflammation

- Dilated sinusoids favor inflammatory morphology.
- Fibrous septa and ductular reaction may coexist.
- These findings can overlap with focal nodular hyperplasia.
- CRP or SAA tumor-cell staining provides a molecularly linked clue.

Atypia points to a high-risk adenoma phenotype

- β -catenin–mutated adenomas may show architectural abnormality.
- Cytologic atypia raises concern for progression or an overt HCC component.
- Atypia is not a uniform feature of all hepatocellular adenomas.
- Interpret morphologic atypia alongside β -catenin status.

Diagnostic subtype IHC: What each signal means

Readout	Pattern in relevant subtype	Interpretation
LFABP	Loss in HNF1 α -inactivated tumor	Downstream of HNF1 α deficiency
CRP / SAA	Overexpressed in inflammatory tumor	JAK–STAT-associated response
β -catenin	Nuclear localization in activated tumor	Wnt pathway activation

Why an internal staining control matters

Tumor compartment

- LFABP absence can be diagnostic evidence.
- Compare lesional staining with surrounding nonneoplastic hepatocytes.

Nonneoplastic compartment

- Preserved LFABP provides a positive internal control.
- An uninterpretable negative stain cannot establish true loss.

Inflammatory adenoma can resemble FNH

- The adenoma may contain fibrous septa and ductular reaction.
- FNH also contains fibrous septa and prominent ductular reaction.
- An overlapping histologic feature is not an identical pathogenic process.
- Use the lesion-wide pattern plus immunophenotype to distinguish them.

Hepatocellular adenoma versus focal nodular hyperplasia

Feature	Adenoma	FNH
Biology	Benign neoplasm	Benign nonneoplastic mass
Typical gross form	Discrete tan mass	Often stellate central scar
Bile ducts / portal areas	Normal portal tracts absent	Prominent ductular reaction in septa
Subtype markers	LFABP / CRP / SAA / β -catenin	Map-like GS staining

The FNH map-like GS pattern

In FNH

- GS immunoreactivity forms characteristic anastomosing map-like areas.
- The pattern reflects unusual hepatic organization.

In adenoma

- Subtype classification relies on different pathway-linked features.
- FNH-like septa in inflammatory adenoma do not themselves establish FNH.

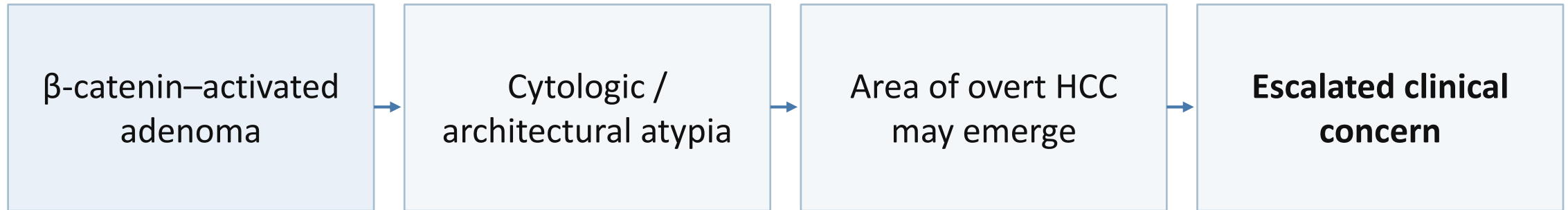
Adenoma versus hepatocellular carcinoma

Diagnostic domain	Hepatocellular adenoma	Hepatocellular carcinoma
Biology	Benign neoplasm	Malignant epithelial tumor
Architecture	Usually thin hepatocyte plates	May show thick plates / sheets
Atypia	May be present in high-risk subtype	Can be pronounced
Relation	Some lesions may transform	May arise within adenoma

Malignant transformation: What the source establishes

- Hepatocellular carcinoma can arise within hepatocellular adenoma.
- Risk is particularly important in β -catenin–activated lesions.
- CTNNB1 exon 3 activation is associated with greater malignant risk.
- Inflammatory adenomas with additional β -catenin activation also carry increased risk.

