

Acinar Cell Carcinoma

Pancreatic exocrine differentiation, morphology, diagnosis and clinical implications

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Learning objectives

- Explain the biological significance of acinar differentiation and zymogen granules.
- Recognize characteristic clinical, gross and histologic patterns.
- Select an immunohistochemical panel for a solid pancreatic neoplasm.
- Integrate Wnt-pathway changes and other genomic findings with diagnostic limits.
- Distinguish acinar carcinoma from its principal pancreatic mimics.

Pancreatic epithelial lineages

Exocrine acinar cells
Digestive enzymes

Exocrine ductal cells
Fluid conduits

Endocrine islet cells
Hormone release

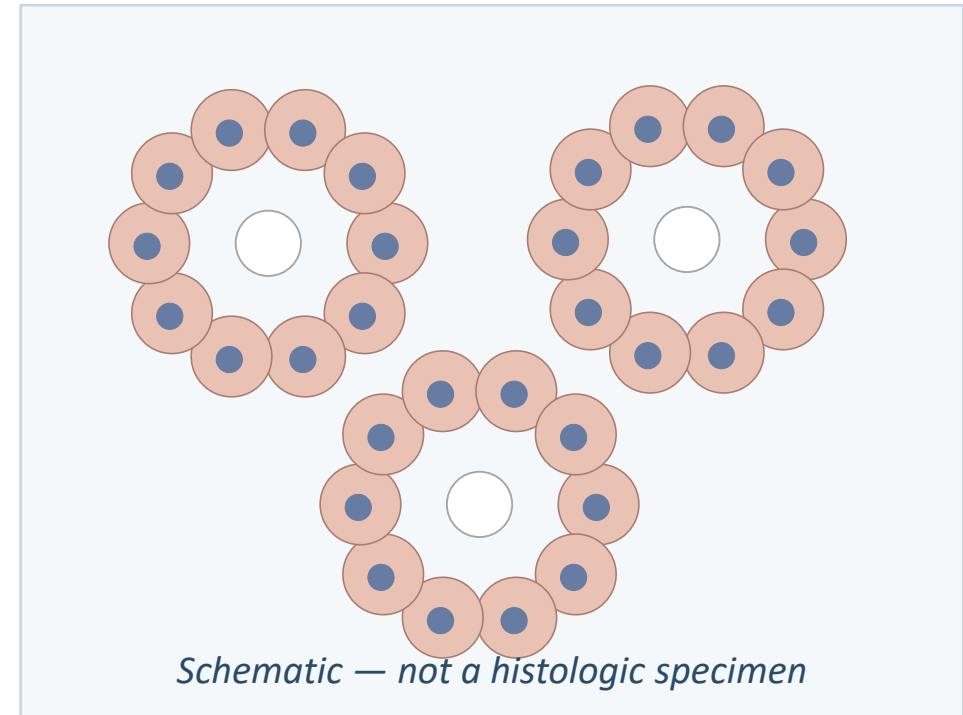
The tumor's differentiation—not simply its organ of origin—defines the diagnostic category.

What defines acinar cell carcinoma?

- A malignant epithelial neoplasm with pancreatic acinar differentiation.
- Neoplastic cells produce digestive enzymes and may retain zymogen granules.
- Architecture ranges from obvious acini to solid and trabecular growth.
- Confirmation of acinar products is crucial when morphology is ambiguous.

