

Familial Adenomatous Polyposis

APC-mediated colorectal neoplasia: molecular pathogenesis, morphology
and clinical implications

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Learning objectives

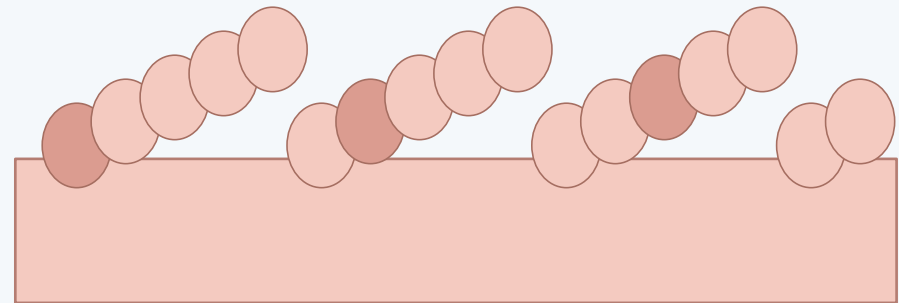
- Explain how an inherited APC defect predisposes colorectal epithelium to adenoma formation.
- Recognize the classic polyp burden and the microscopic features of colorectal adenomas.
- Connect untreated FAP to the timing and near-certainty of colorectal carcinoma.
- Identify extracolonic manifestations and distinguish FAP from MUTYH-associated polyposis.

FAP is a hereditary adenomatous polyposis syndrome

- Autosomal dominant predisposition to numerous colorectal adenomas.
- Polyps commonly begin during the teenage years.
- Underlying defect: Germline alteration of the APC tumor-suppressor gene.
- Neoplastic risk reflects the cumulative burden of adenomas.

Numerous mucosal adenomas

Independent neoplastic polyps can arise across the colorectum



Schematic — not a specimen

What “familial” signifies—and what it does not

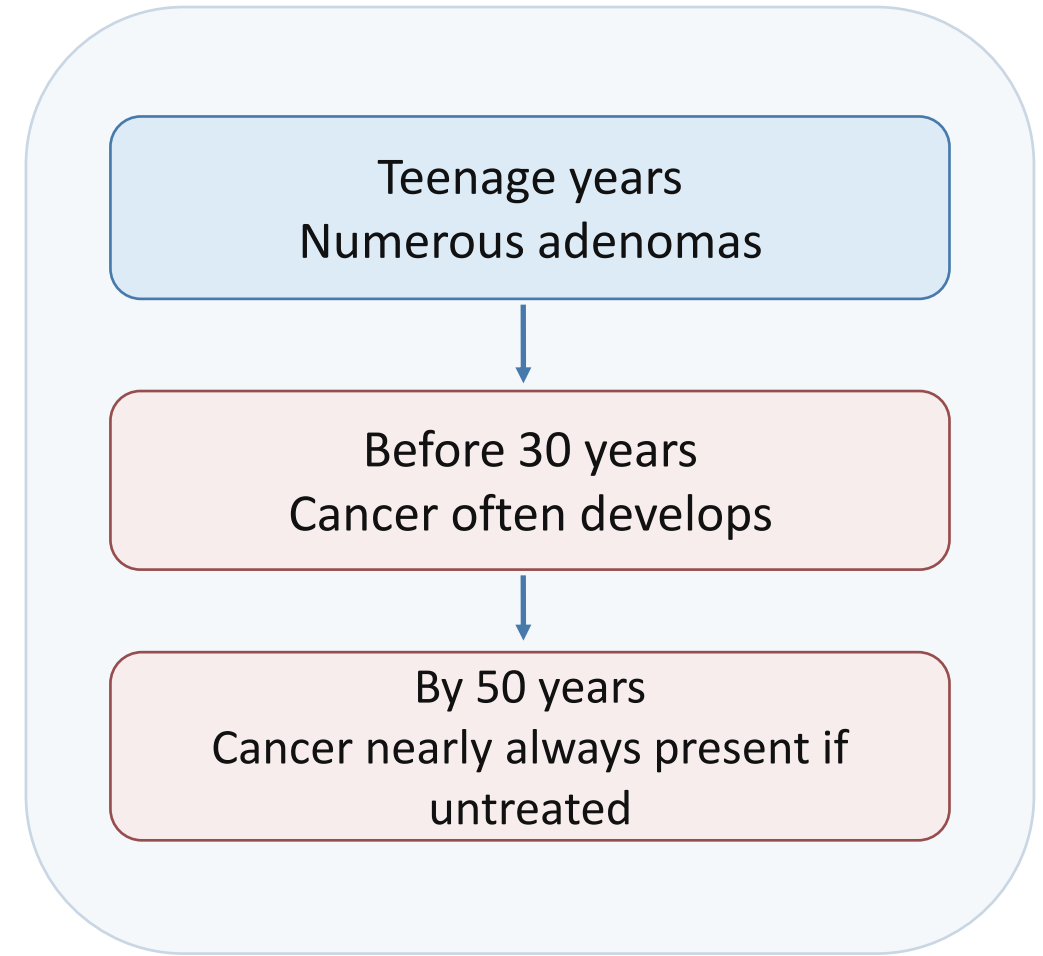
- About three quarters of classic FAP cases are inherited from an affected parent.
- The remaining cases apparently arise from de novo germline mutations.
- Absence of a recognized family history therefore does not exclude FAP.
- A familial phenotype is explained by a constitutional predisposition, not transmitted polyps.

INTERPRETATION

A de novo APC mutation can still be transmitted to the next generation.

Adenomas appear early in life

- The classic phenotype begins with many colorectal adenomas in adolescence.
- Untreated disease follows a distinctive age-related neoplastic course.
- Histology and family history must be interpreted together.



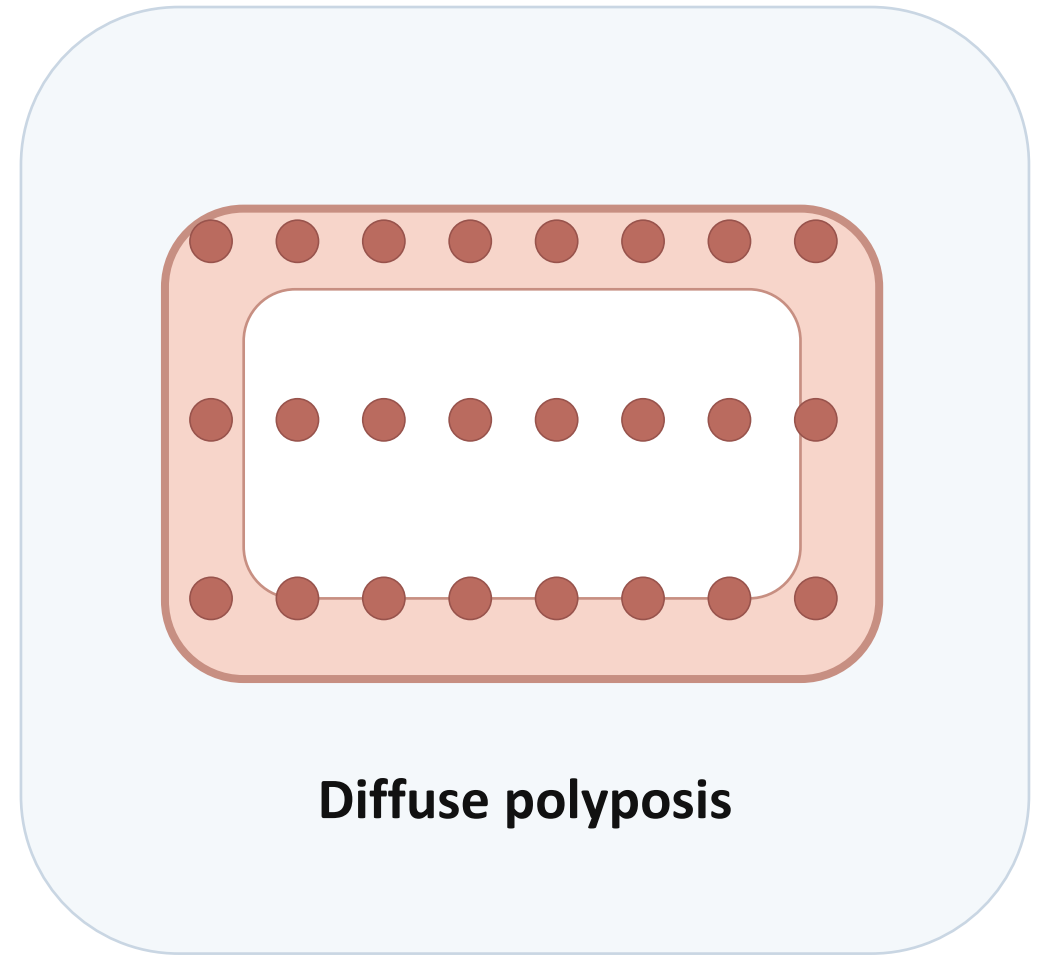
Classic FAP: The conventional polyp threshold

At least 100 colorectal adenomas

The textbook uses ≥ 100 polyps for classic FAP; Thousands may be present. This threshold does not describe every APC-related phenotype.

Polyp multiplicity is more characteristic than appearance

- Hundreds to thousands of mucosal adenomas may coexist.
- An individual adenoma can look like a conventional sporadic adenoma.
- The striking clue is multiplicity throughout the large bowel.

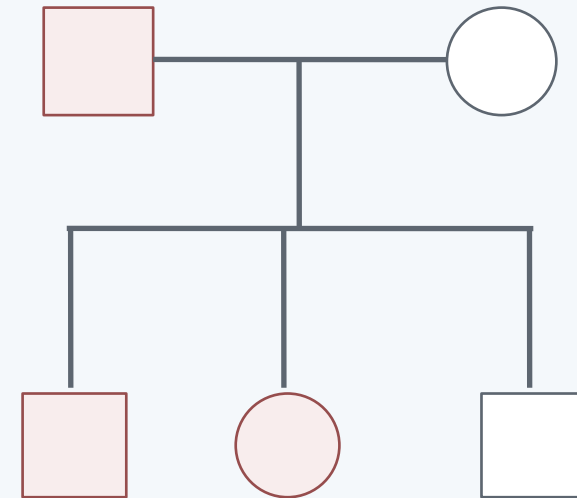


Schematic bowel wall, not a gross photograph

Autosomal dominant inheritance

- A constitutional APC mutation can segregate vertically through a family.
- An inherited mutation is present before adenomas appear.
- The phenotype arises after additional alterations in individual colonic crypts.

Illustrative autosomal dominant transmission



Shading denotes a hypothetical affected relative

Inherited versus de novo FAP

$\approx 75\%$ inherited

The remaining $\approx 25\%$ appear de novo in the source text; These are textbook proportions, not a patient-specific probability.

APC: The initiating molecular lesion

- APC is a negative regulator of the Wnt/ β -catenin signaling pathway.
- Its normal tumor-suppressive role restrains epithelial proliferation.
- A germline pathogenic change predisposes many colonic epithelial cells to acquire a second event.
- Loss of APC function is a central early event in the classic adenoma–carcinoma sequence.

APC is a tumor-suppressor gene on chromosome 5q21

- The inherited allele carries a loss-of-function defect.
- Each adenoma arises only after remaining APC function is sufficiently lost.
- This recessive cellular mechanism produces an autosomal dominant family phenotype.