Morphologic warning sequence

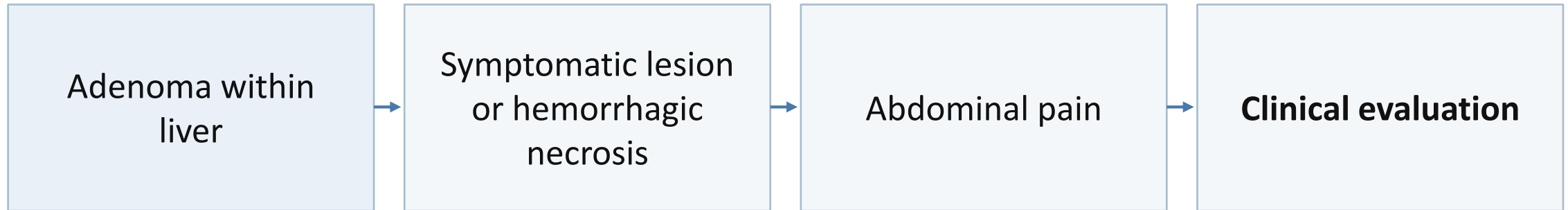


A possible pathologic relationship, not an obligatory progression in every case.

Clinical presentation: Incidental discovery

- Lesions may be detected unexpectedly on liver imaging.
- An asymptomatic course does not eliminate future hemorrhage risk.
- Clinical history and tumor characteristics are needed for stratification.
- Imaging establishes detection; The source does not provide a definitive subtype imaging algorithm.

Why pain may develop

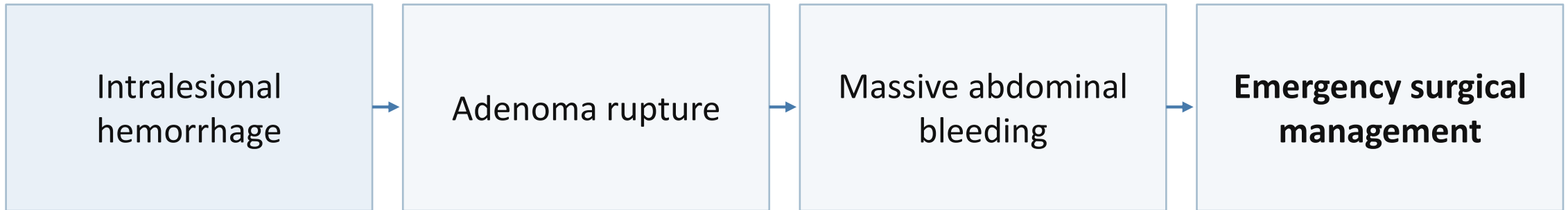


The source describes abdominal pain or hemorrhagic necrosis as presentations.

Hemorrhagic necrosis: A clinically important change

- Bleeding may occur within a hepatocellular adenoma.
- Hemorrhagic necrosis can make a previously silent lesion symptomatic.
- Rupture can cause substantial intraperitoneal blood loss.
- Clinical urgency is determined by bleeding consequences, not benign histology.

Rupture of an adenoma is a surgical emergency



This is the major acute complication highlighted by Robbins.

Two distinct adverse outcomes

Hemorrhage

- Can occur without malignant transformation.
- Sonic hedgehog subtype has marked hemorrhage propensity.
- Rupture may trigger a surgical emergency.

Malignant transformation

- Linked especially to β -catenin activation.
- Exon 3 activation is a high-risk molecular feature.
- Treatment choices must consider both outcomes.

Risk factors that affect the management recommendation

Feature	Implication in the textbook
Male patient	Resection recommended
β -catenin–activated adenoma	Resection recommended
Lesion ≥ 5 cm	Resection recommended
Small lesion without β activation	Observation and exposure cessation may suffice

The 5-cm threshold: What it means

- Robbins recommends resection for adenomas 5 cm or larger.
- The rationale includes both hemorrhage and malignant risk.
- The threshold is one consideration, not a substitute for molecular and sex-related risk.
- This is a textbook management summary, not a complete contemporary treatment guideline.