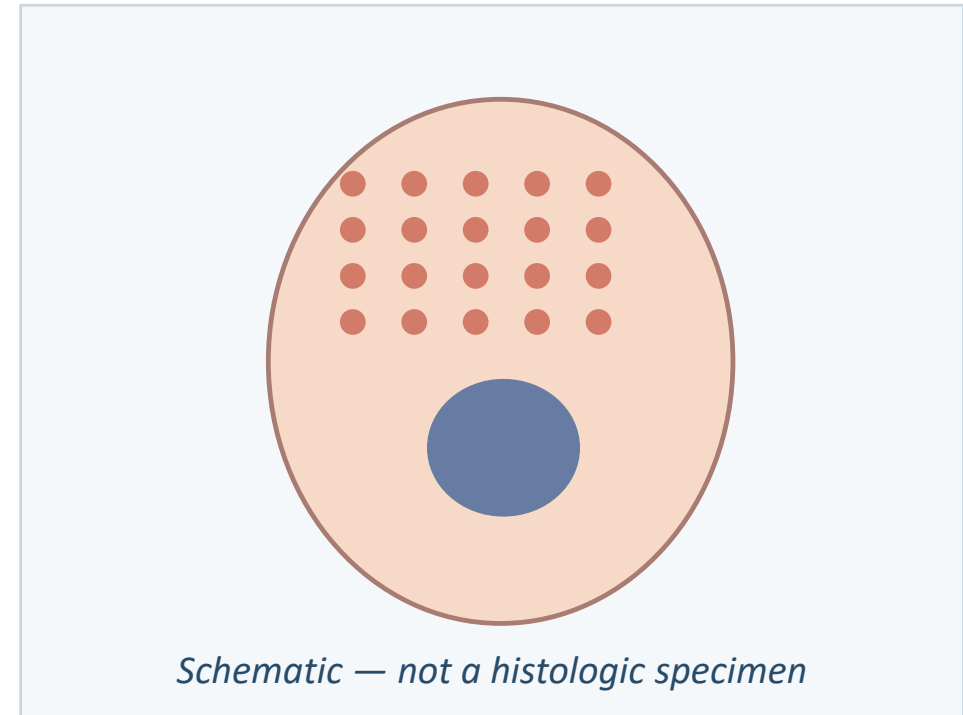
Normal acinar organization

- Secretory cells form small polarized units around a lumen.
- Nuclei are typically positioned toward the basal cell pole.
- Apical cytoplasm contains enzyme-rich secretory granules.

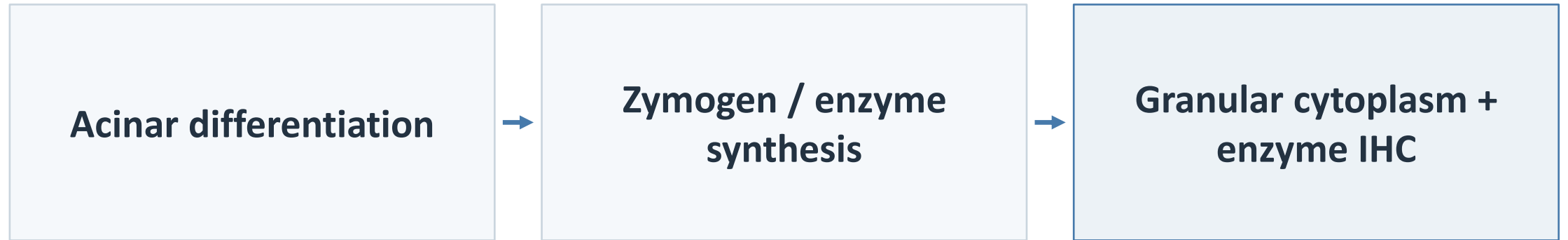


Secretory granules explain the phenotype

- Zymogen granules store pancreatic digestive enzyme precursors.
- Tumor cells can preserve the machinery of enzyme synthesis.
- The granular cytoplasm is a morphologic clue, not proof alone.



From acinar program to diagnostic evidence



Histology suggests acinar differentiation; Immunophenotypic demonstration confirms it.

Epidemiology: A rare pancreatic malignancy

- Acinar cell carcinoma in approximately 1%–2% of adult pancreatic tumors.
- Its rarity limits the size and certainty of many clinical series.
- Incidence estimates vary with denominator, geography and case ascertainment.
- Acinar carcinoma must not be equated with common pancreatic ductal adenocarcinoma.

Age and sex distribution

- Most cases occur in adults; The typical presentation is around later middle age.
- Male predominance is described across multiple published series.
- Rare pediatric cases occur and demand a broader differential diagnosis.
- Demography supports context but cannot establish tissue lineage.

Acinar carcinoma versus ductal carcinoma

Acinar cell carcinoma

- Enzyme-producing differentiation.
- Often a large, fleshy, cellular mass.
- Limited fibrous stroma is common.
- Acinar markers support the diagnosis.

Ductal adenocarcinoma

- Duct-forming differentiation.
- Desmoplastic infiltrative glands.
- May produce marked stromal fibrosis.
- Ductal phenotype dominates.

Hereditary associations: Interpretation

- Most acinar carcinomas are considered sporadic.
- Rare syndromic or germline-associated cases have been reported.
- A tumor variant does not itself prove a hereditary syndrome.
- Germline evaluation depends on clinical context and genetic findings.

Common symptoms are nonspecific

- Abdominal pain or discomfort may accompany a pancreatic mass.
- Unintentional weight loss and constitutional symptoms can occur.
- Nausea or vomiting may reflect mass effect or advanced disease.
- A symptom-based diagnosis is therefore unreliable.