APC alleles in one epithelial cell

Inherited altered allele

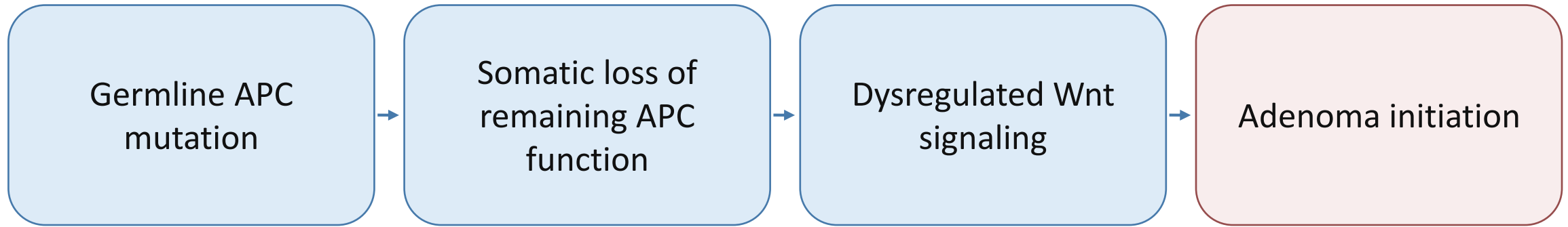
Remaining functional allele



Somatic inactivation ("second hit")

Schematic — sequential hits

The two-hit model explains an inherited cancer risk



Two genetic “hits” are required at the cell level, even though the syndrome transmits dominantly.

First hit is inherited; Second hit occurs in the epithelium

- At birth, colonic cells already carry one altered APC allele.
- A second somatic inactivation can arise in a susceptible epithelial clone.
- Independent second hits help explain multiple separate adenomas.

APC alleles in one epithelial cell

Inherited altered allele

Remaining functional allele



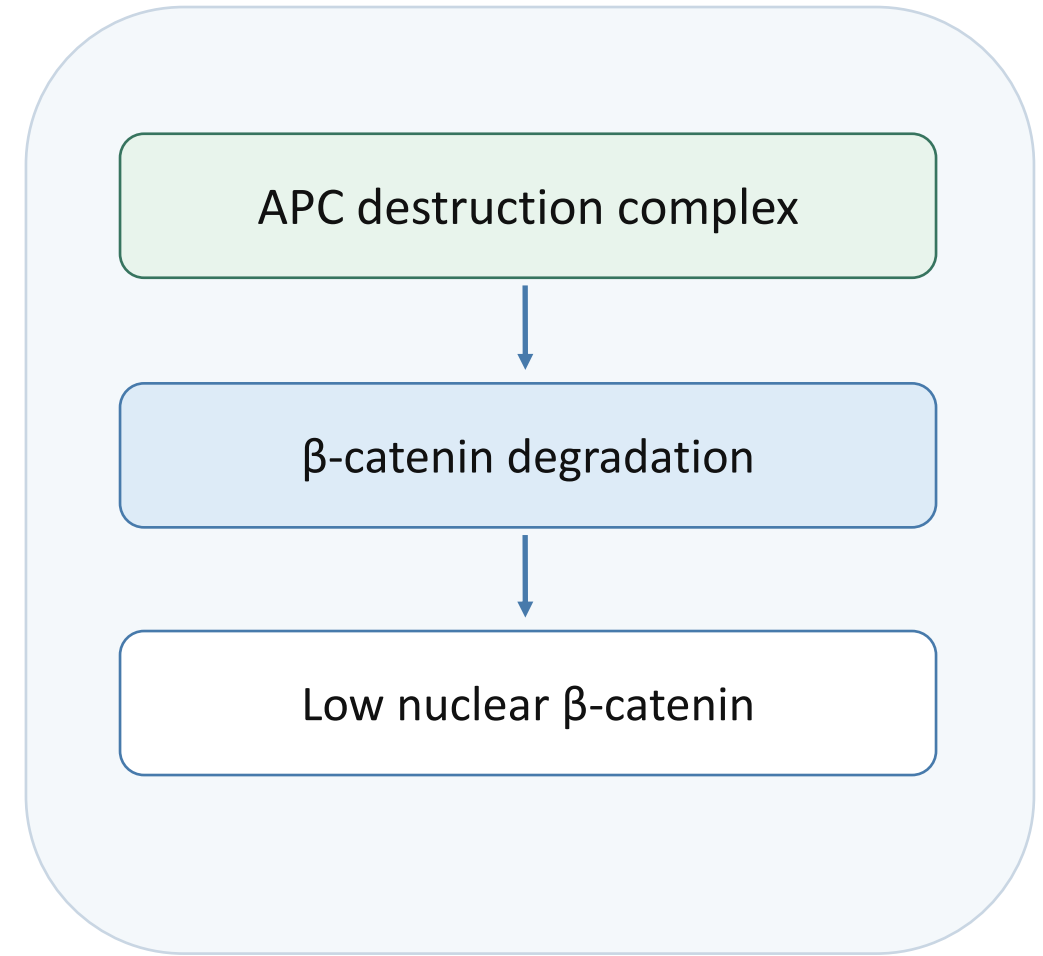
Somatic inactivation ("second hit")

The multiplicity of polyps reflects clonal opportunity

- Extensive colorectal mucosa provides many susceptible epithelial crypts.
- The predisposition increases opportunities for independent adenoma initiation.
- Each visible polyp represents a localized neoplastic epithelial population.
- The syndrome is not a single polyp extending throughout the colon.

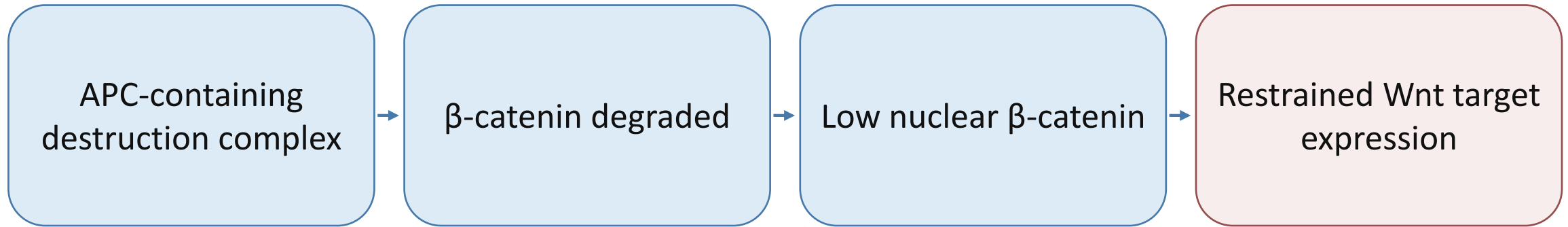
Wnt signaling is normally regulated

- Wnt ligand binding alters the fate of intracellular β -catenin.
- In unstimulated cells, an APC-containing complex promotes β -catenin destruction.
- Low nuclear β -catenin restricts the transcriptional growth program.



APC intact; No Wnt stimulation

Normal colon epithelium without a Wnt signal



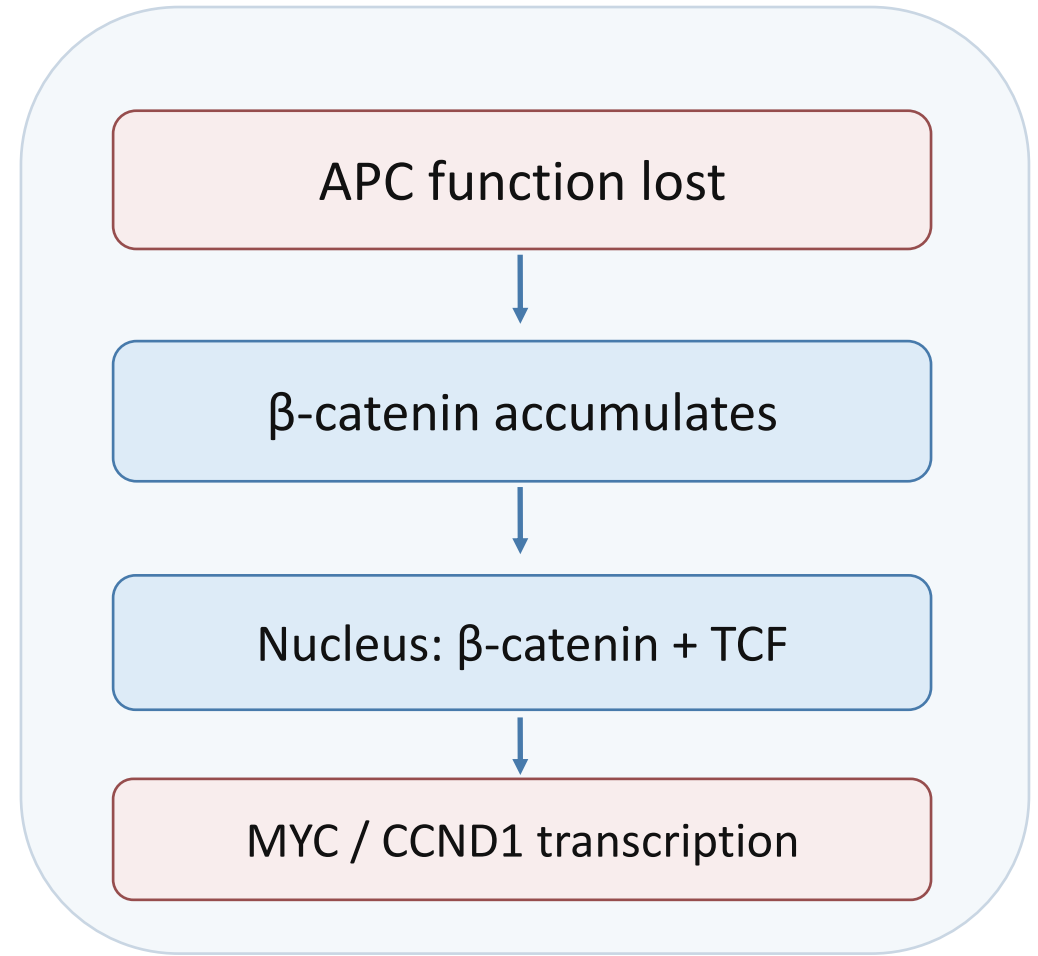
The destruction pathway is an active growth-control mechanism, not passive absence of stimulation.

Normal Wnt stimulation is a regulated proliferative signal

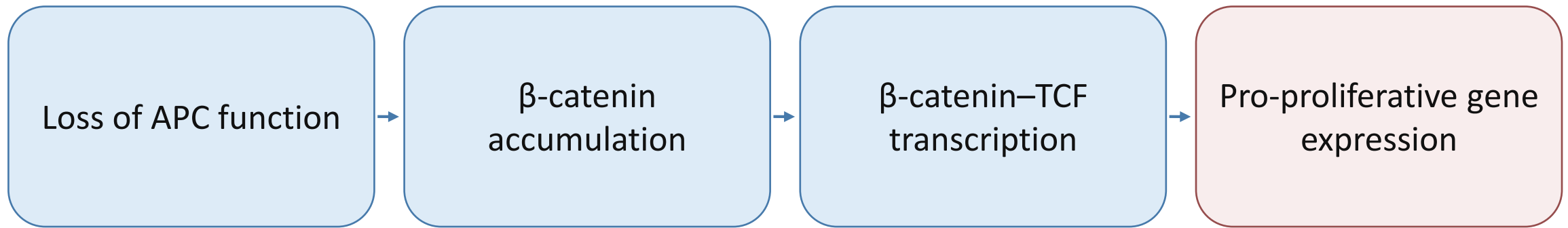
- Wnt binds cell-surface receptors in the Frizzled family.
- Wnt signaling prevents formation of the β -catenin destruction complex.
- Stabilized β -catenin can enter the nucleus and cooperate with TCF.
- Target-gene activation is physiologically controlled by external signaling.