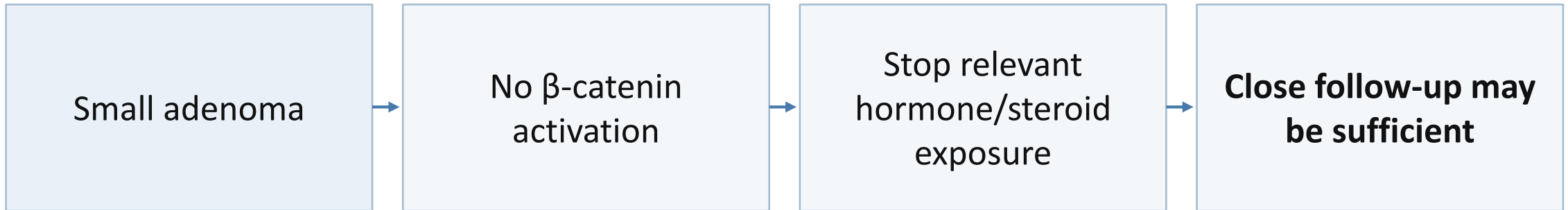
Male patients require separate consideration

- The textbook recommends resection for hepatocellular adenoma in male patients.
- This applies regardless of other high-risk features.
- The sex-based recommendation should not be conflated with the frequency of adenomas in males.
- Clinical decisions are individualized outside the scope of this pathology text.

Why β -catenin activation can change management

- The pathway defines a biologically higher-risk group.
- An exon 3 CTNNB1 mutation is particularly concerning.
- Robbins recommends resection of β -catenin–activated tumors.
- Risk assessment must not depend on size alone.

Lower-risk conservative pathway in the source



This pathway is conditional; The textbook does not prescribe exact follow-up intervals.

Exposure cessation has a specific role

- Cessation of oral contraceptives or anabolic steroids may accompany surveillance.
- This approach is discussed for smaller tumors without β -catenin activation.
- It should not override resection indications for higher-risk lesions.
- The source does not specify a universal regression rate after cessation.

Management considerations: An editable decision map

Hepatocellular adenoma

Male sex / β -catenin activation / ≥ 5 cm

Resection recommended

Smaller and no β -catenin activation

**Close follow-up + stop relevant exposure
may suffice**

Teaching case: Incidental adenoma

Hypothetical teaching scenario

A young woman has a small incidental adenoma. Tumor hepatocytes show steatosis and loss of LFABP, with preserved staining in surrounding liver.

Which molecular subtype best explains the pathology?

Interpretation

HNF1 α -inactivated adenoma: HNF1A loss is linked to steatosis and tumor-cell LFABP loss.

Teaching case: Inflammatory pattern

Hypothetical teaching scenario

A hepatocellular lesion shows sinusoidal dilatation, fibrous septa and ductular reaction. Neoplastic hepatocytes strongly express CRP.

What pathway explains the immunophenotype?

Interpretation

The inflammatory adenoma pathway: Activating gp130 alteration with constitutive JAK–STAT signaling.

Teaching case: High-risk genotype

Hypothetical teaching scenario

A hepatocellular adenoma shows architectural atypia and strong nuclear β -catenin staining. Sequencing identifies a CTNNB1 exon 3 mutation.

What risk concern predominates?

Interpretation

Malignant transformation to hepatocellular carcinoma; Exon 3 activation is a high-risk subtype.

Teaching case: Sudden deterioration

Hypothetical teaching scenario

A patient with a known hepatic adenoma develops acute abdominal pain, and evaluation demonstrates intraperitoneal hemorrhage.

Which complication mandates urgent action?

Interpretation

Adenoma rupture with massive abdominal bleeding is a surgical emergency.

Five discriminators worth retaining

Question	Most informative source-supported answer
Steatosis + LFABP loss?	HNF1 α -inactivated subtype
CRP / SAA upregulation?	Inflammatory subtype
Nuclear β -catenin + atypia?	Wnt/ β -catenin–activated subtype
GLI1 fusion + hemorrhage?	Sonic hedgehog subtype
Male / ≥ 5 cm / β -catenin activated?	Textbook resection recommendation

Final synthesis: Diagnose biology, not only a mass

- Identify adenoma by hepatocellular morphology and the absence of normal portal tracts.
- Use morphology and pathway-linked immunostains to assign molecular phenotype.
- Consider hemorrhage and malignant transformation as separate consequences.
- Integrate sex, size and β -catenin status when discussing resection risk.

Reference and interpretation notes

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 18: Liver and Gallbladder. Hepatocellular Adenoma, pp. 788–790.

- Molecular frequencies and treatment statements reproduce the supplied chapter extract.
- Simplified histology and immunostain drawings are original editable schematics, not specimen images.
- Original printed-page PDF figures were not provided; direct figure-level verification was not possible.