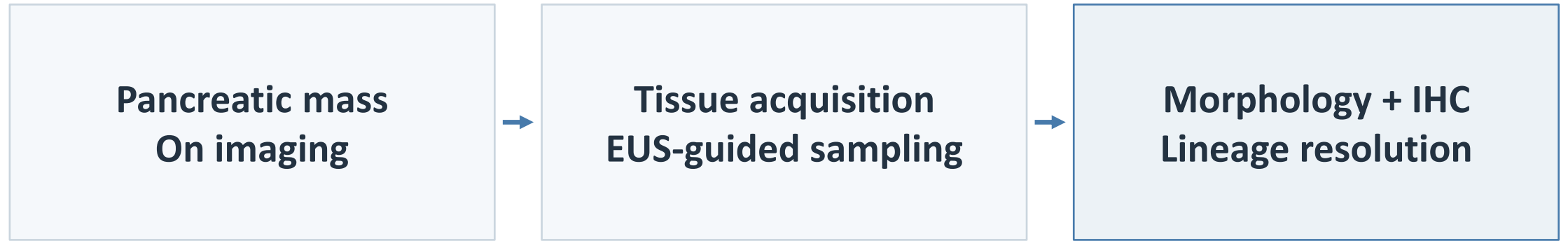
Why jaundice may be absent

- Acinar carcinoma can arise anywhere within the pancreas.
- Biliary obstruction depends on local anatomy and the pattern of growth.
- Jaundice is reported less often than with pancreatic ductal adenocarcinoma.
- Absence of jaundice does not imply indolent behavior.

Imaging: Initial mass characterization

- CT or MRI often demonstrates a solid pancreatic mass.
- Larger lesions may show necrosis, hemorrhage or cystic degeneration.
- A circumscribed appearance does not establish benignity.
- Imaging defines anatomy; Tissue sampling defines differentiation.

Clinical-to-pathologic diagnostic pathway



Consider molecular analysis on adequate tissue when clinically relevant.

Serum lipase: Elevation versus syndrome

- Some patients have elevated circulating lipase concentrations.
- Biochemical elevation is not synonymous with metastatic fat necrosis syndrome.
- The clinical syndrome in up to 15% of affected patients.
- Test results require correlation with the mass, symptoms and morphology.

Lipase-associated fat necrosis syndrome



The mechanistic link is ectopic enzymatic fat digestion, not simply tumor dissemination into fat.

Metastatic fat necrosis: The clinical clues

- Tender subcutaneous nodules may reflect fat necrosis.
- Polyarthralgia or polyarthrititis can accompany the systemic syndrome.
- The “metastatic” designation describes a distant enzymatic effect.
- The syndrome is distinctive but absent in most acinar carcinomas.

Fat necrosis syndrome: Avoid two errors

Supported inference

- Lipase release can produce distant adipose damage.
- Skin and joint findings may guide the search for a pancreatic source.
- The syndrome does not require tumor in the involved skin.

Unsupported inference

- Every elevated serum lipase reflects acinar carcinoma.
- Every acinar carcinoma has lipase hypersecretion.
- Cutaneous nodules automatically represent tumor metastases.

Gross growth pattern

- Tumors are often large and relatively circumscribed.
- A partial fibrous capsule may be present.
- Cut surfaces are commonly soft, fleshy and tan to reddish.
- Invasion can occur despite a deceptively circumscribed outline.

Scant desmoplasia changes the texture

- Acinar carcinomas are generally hypercellular.
- The tumor often contains less fibrous stroma than ductal adenocarcinoma.
- Consequently, a soft or friable gross consistency is characteristic.
- The gross impression is a diagnostic clue, not a criterion in isolation.

Hemorrhage, necrosis and cystic change

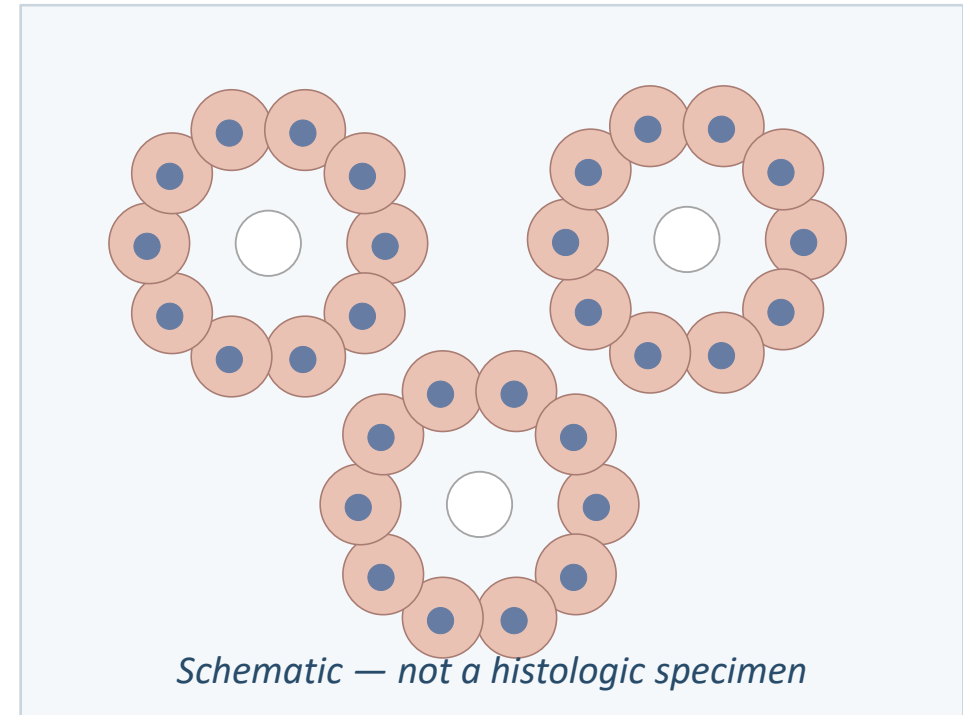
- Rapidly growing large lesions may outstrip their blood supply.
- Necrosis and hemorrhage can alter the cut surface and imaging appearance.
- Secondary cystic spaces need not imply a primary cystic neoplasm.
- Extensive sampling is important in heterogeneous lesions.