APC loss simulates persistent Wnt stimulation

- In the absence of functional APC, β -catenin destruction is impaired.
- β -catenin accumulates even without normal upstream stimulation.
- This activates a persistent epithelial growth program.



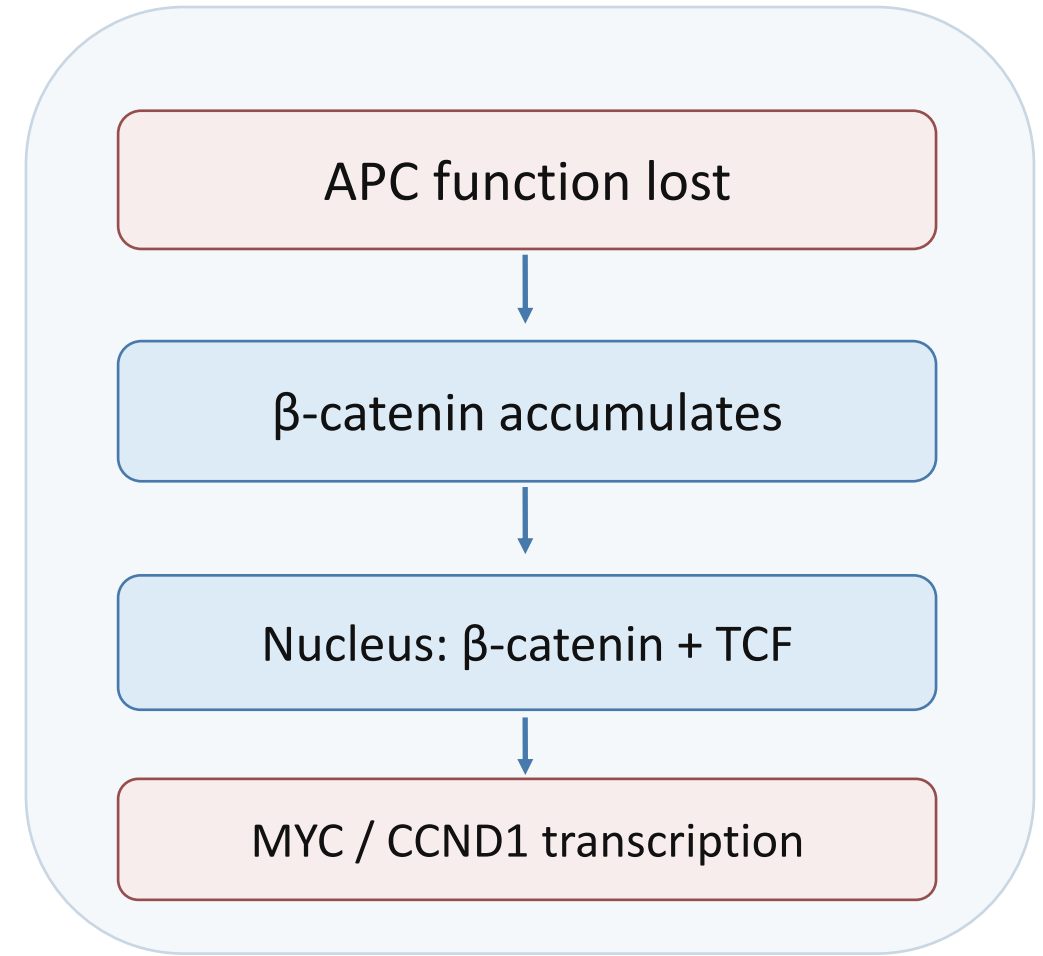
APC deficiency links genotype to growth signaling



The pathway is a molecular explanation for adenomatous epithelial expansion.

β -catenin enters the nucleus and partners with TCF

- APC normally helps retain β -catenin below a proliferative threshold.
- Without functional destruction, β -catenin translocates to the nucleus.
- β -catenin interacts with TCF to activate transcription.



MYC and cyclin D1 connect signaling to cell growth

- Wnt-responsive genes include MYC and CCND1.
- CCND1 encodes cyclin D1, a regulator of cell-cycle progression.
- Elevated expression contributes to epithelial proliferation.
- APC loss thus perturbs growth control rather than merely changing polyp shape.

Normal Wnt regulation versus APC loss

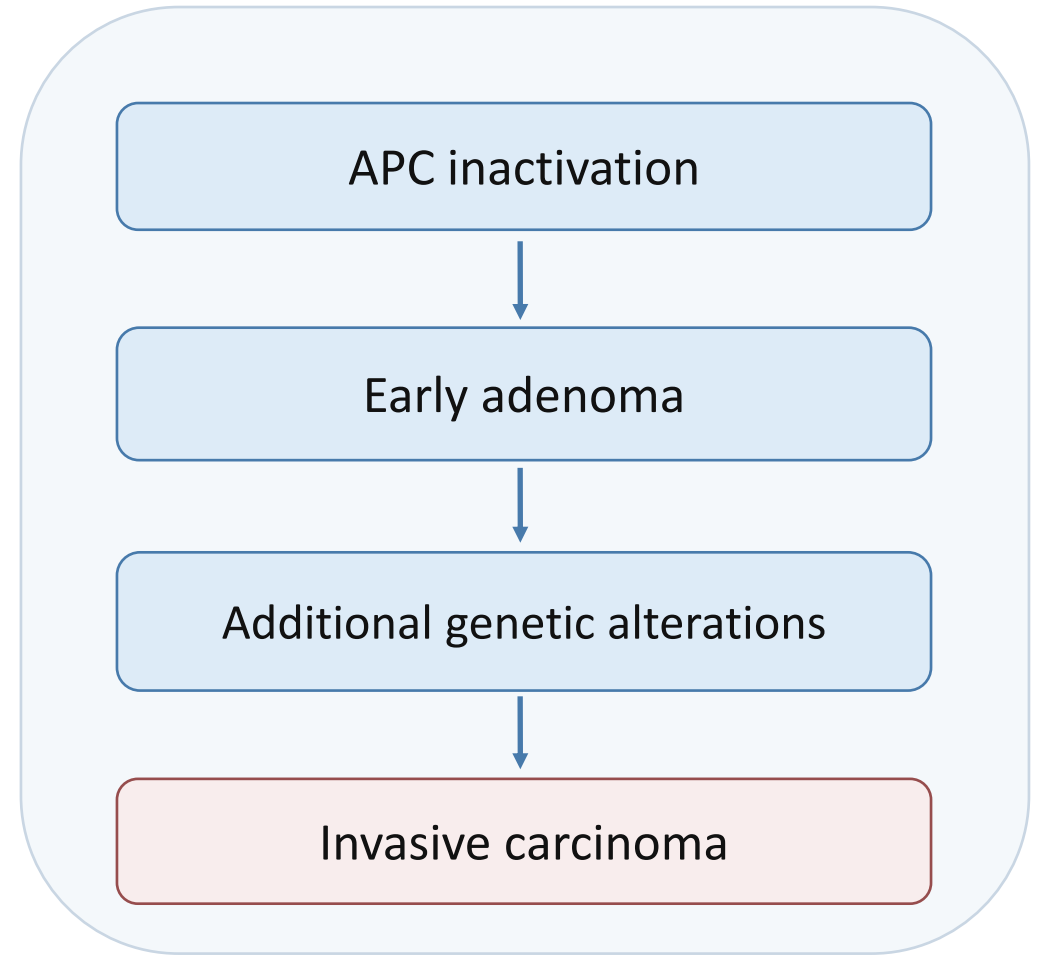
Process	APC function preserved	APC function lost
β -catenin handling	Targeted degradation without Wnt	Accumulation despite absent upstream signal
Nuclear β -catenin	Low without Wnt	Increased
TCF target genes	Regulated induction	Persistent stimulation
Epithelial consequence	Controlled proliferation	Increased neoplastic potential

APC loss initiates adenomas but does not complete carcinogenesis

- Loss of both functional APC copies promotes the transition to an adenoma.
- Additional somatic alterations accumulate with neoplastic progression.
- The classic adenoma–carcinoma pathway is multistep.
- This distinction explains why adenoma and carcinoma are different diagnoses.

The adenoma–carcinoma sequence is multistep

- APC inactivation is an early initiating alteration.
- Additional mutations affect growth, apoptosis and cell-cycle control.
- Advanced lesions may progress to invasive colorectal adenocarcinoma.

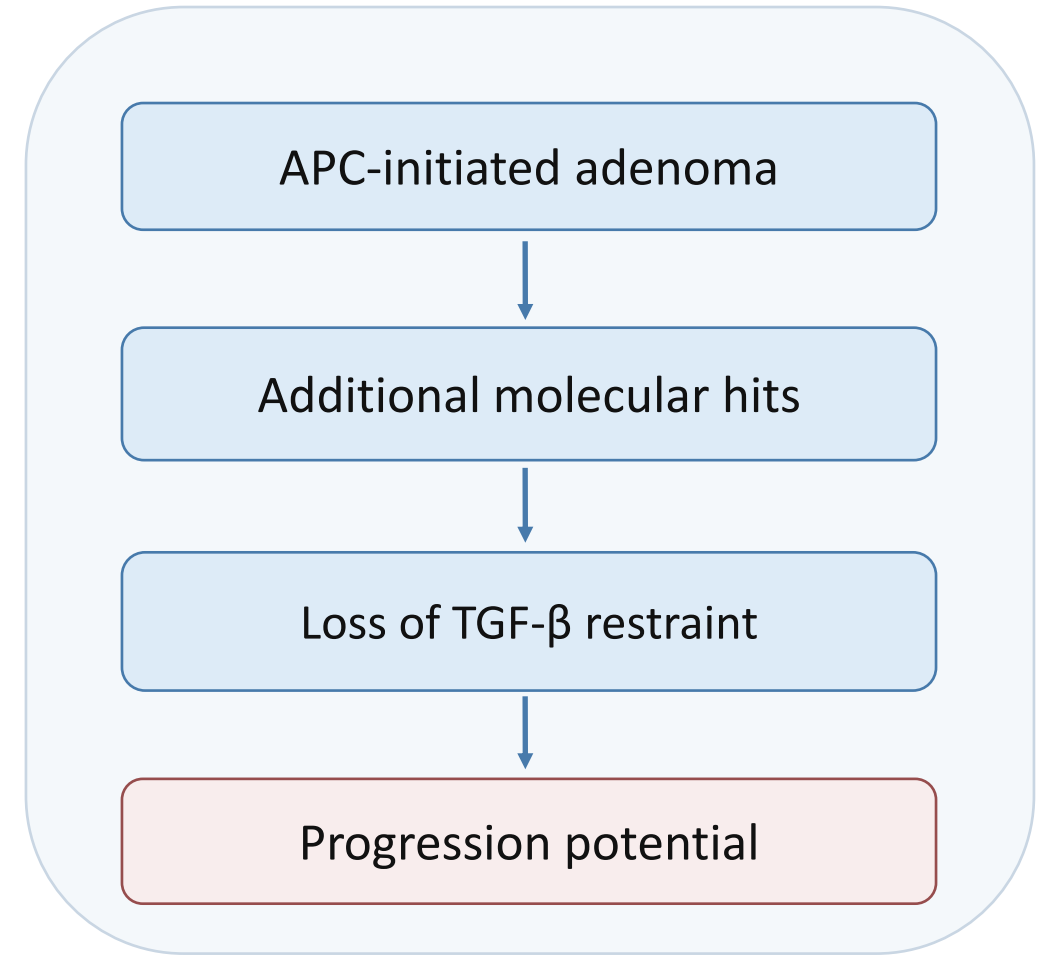


KRAS activation accompanies later adenoma progression

- Activating KRAS mutations can promote cell growth and reduce apoptosis.
- The source places KRAS changes later than APC loss.
- For sporadic adenomas, KRAS mutations become more frequent as lesions enlarge.
- These population-level correlations are not a molecular diagnostic rule for any individual FAP polyp.