Scanning magnification: The key pattern

- High cellularity is typical of many pancreatic acinar carcinomas.
- Thin stromal septa may divide broad tumor lobules.
- Necrosis can be conspicuous at low magnification.
- The low-power pattern helps distinguish a fleshy tumor from desmoplastic PDAC.

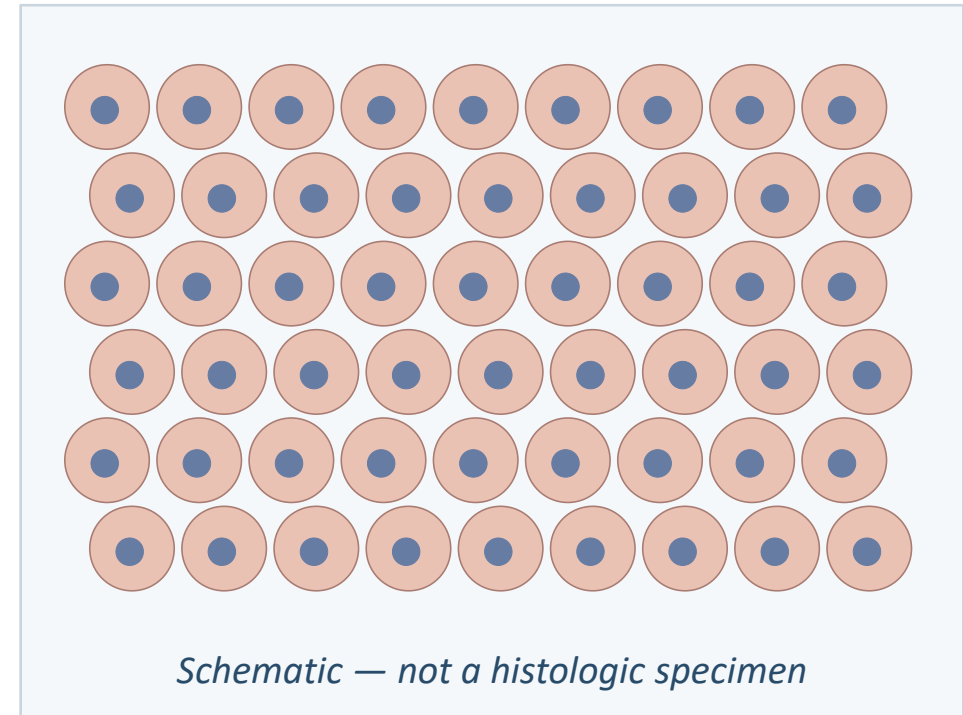
Acinar pattern: Lumen and polarity

- Small lumen-forming units resemble exocrine acini.
- Tumor cells may form a single layer with basal nuclei.
- Recognizable acini strongly suggest acinar differentiation.