SMAD2 and SMAD4: Removal of growth inhibition

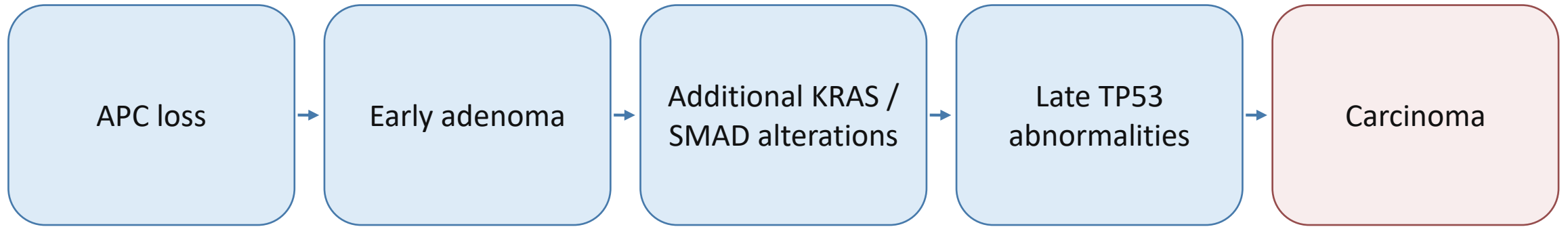
- SMAD2 and SMAD4 are effectors of TGF- β growth-inhibitory signaling.
- Loss of their tumor-suppressive function reduces constraints on proliferation.
- These alterations can contribute to further progression.



TP53 changes belong mainly to advanced progression

- The source describes TP53 mutation as common in colorectal carcinomas.
- It is uncommon in adenomas, placing it relatively late in this pathway.
- TP53 loss helps remove safeguards against malignant evolution.
- Do not conflate APC-mediated initiation with TP53-associated late events.

Molecular progression: A simplified teaching sequence



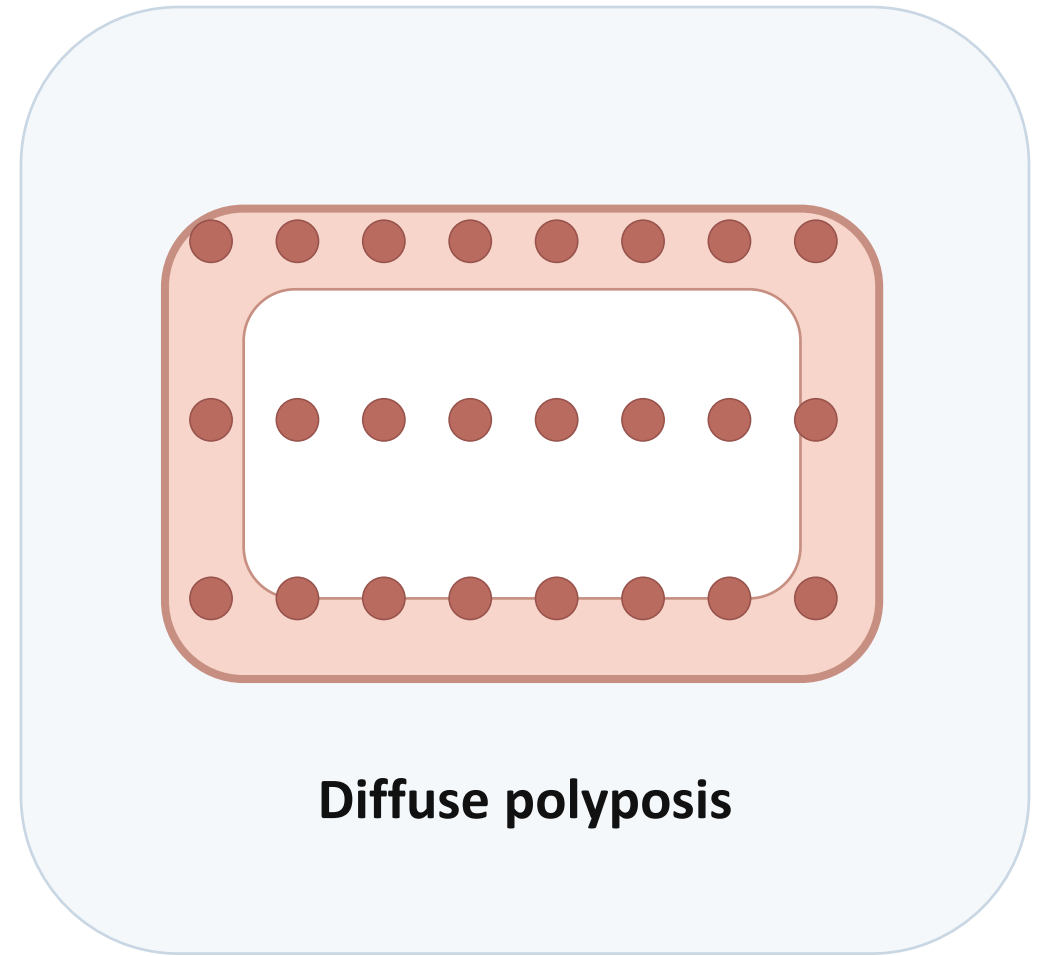
The diagram is conceptual: Individual tumors need not follow a uniform molecular order.

Why FAP informed sporadic colorectal cancer biology

- Germline APC mutations identify a causal initiating mechanism in FAP.
- Acquired APC defects occur in a large proportion of sporadic adenomas and colorectal cancers.
- The shared APC/ β -catenin pathway links inherited and sporadic tumorigenesis.
- An inherited syndrome can illuminate a common molecular route to cancer.

Morphologic signature: A bowel filled with adenomas

- Numerous discrete adenomas populate colorectal mucosa.
- FAP polyps are not individually distinguishable from sporadic adenomas.
- A carpet-like distribution is strongly suggestive when combined with the clinical phenotype.



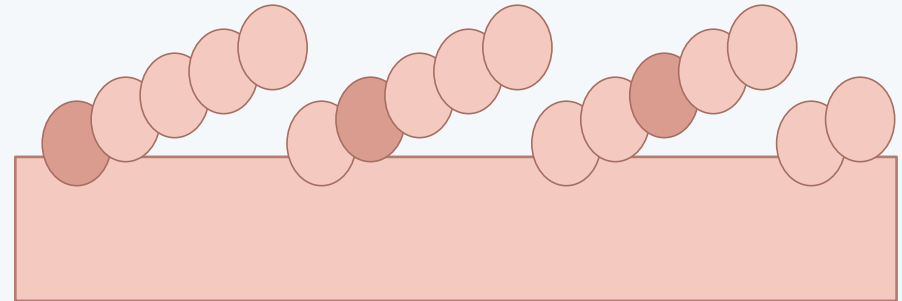
Schematic bowel wall, not a gross photograph

Gross disease burden can exceed a thousand polyps

- The threshold for classic FAP is at least 100 polyps.
- Thousands of adenomas may occur within the colon.
- Polyps may differ in size and shape within the same bowel.

Numerous mucosal adenomas

Independent neoplastic polyps can arise across the colorectum

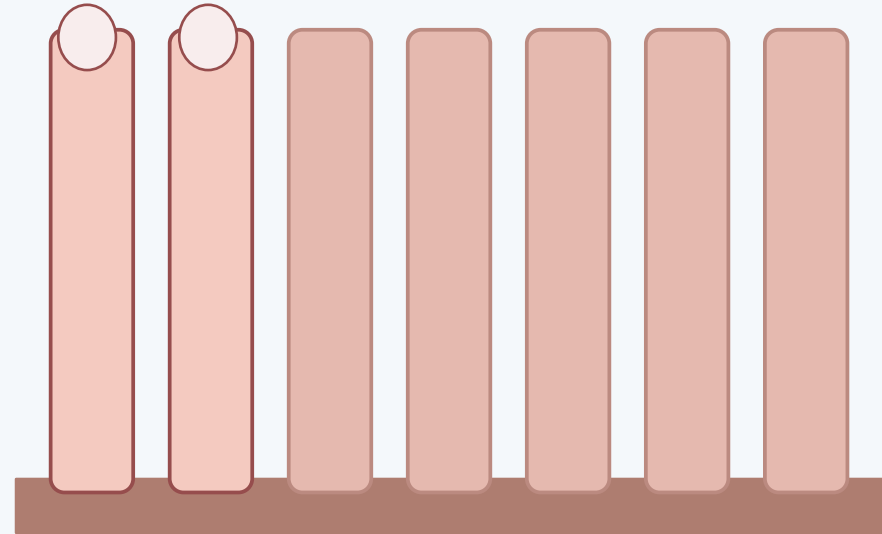


Schematic — not a specimen

Many adenomas may coexist in a single field

- The source figure illustrates three tubular adenomas in one microscopic field.
- Neoplastic multiplicity is visible at histologic as well as gross scale.
- Each lesion should still be evaluated by usual adenoma morphology.

Adenomatous change can begin in very few crypts

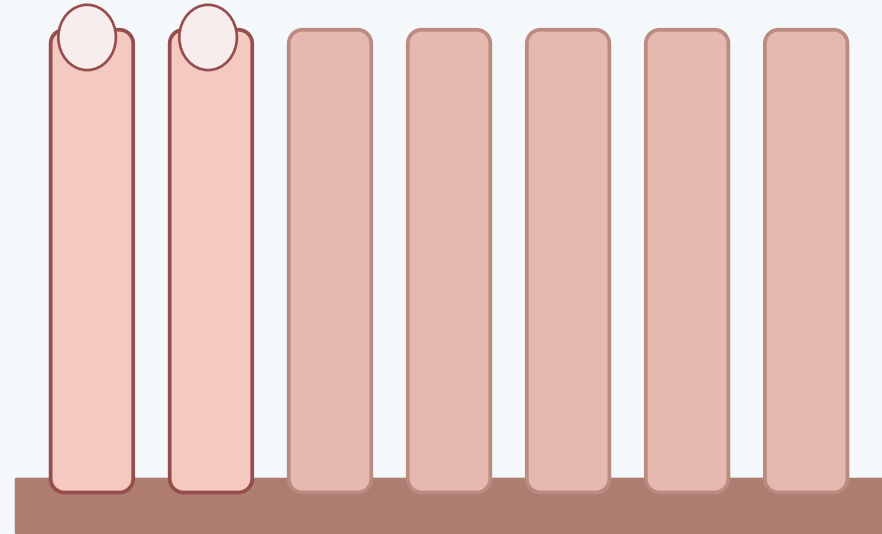


Schematic crypt field

Microscopic adenomas can involve one or two crypt profiles.

- Dysplasia may be limited to one or two crypt profiles.
- Overlying mucosa can appear normal to the naked eye.
- This supports the concept of early crypt-level neoplastic initiation.

Adenomatous change can begin in very few crypts



Schematic crypt field

Flat and depressed adenomas occur in FAP

- Not every FAP adenoma protrudes as a conspicuous polyp.
- Flat or depressed lesions are also prevalent in FAP.
- The broad surface morphology must not be used to exclude an adenomatous lesion.
- Invisible microscopic adenomas further widen the morphologic spectrum.

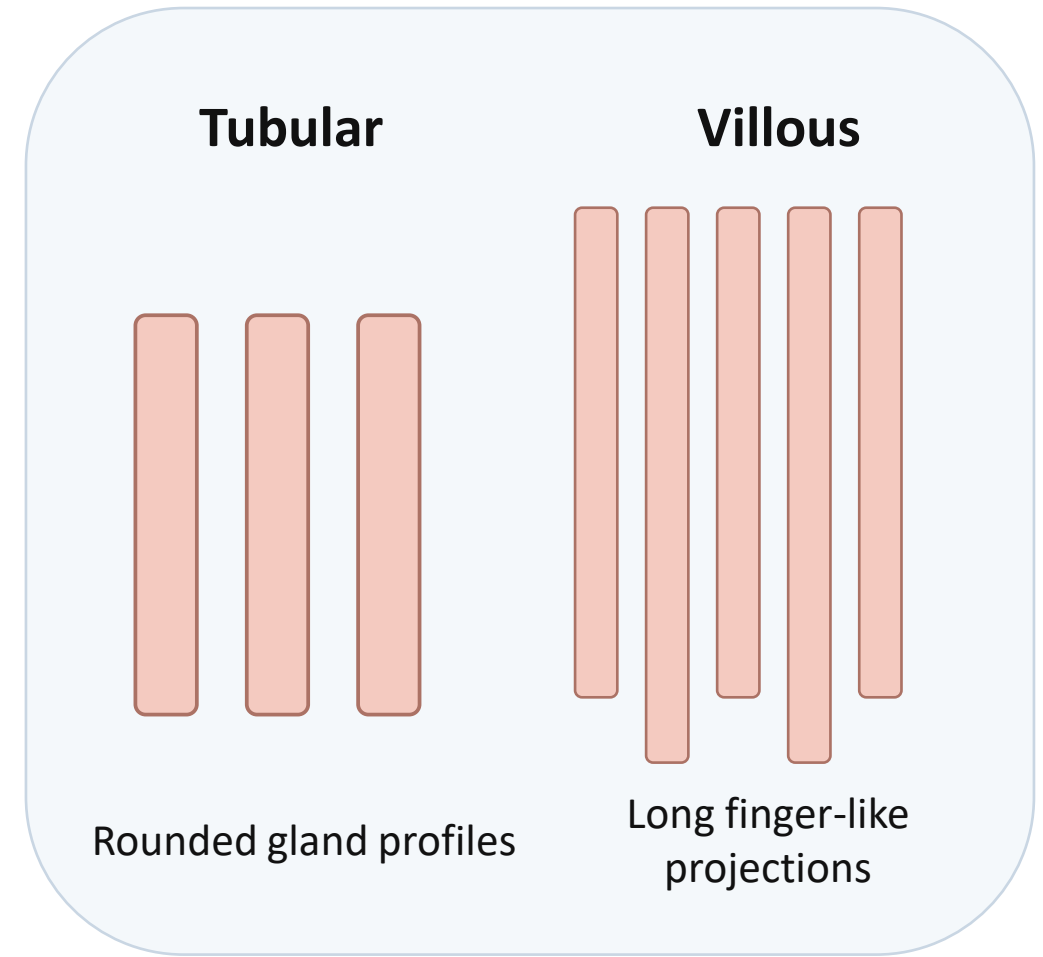
Adenoma histology does not identify hereditary origin

Indistinguishable

Apart from their multiplicity, FAP-associated adenomas are morphologically indistinguishable from sporadic adenomas.

Tubular adenoma: Gland-forming architecture

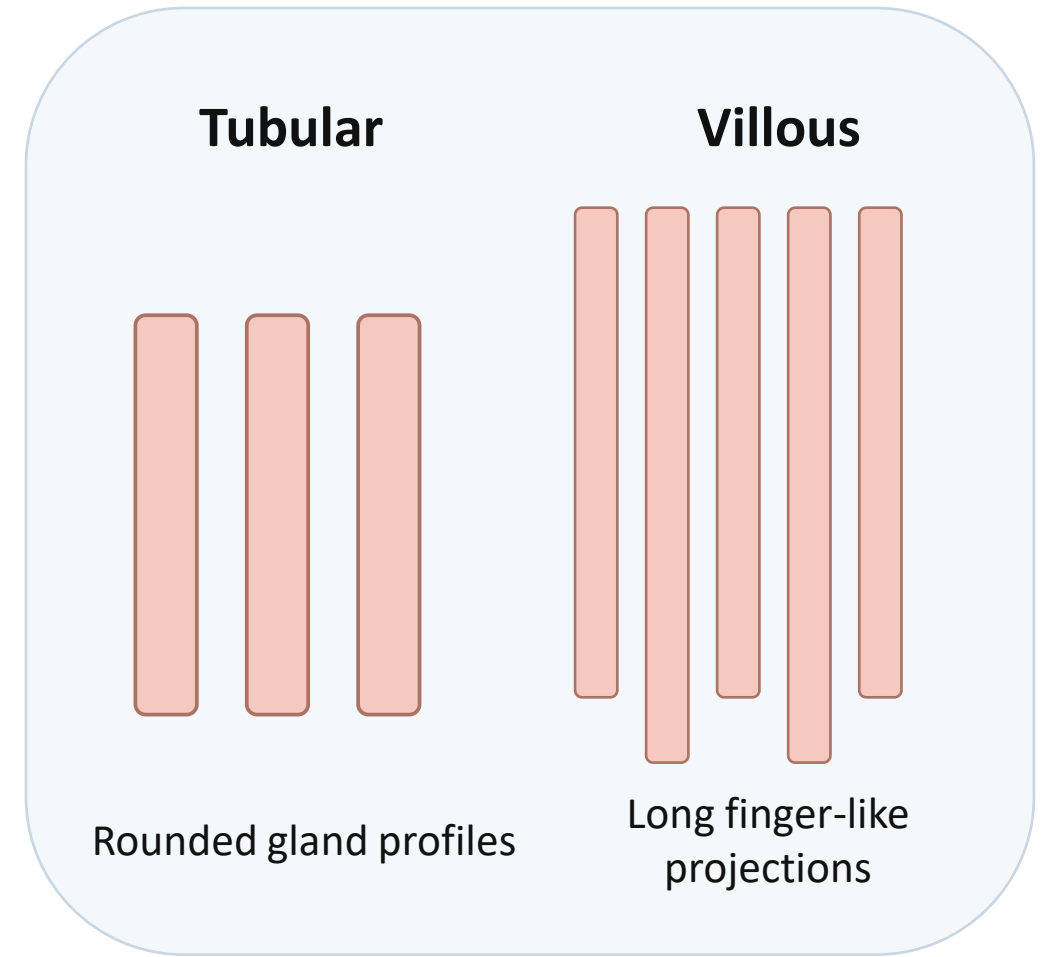
- Tubular adenomas have rounded or tubular glands.
- They are often relatively small and may be pedunculated.
- Architectural classification is separate from the diagnosis of dysplasia.



Architectural schematic; Not histology

Villous adenoma: Elongated mucosal projections

- Villous adenomas feature slender villous projections.
- Villous architecture is associated with more frequent carcinoma, partly through larger lesion size.
- Dysplasia remains the defining neoplastic epithelial abnormality.



Architectural schematic; Not histology

Tubulovillous adenomas combine two architectural patterns

- Tubular glands coexist with villous projections.
- Classification records architecture rather than a distinct hereditary etiology.
- As with tubular and villous adenomas, cytologic epithelial dysplasia is present.

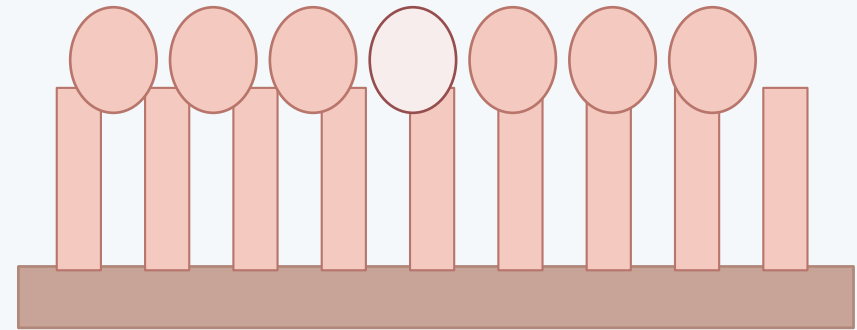
Architecture: Useful language, limited prognostic isolation

Adenoma pattern	Dominant architecture	Interpretive caution
Tubular	Rounded / tubular glands	Morphology alone does not imply FAP
Villous	Slender villous projections	Often larger; size influences cancer risk
Tubulovillous	Mixed tubular and villous	Architecture alone has limited clinical significance

Pedunculated adenomas develop a fibromuscular stalk

- A polyp may have a slender stalk containing vessels from the submucosa.
- The stalk is usually covered by non-neoplastic epithelium.
- Dysplasia may also extend onto the stalk in some polyps.

Epithelial dysplasia is the defining histologic feature



Schematic surface epithelium

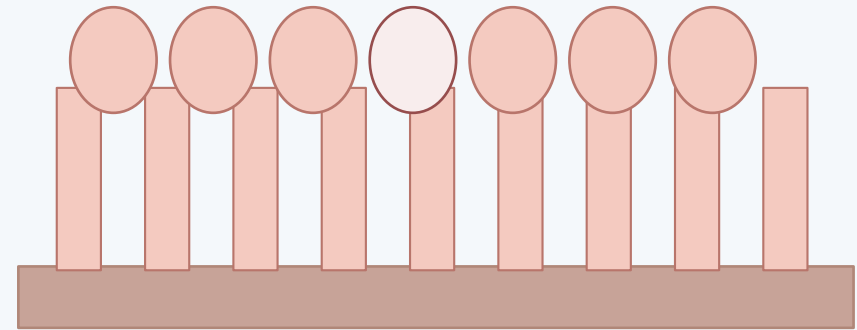
Sessile lesions need the same dysplasia assessment

- Sessile adenomas have a broad attachment to mucosa.
- Gross configuration does not establish biologic grade.
- Flat, depressed, sessile and pedunculated lesions can all contain neoplastic epithelium.

Adenomatous dysplasia: The nuclear phenotype

- Nuclei become hyperchromatic and elongated.
- Nuclear stratification disrupts orderly epithelial maturation.
- Changes are often most evident near the luminal surface.

Epithelial dysplasia is the defining histologic feature



Schematic surface epithelium

Additional cytologic changes support dysplasia

- Prominent nucleoli may accompany nuclear atypia.
- Eosinophilic cytoplasm can be conspicuous.
- Goblet cells are often reduced relative to normal mucosa.
- Interpret these findings within an adenomatous architectural context.