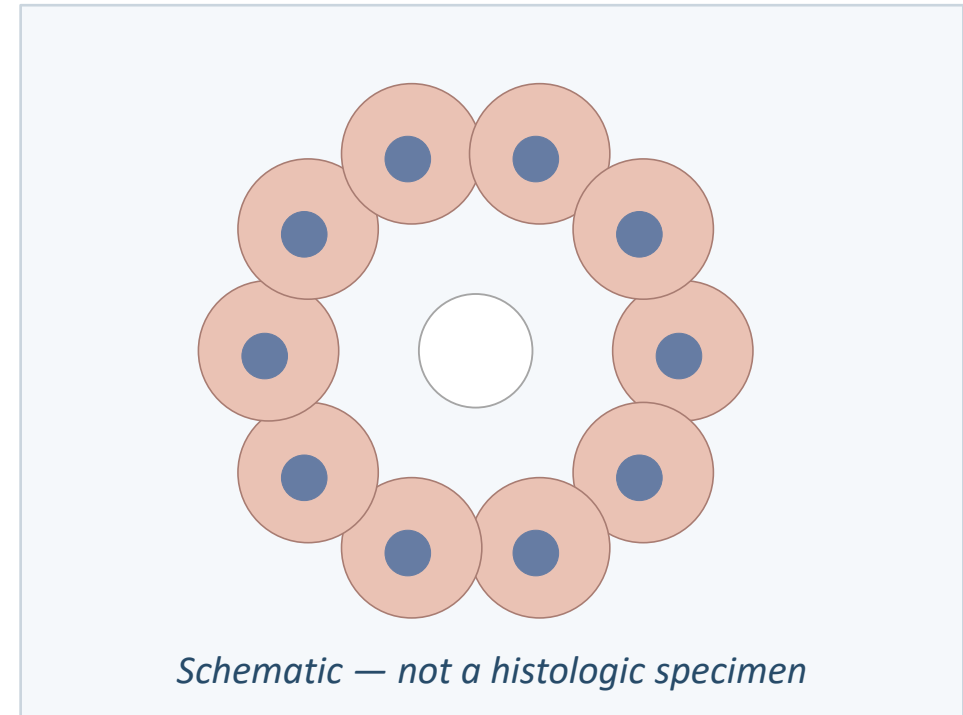
Solid pattern: Loss of obvious lumina

- Large cohesive sheets can replace recognizable acini.
- The neoplasm may appear monotonous at low power.
- Acinar enzyme immunostains become central to classification.



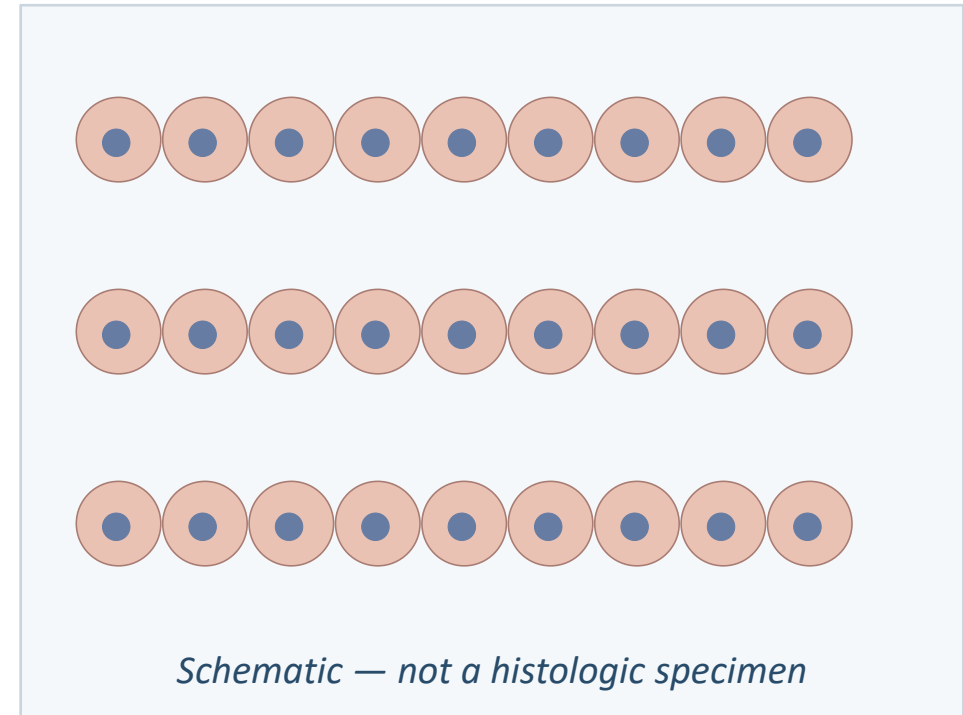
Glandular pattern: Dilated lumina

- Expanded lumina produce a gland-like architecture.
- Epithelial cells can be crowded or multilayered.
- Do not infer ductal lineage solely from a glandular outline.



Trabecular pattern: Endocrine mimic

- Interlacing ribbons can resemble pancreatic neuroendocrine tumors.
- Cellular polarity and cytoplasmic granules may provide clues.
- A lineage-specific IHC panel is required in ambiguous cases.



Architectural diversity of acinar carcinoma

Pattern	Dominant architecture	Potential diagnostic trap
Acinar	Small lumina, polarized cells	Resembles normal acini
Solid	Compact tumor-cell sheets	PanNET or solid tumor
Glandular	Widened lumina	Ductal carcinoma
Trabecular	Narrow ribbons of cells	PanNET

Cytologic morphology

- Tumor cells frequently possess abundant granular eosinophilic cytoplasm.
- Round to oval nuclei are often basally oriented in well-formed acini.
- A conspicuous single nucleolus is a useful clue.
- Atypia and mitotic activity vary with tumor differentiation.

Zymogen granules and PAS staining

- Cytoplasmic granules contain enzyme-rich secretory material.
- Granules may be PAS-positive and resistant to diastase digestion.
- PAS-D positivity is supportive but not lineage-defining.
- IHC for acinar products is more useful for definitive classification.