Polyp size correlates with invasive cancer risk

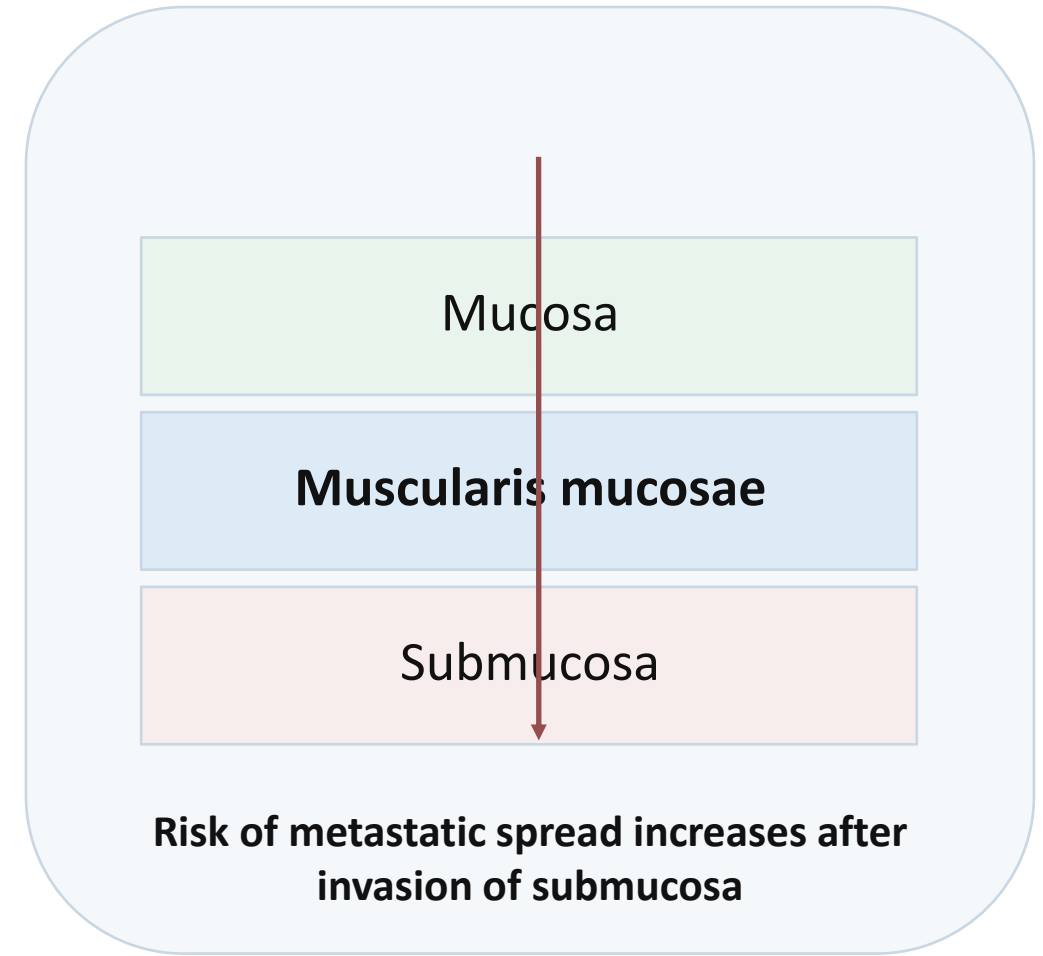
- Most small conventional adenomas do not contain invasive carcinoma.
- The source identifies lesion size as the strongest gross correlate of invasive cancer.
- Its example: Invasive cancer is rare in adenomas below 1 cm, but nearly 40% of those over 4 cm have invasive foci.
- These estimates describe adenomas generally, not a FAP-specific per-polyp prediction.

High-grade dysplasia: Local lesion risk, not a field label

- High-grade dysplasia increases the likelihood of cancer within that adenoma.
- The source states it does not itself increase cancer risk in other separate polyps of the same patient.
- In FAP, the total risk is nevertheless substantial because the number of adenomas is very high.

Intramucosal carcinoma is not the same as deep invasion

- Intramucosal carcinoma invades lamina propria but does not extend through muscularis mucosae.
- Functional lymphatics are absent from colonic mucosa, so metastatic potential is minimal.
- Submucosal invasion creates clinically meaningful risk of spread.



Depth of invasion changes clinical interpretation

Lesion level	Anatomic extent	Clinical implication
Adenoma / dysplasia	Confined above basement membrane	Premalignant lesion
Intramucosal carcinoma	Invades lamina propria; not through muscularis mucosae	Little/no metastatic potential
Invasive adenocarcinoma	Invades through muscularis mucosae into submucosa or beyond	Potential for metastatic spread

Pathology of an invasive carcinoma drives management decisions

- Depth of invasion is a key feature in an adenoma containing carcinoma.
- The invasive component is assessed for grade and vascular / lymphatic invasion.
- Distance to the resection margin also informs further therapy.
- These are lesion-level considerations distinct from management of the inherited predisposition.

Untreated classic FAP has near-certain colorectal cancer

- 100% of untreated patients develop colorectal adenocarcinoma.
- Risk arises from progressive neoplasia in a very large population of adenomas.
- This statement applies to untreated classic FAP, not every attenuated phenotype.

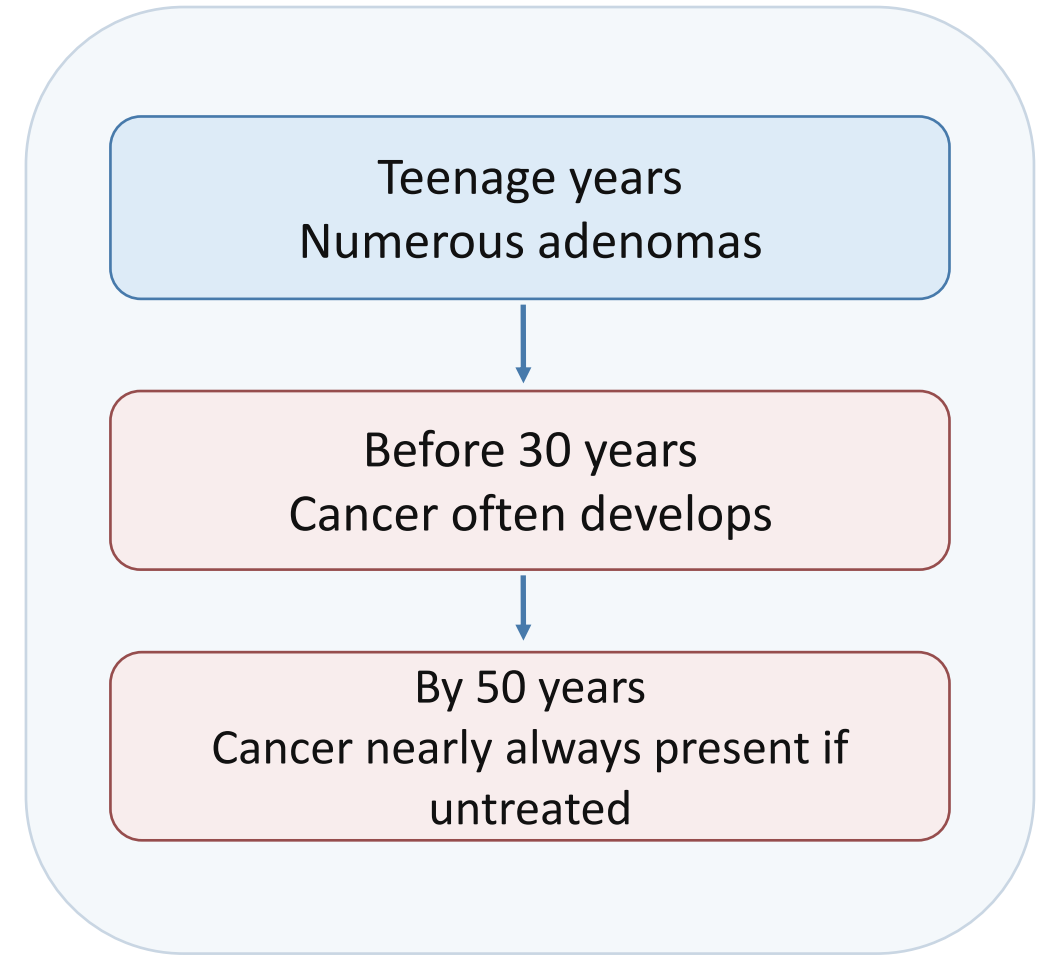
100%

**Colorectal adenocarcinoma
risk without treatment**

Risk estimate in the stated textbook cohort

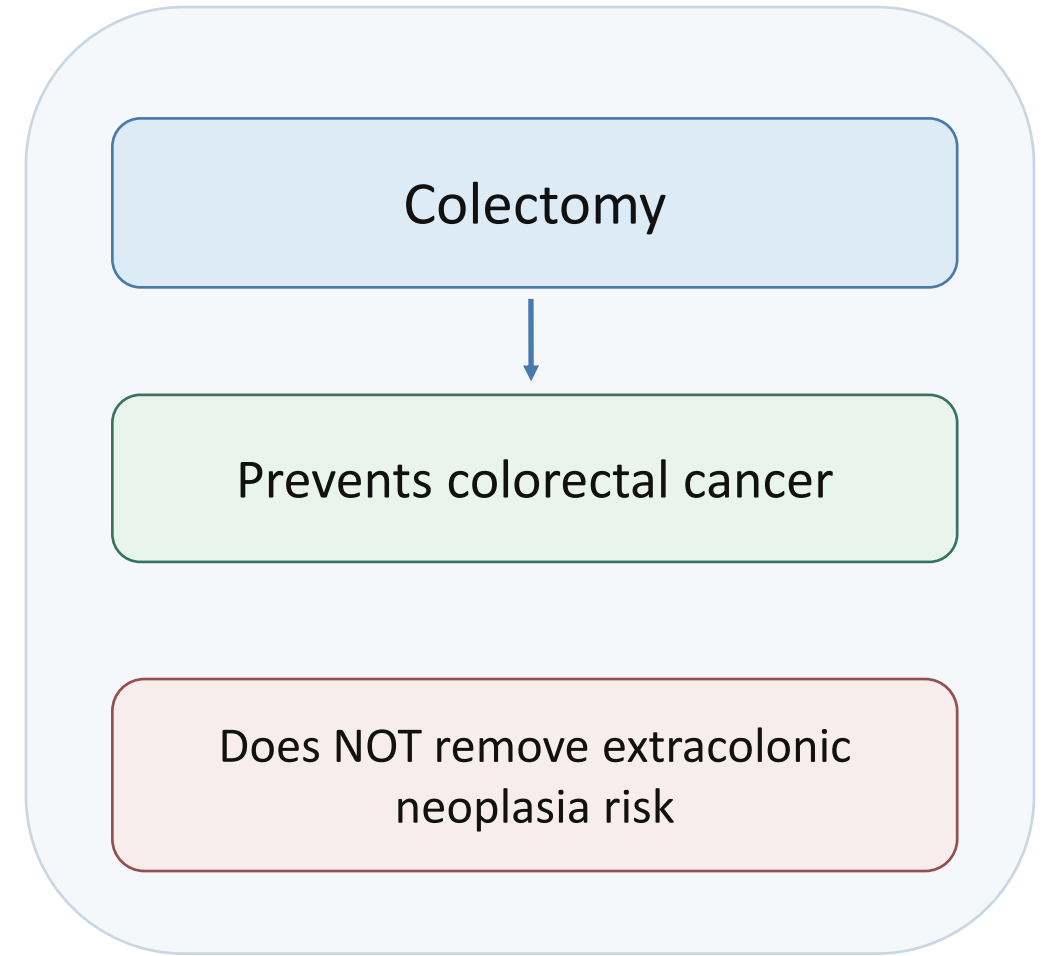
Carcinoma appears at a much younger age than sporadic CRC

- Cancer develops often before age 30 years in untreated FAP.
- It is described as occurring nearly always by age 50 years.
- Early adolescent adenoma formation creates a prolonged interval of neoplastic risk.



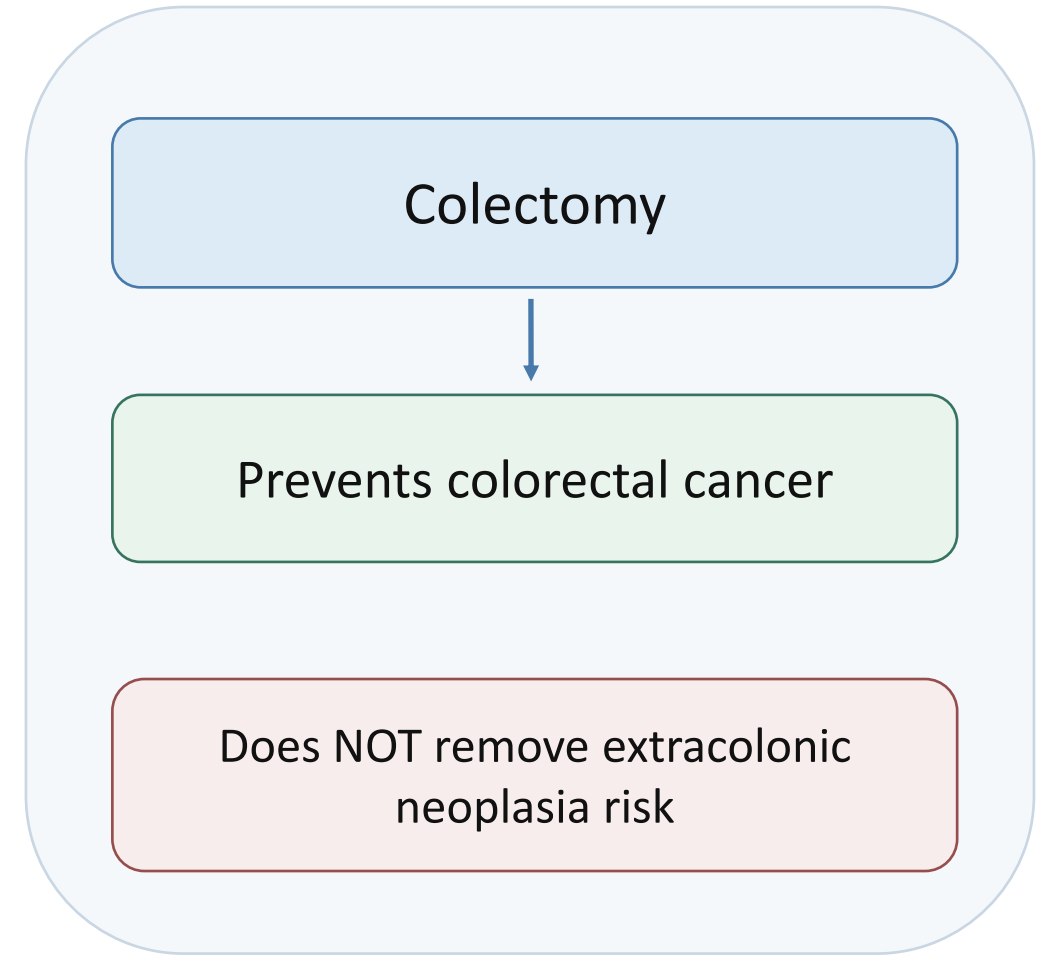
Prophylactic colectomy addresses colorectal risk

- The untreated cancer risk underpins proactive surgical management.
- Prophylactic colectomy as standard care.
- Removing the at-risk colon prevents the colorectal cancer trajectory described for untreated FAP.



Colectomy does not eliminate all FAP neoplasia

- Colorectal cancer prevention is not synonymous with cure of a multisite predisposition.
- Extracolonic gastrointestinal adenomas and cancers remain possible.
- Management must therefore account for residual risk outside the removed colon.



The ampulla of Vater is an extracolonic neoplasia site

- The ampulla of Vater as a common extracolonic site of adenomas.
- Malignant progression can occur without treatment.
- Upper gastrointestinal risk persists after colorectal surgery.

Colorectum — many adenomas

Ampulla of Vater — adenomas /
cancer

Stomach — adenomas / cancer

Sites named (not scale diagram)

Gastric adenomas and carcinomas can accompany FAP

- The stomach is another extracolonic site highlighted.
- Adenomas may arise outside the colorectum in affected patients.
- Colorectal polyp count alone does not capture the syndrome's full neoplastic spectrum.

Colorectum — many adenomas

Ampulla of Vater — adenomas /
cancer

Stomach — adenomas / cancer

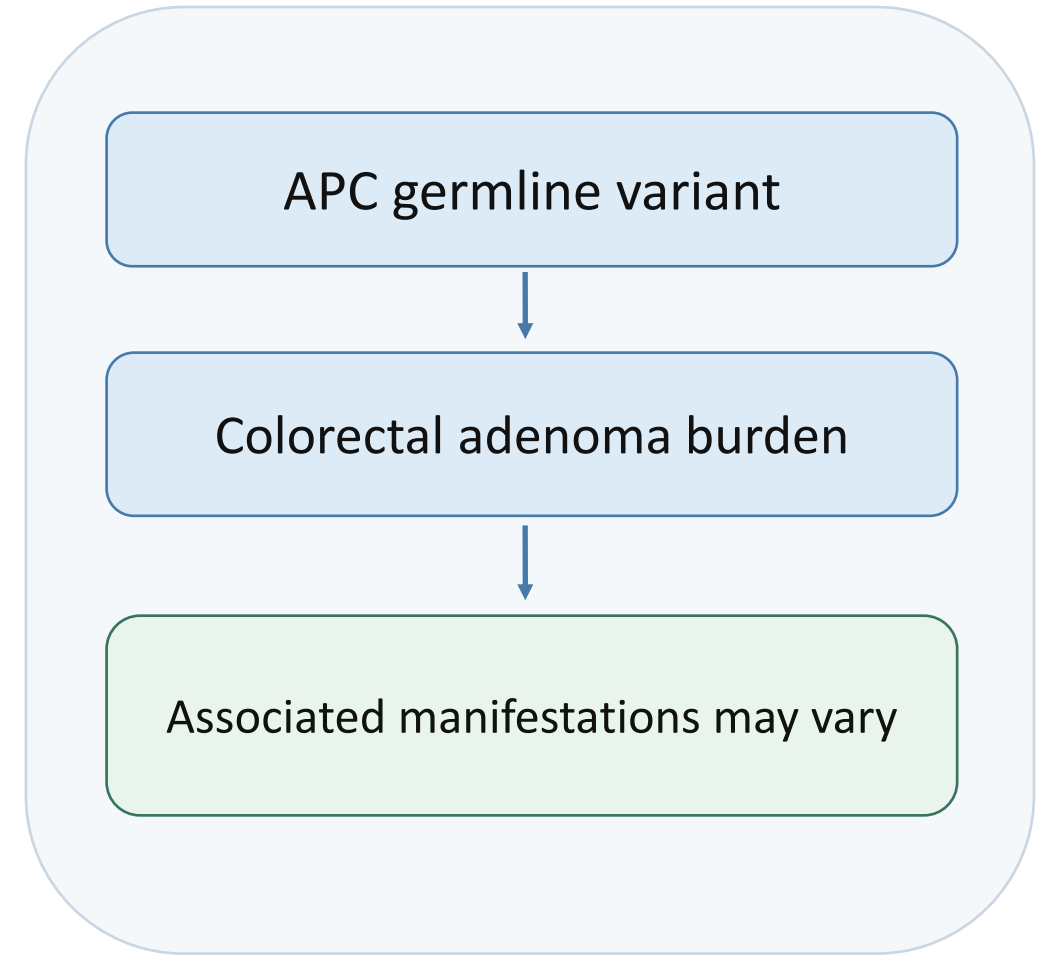
Sites named (not scale diagram)

Congenital retinal pigment epithelial hypertrophy

- Congenital hypertrophy of retinal pigment epithelium (CHRPE) may occur in FAP.
- It can be detected at birth, before colorectal polyposis emerges.
- The source presents it as a potential adjunct to early screening.
- It is an associated finding, not by itself a sufficient diagnosis of FAP.

Gardner syndrome belongs to the APC-related spectrum

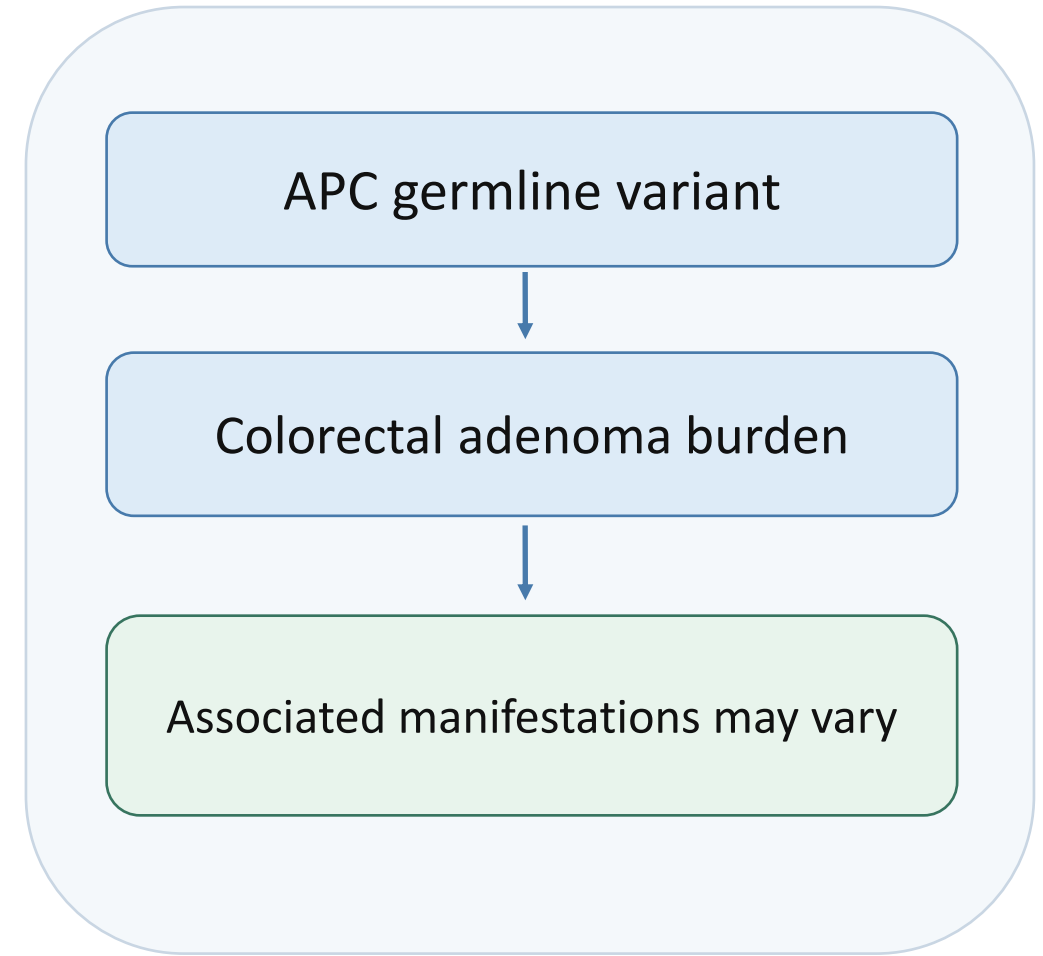
- The source associates Gardner syndrome with APC variants.
- It combines adenomatous polyposis with possible osteomas and desmoid tumors.
- Skin cysts and thyroid tumors are also listed in the source table.