Ultrastructural correlates

**Rough endoplasmic
reticulum**



**Golgi / secretory
machinery**



**Electron-dense zymogen
granules**

Electron microscopy is biologically informative but rarely essential when acinar IHC is available.

Heterogeneity creates sampling risk

- Different architectural patterns can coexist within one tumor.
- Small biopsies may sample only solid or neuroendocrine-like areas.
- Necrosis and crush artifact can obscure differentiation.
- Use a sufficiently broad marker panel rather than architecture alone.

Immunohistochemistry: Diagnostic objective

- Demonstrate pancreatic acinar enzyme synthesis in neoplastic cells.
- Choose more than one marker when material and availability permit.
- Interpret positivity in the context of distribution and morphology.
- Screen competing endocrine and ductal lineages when indicated.

Trypsin: Primary acinar marker

- Trypsin immunoreactivity supports exocrine acinar differentiation.
- It is among the most useful diagnostic markers for this entity.
- Patchy labeling may occur in limited samples.
- A negative result should trigger review of tissue and companion stains.

Chymotrypsin: Complementary evidence

- Chymotrypsin identifies a second exocrine acinar enzyme.
- Combined trypsin/chymotrypsin testing improves recognition.
- Reported sensitivity varies between series and methods.
- Marker concordance strengthens an acinar-lineage interpretation.

BCL10 antibody: An important nuance

- A commonly used BCL10 clone cross-reacts with carboxyl ester lipase.
- Thus, staining indicates acinar enzyme-associated antigenicity.
- It should not be interpreted as evidence of BCL10 pathway activation.
- Integrate with trypsin and histology, particularly on small biopsies.

Lipase and amylase immunostains

- Tumor enzyme expression is variable across acinar markers.
- Lipase can provide supportive evidence of acinar differentiation.
- Amylase is less consistently detected in acinar carcinomas.
- Negative individual stains do not exclude the diagnosis.

Cytokeratins confirm epithelial lineage

- Pan-cytokeratins support carcinoma rather than a nonepithelial mass.
- CK8 and CK18 expression is characteristic of acinar epithelial cells.
- CK7 and CK19 are often absent but may be expressed focally.
- CK7 positivity by itself cannot convert an acinar tumor into PDAC.

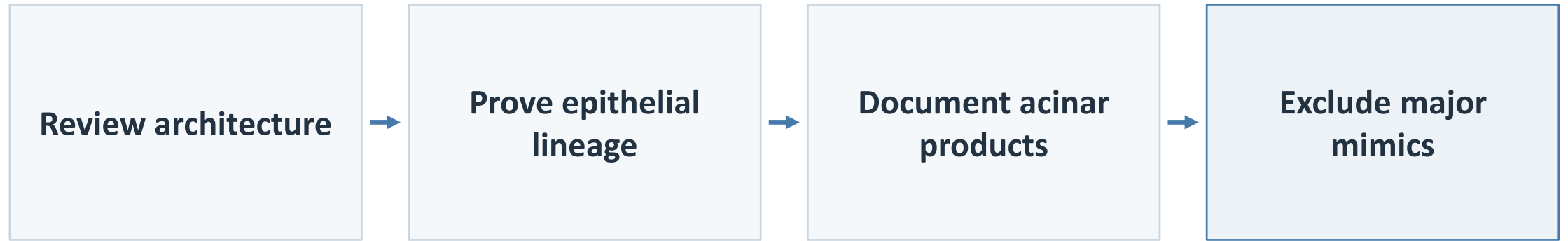
Neuroendocrine markers: Focal pitfalls

- Some acinar carcinomas express synaptophysin or chromogranin in a subset of cells.
- Focal endocrine marker reactivity does not alone define a PanNET.
- Coexpression must be interpreted with architecture and acinar enzyme staining.
- The distinction matters because tumor types have different behavior.

A focused IHC decision panel

Question	Useful tests	Interpretive caution
Is it epithelial?	Pan-cytokeratin	Does not specify acinar lineage
Is it acinar?	Trypsin, chymotrypsin, BCL10	Panel and pattern beat one stain
Is it endocrine?	Synaptophysin, chromogranin	Focal expression can occur in ACC
Is there an alternative lineage?	CK7/CK19 and context-dependent stains	Expression is not perfectly binary

Practical approach to a solid pancreatic biopsy



Integrate clinical imaging, biopsy adequacy, morphology and a deliberately selected IHC panel.

PanNET: The closest everyday mimic

- PanNET and acinar carcinoma may both be cellular and circumscribed.
- Trabeculae and solid sheets can look similar on H&E.
- A typical PanNET shows convincing neuroendocrine marker expression.
- Diffuse acinar enzyme labeling supports acinar carcinoma instead.

Acinar carcinoma versus PanNET

Acinar carcinoma

- Granular eosinophilic cytoplasm.
- Prominent nucleolus may stand out.
- Trypsin/BCL10 often support lineage.
- Endocrine stains may be only focal.