Genotype–phenotype relation is incomplete

Turcot syndrome includes colorectal polyposis and CNS tumors

- The Robbins polyposis table groups an APC-associated Turcot phenotype with FAP.
- Medulloblastoma and glioblastoma are listed as associated CNS neoplasms.
- The term has broader historical usage; The slide follows the supplied APC-centered table.



Genotype–phenotype relation is incomplete

APC-associated extraintestinal findings

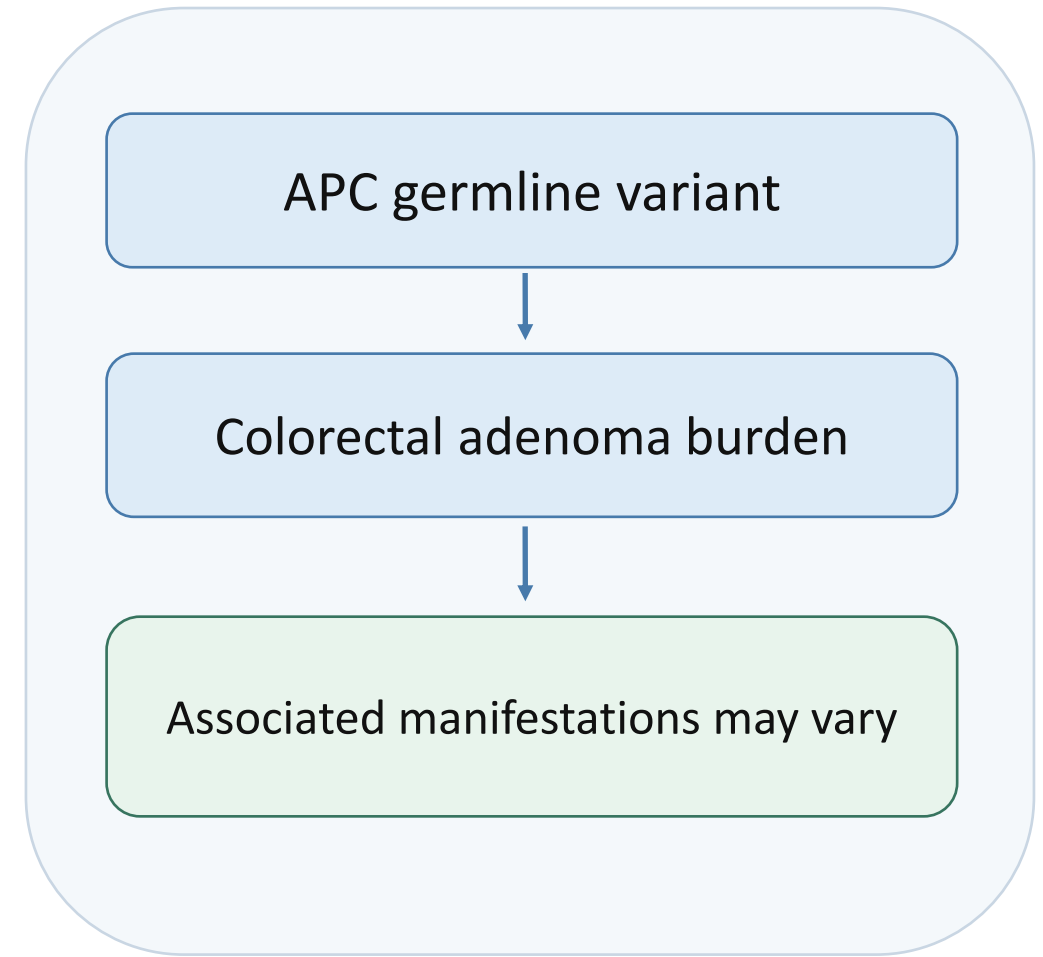
Phenotype	Selected manifestations	Teaching significance
Classic FAP	CHRPE	May precede intestinal polyps
Gardner phenotype	Osteomas, desmoid and thyroid tumors, skin cysts	Extracolonic phenotype
Turcot phenotype (APC-associated)	CNS tumors listed: medulloblastoma, glioblastoma	Broader syndromic spectrum

Attenuated FAP is included in the APC spectrum

- The source table explicitly recognizes attenuated FAP as APC-associated.
- The designation distinguishes it from the classic high-burden presentation.
- The supplied excerpt does not define an exact polyp-count or age cutoff for attenuated FAP.
- Do not apply the classic ≥ 100 criterion indiscriminately across all APC-associated phenotypes.

APC variants show genotype–phenotype associations

- Specific APC mutations have been associated with differences in manifestations.
- Gardner and Turcot phenotypes exemplify syndromic heterogeneity.
- The source does not supply a comprehensive codon-level map or deterministic predictions.



Genotype–phenotype relation is incomplete

Adenomatous polyposis may occur without an APC defect

- Patients with multiple polyps but without APC loss.
- Some have pathogenic alterations in the MUTYH base-excision repair gene.
- This defines MUTYH-associated polyposis (MAP), a separate hereditary syndrome.
- Multiple adenomas therefore do not prove APC-associated FAP.

MUTYH-associated polyposis is autosomal recessive

- MAP is caused by biallelic MUTYH mutations.
- The relevant molecular pathway is base-excision DNA repair.
- The inheritance pattern differs fundamentally from autosomal dominant classic FAP.

FAP: APC; Autosomal dominant

MAP: MUTYH; Autosomal
recessive

Hereditary mechanisms are distinct

MAP tends to have fewer polyps and later presentation

- The source describes MAP as often involving fewer than 100 polyps.
- Clinical presentation generally occurs at later ages than classic FAP.
- Colorectal cancer development is correspondingly delayed.
- There is phenotypic overlap; Polyp number alone is not a molecular diagnosis.

Classic FAP versus MUTYH-associated polyposis

Feature	Classic FAP	MAP
Causal gene	APC	MUTYH
Inheritance	Autosomal dominant	Autosomal recessive
Repair/signaling process	Wnt / β -catenin regulation	Base-excision repair
Typical polyp burden	≥ 100 , sometimes thousands	Often < 100
Cancer chronology	Early if untreated	Later than classic FAP

MAP may contain serrated and hyperplastic polyps

- Sessile serrated and hyperplastic polyps frequently coexist in MAP.
- KRAS mutations are often identified in these lesions.
- This mixed polyp spectrum contrasts with a purely adenomatous shorthand.
- The source does not claim that serrated morphology is diagnostic of MAP.

Lynch syndrome differs by mismatch-repair deficiency

- Hereditary nonpolyposis colorectal cancer (Lynch syndrome) is linked to inherited mismatch-repair gene mutations.
- The cited textbook highlights MSH2 and MLH1 among implicated genes.
- Its presentation is not defined by hundreds of adenomatous polyps.
- This mechanism is distinct from APC loss and MUTYH-associated base-excision repair deficiency.

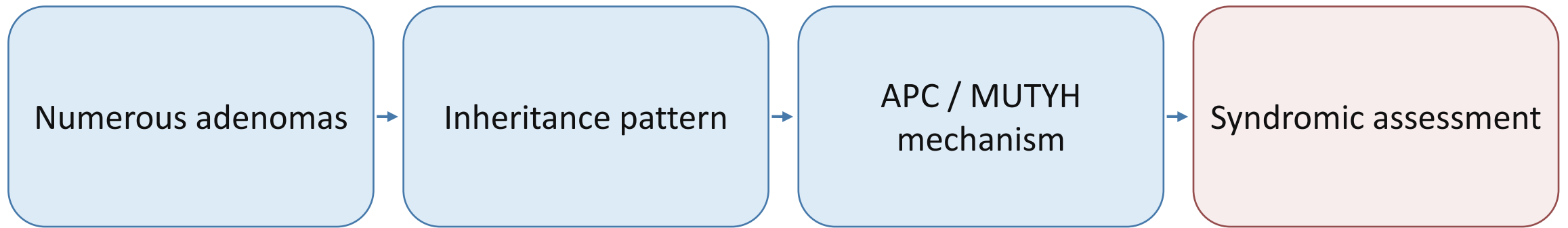
Three hereditary colorectal-neoplasia mechanisms

Syndrome	Core molecular lesion	Inheritance / typical phenotype
Familial adenomatous polyposis	APC → Wnt/ β -catenin deregulation	Autosomal dominant; numerous adenomas
MUTYH-associated polyposis	MUTYH → base-excision repair defect	Autosomal recessive; fewer polyps, later
Lynch syndrome	Mismatch-repair genes (e.g., MSH2, MLH1)	Autosomal dominant; nonpolyposis phenotype

Diagnostic reasoning starts with phenotype and family pattern

- Characterize the number and histologic type of colorectal polyps.
- Ask whether the pattern suggests an autosomal dominant or recessive disorder.
- Interpret APC versus MUTYH versus mismatch-repair mechanisms in context.
- The provided Robbins section does not specify a current genetic-testing panel or surveillance protocol.

Conceptual diagnostic distinction



Conceptual educational flow; It is not a clinical genetic-testing guideline.

Clinical implications for relatives follow from inheritance

- Autosomal dominant transmission creates risk across successive generations.
- De novo APC disease explains an isolated proband despite an absent family history.
- Affected individuals may have extracolonic manifestations before bowel symptoms.
- Disease recognition has implications beyond the patient in whom polyps were discovered.

Case 1: Numerous adenomas in adolescence

HYPOTHETICAL TEACHING CASE

A teenager undergoes evaluation and is found to have hundreds of colorectal adenomas. One parent had a colectomy in early adulthood.

- Which hereditary mechanism is most consistent with the phenotype?
- Why do many independent adenomas arise?
- What is the principal consequence of leaving the colon untreated?

Case 2: FAP without a family history

HYPOTHETICAL TEACHING CASE

A patient has a classic FAP-type polyp burden, but neither parent reports colorectal polyps or cancer.

- Does the negative family history rule out FAP?
- What genetic explanation is specifically mentioned by Robbins?
- Which extracolonic observations might provide additional clues?

Case 3: Fewer adenomas with later presentation

HYPOTHETICAL TEACHING CASE

An adult presents later in life with several dozen colorectal adenomas. The family pattern does not suggest clear vertical transmission.

- Which alternative inherited polyposis syndrome should be considered?
- Which DNA repair pathway is affected?
- How does inheritance differ from classic FAP?

Integrated synthesis: Four essential pathology connections

- APC loss removes a restraint on β -catenin/TCF-driven epithelial growth.
- A constitutional first hit leads to numerous separate adenomas after additional local events.
- The adenomas resemble sporadic adenomas but carry an overwhelming aggregate cancer risk.
- Colectomy prevents colorectal carcinoma while extracolonic neoplasia risk remains.

Reference and source boundaries

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 17, pp. 738–743.
- Mechanistic parent context: Chapter 7, pp. 264–265 (APC and Wnt/ β -catenin).
- Source tables and figure descriptions were consulted in Markdown; the original chapter PDF was not supplied.
- All slide diagrams are original editable schematics, not digitized Robbins figures or genuine microscopy.