PanNET

- Finely stippled nuclear chromatin may be evident.
- Organoid or trabecular growth common.
- Diffuse synaptophysin/chromogranin is typical.
- Acinar markers generally absent.

Acinar carcinoma versus PDAC

Acinar carcinoma

- Cell-rich tumor with relatively scant stroma.
- Acinar, solid or trabecular growth.
- Enzyme-associated markers positive.
- KRAS alterations less characteristic.

Pancreatic ductal adenocarcinoma

- Infiltrative duct-forming glands.
- Prominent desmoplastic response.
- Duct-associated mucin phenotype.
- KRAS pathway alterations common.

Solid pseudopapillary neoplasm (SPN)

- SPN can form solid or pseudopapillary pancreatic masses.
- Nuclear β -catenin expression is typical of SPN.
- Acinar carcinoma may also show Wnt-pathway alterations.
- β -catenin staining alone is not sufficient to determine lineage.

Pancreatoblastoma: Related acinar differentiation

- Both tumors may exhibit acinar enzyme production.
- Pancreatoblastoma occurs predominantly in pediatric patients.
- Squamoid nests or morules are a key histologic clue to pancreatoblastoma.
- Shared Wnt-pathway changes do not erase morphologic distinctions.

Mixed acinar-neuroendocrine neoplasia

- An acinar carcinoma may contain endocrine marker-positive cells.
- Substantial, morphologically significant dual differentiation raises a mixed tumor.
- A few synaptophysin-positive cells alone are insufficient.
- Evaluate component extent on the whole specimen when possible.

Differential diagnosis at a glance

Entity	Supporting clue	Best discrimination
Acinar carcinoma	Granular acinar / solid tumor	Trypsin / chymotrypsin / BCL10
PanNET	Organoid, salt-pepper chromatin	Broad endocrine phenotype
PDAC	Infiltrative glands + desmoplasia	Ductal phenotype + architecture
SPN	Pseudopapillae; nuclear β -catenin	Compatible phenotype; no acinar enzymes
Pancreatoblastoma	Squamoid morules, often pediatric	Morules + acinar phenotype

Canonical Wnt control: Simplified pathway



APC loss-of-function and activating CTNNB1 mutations as routes to aberrant Wnt signaling.

APC loss-of-function in acinar carcinoma

- APC normally contributes to regulation of β -catenin abundance.
- Loss of functional APC can promote constitutive Wnt signaling.
- This mechanism in acinar carcinoma.
- An alteration in one tumor does not imply a universal driver.

CTNNB1 activation

- CTNNB1 encodes β -catenin, a key Wnt-pathway effector.
- Activating CTNNB1 mutations can increase β -catenin signaling.
- Activating point mutations in acinar carcinoma.
- Molecular findings must be placed alongside histology and IHC.

Acinar and ductal carcinoma: Molecular context

Acinar carcinoma

- Heterogeneous genomic alterations.
- Wnt pathway abnormalities occur.
- DNA-repair gene defects in a subset.
- Typical PDAC driver set often absent.

Ductal adenocarcinoma

- KRAS alteration is a frequent central event.
- TP53/CDKN2A/SMAD4 patterns characteristic.
- Different recurrent alterations shape biology.
- Molecular profiles overlap imperfectly.

Beyond Wnt: Genomic diversity

- Comprehensive sequencing shows diverse alterations rather than one universal driver.
- Homologous recombination repair genes may be altered in a subset.
- Rare actionable kinase alterations or fusions have been reported.
- Testing must be interpreted using tumor-specific evidence and current practice.

DNA repair defects: Clinical interpretation



Potential therapeutic relevance requires clinical validation; Genotype is not a guarantee of drug response.

Actionable alterations: Evidence threshold

- Molecular testing may reveal repair defects or targetable alterations.
- Case series and reports suggest benefit from some matched treatments.
- Many therapy associations lack prospective acinar-specific validation.
- Report predictive assertions with their level of evidence.

Mismatch repair and immunotherapy

- Deficient mismatch repair / high microsatellite instability is uncommon but reported.
- These findings may have therapeutic implications across tumor types.
- The assay and interpretation should follow validated laboratory methods.
- Do not infer immunotherapy sensitivity from histologic subtype alone.

Local invasion and metastatic routes

- A circumscribed tumor can still invade pancreas-adjacent structures.
- Regional lymph nodes and liver are important metastatic sites.
- Staging incorporates anatomic extent and distant disease.
- Extent of disease directly determines resectability discussions.

Surgical decision: Conceptual framework



For localized, operable disease, resection is the principal potentially curative approach.

Treatment: Evidence is limited by rarity

- Radical resection is commonly favored when disease is resectable.
- Recurrence after surgery remains a major clinical problem.
- The optimal postoperative systemic regimen is not established.
- Unresectable-disease therapy is based mainly on retrospective evidence.

Systemic therapy: Interpret cautiously

- Retrospective reports support activity of fluoropyrimidine/platinum-containing regimens.
- Some advanced cases respond to combination regimens such as FOLFIRINOX.
- Matched molecular therapy may be considered for qualifying alterations.
- None of these observations replaces individualized oncology assessment.

Prognosis: Different from ductal cancer

- Outcomes are generally more favorable than for pancreatic ductal adenocarcinoma.
- Nevertheless, acinar carcinoma is an aggressive malignant neoplasm.
- Stage, resection status and disease recurrence remain important.
- Published survival estimates differ across cohorts and treatment eras.

Case 1 — solid pancreatic mass

A pancreatic biopsy shows a hypercellular neoplasm with minimal stroma and solid-to-trabecular growth. Synaptophysin is focal; Cytokeratin is positive.

Which lineage-defining tests should be prioritized?

Case 1 — diagnostic resolution

- Use trypsin and/or chymotrypsin with BCL10 to evaluate acinar differentiation.
- Interpret focal synaptophysin cautiously; It does not establish PanNET.
- Correlate stains with granularity, nucleoli and growth architecture.
- Classify the tumor by the integrated morphologic and immunophenotypic pattern.

Case 2 — systemic lipase effect

A patient with a pancreatic mass develops tender subcutaneous nodules and arthralgias. Serum lipase is elevated.

Which paraneoplastic mechanism should be considered?

Case 2 — mechanism and limits

- A lipase-secreting acinar carcinoma can cause metastatic fat necrosis syndrome.
- Circulating lipase may injure adipose tissue at distant sites.
- The presentation should prompt targeted diagnostic evaluation, not presumptive diagnosis.
- Most acinar carcinomas do not produce the complete clinical syndrome.

Case 3 — β -catenin is not enough

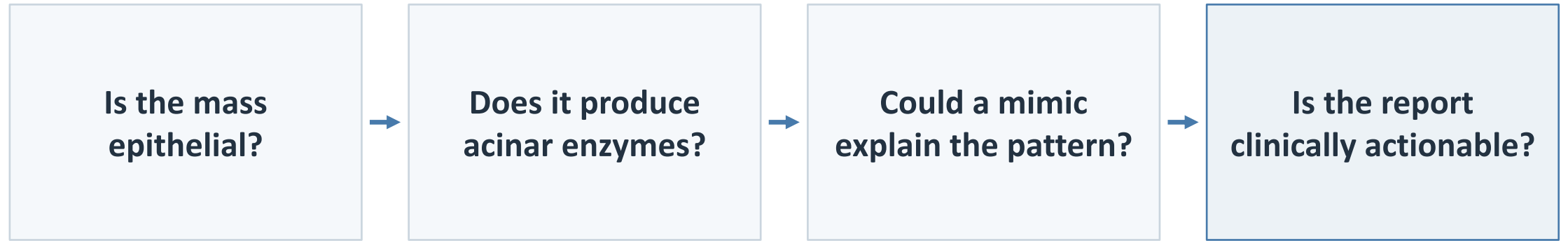
A solid pancreatic neoplasm shows nuclear β -catenin labeling. Imaging and morphology do not securely distinguish acinar carcinoma from SPN.

What additional evidence is necessary?

Case 3 — avoid a marker trap

- Nuclear β -catenin is not exclusive to one pancreatic neoplasm.
- Assess the architecture and phenotype expected for SPN.
- Demonstrate or exclude acinar differentiation using enzyme-associated stains.
- Resolve the diagnosis on the full panel, not the Wnt pathway alone.

Integrated diagnosis in four questions



A defensible diagnosis links cellular differentiation to morphology, IHC and clinical context.

Essential morphologic takeaways

- Acinar differentiation may be architecturally overt or deceptively subtle.
- Solid, glandular and trabecular patterns overlap with other pancreatic tumors.
- Abundant granular cytoplasm, conspicuous nucleoli and scant stroma are useful clues.
- Definitive diagnosis relies on evidence of acinar enzyme expression.

Essential clinical and molecular takeaways

- This tumor is uncommon and biologically distinct from PDAC.
- Lipase-related metastatic fat necrosis is characteristic but infrequent.
- APC/CTNNB1-related Wnt activation is one documented molecular mechanism.
- Selected molecular findings may matter therapeutically, but evidence varies.

Core reference sources

Source	Contribution
Robbins, Cotran & Kumar, 11th ed., ch. 19 (2026)	Primary excerpt: rarity, acinar secretions, fat necrosis, APC/CTNNB1
La Rosa et al., Front Med. 2015;2:41	Morphology, differential diagnoses, Wnt biology
Calimano-Ramirez et al., WJG. 2022;28:5827–5844	Pathology and immunohistochemical differentials
Ikezawa et al., JCO. 2024;54:271–281	Clinical features, genomics, and treatment evidence