

Peutz–Jeghers Syndrome

Hamartomatous polyposis · STK11 tumor suppression · cancer predisposition

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Define Peutz–Jeghers syndrome and its inherited clinical phenotype.
- Explain STK11 function and the tumor-suppressor model.
- Recognize characteristic gross and microscopic polyp architecture.
- Relate gastrointestinal complications and multiorgan cancer risk to clinical evaluation.

Phenotype

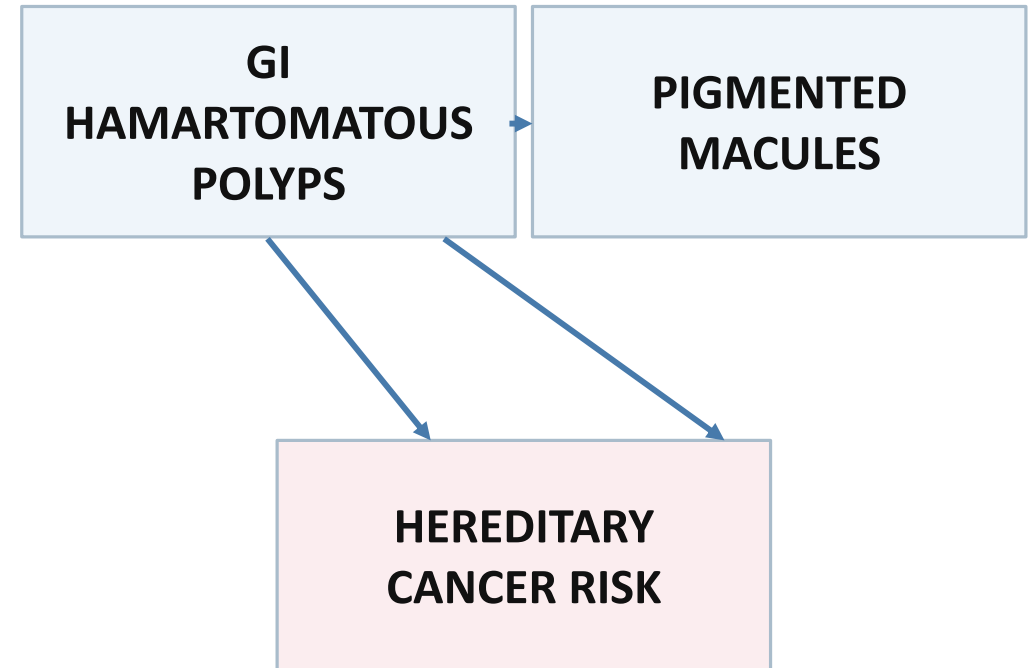
STK11 biology

Arborizing histology

Cancer surveillance

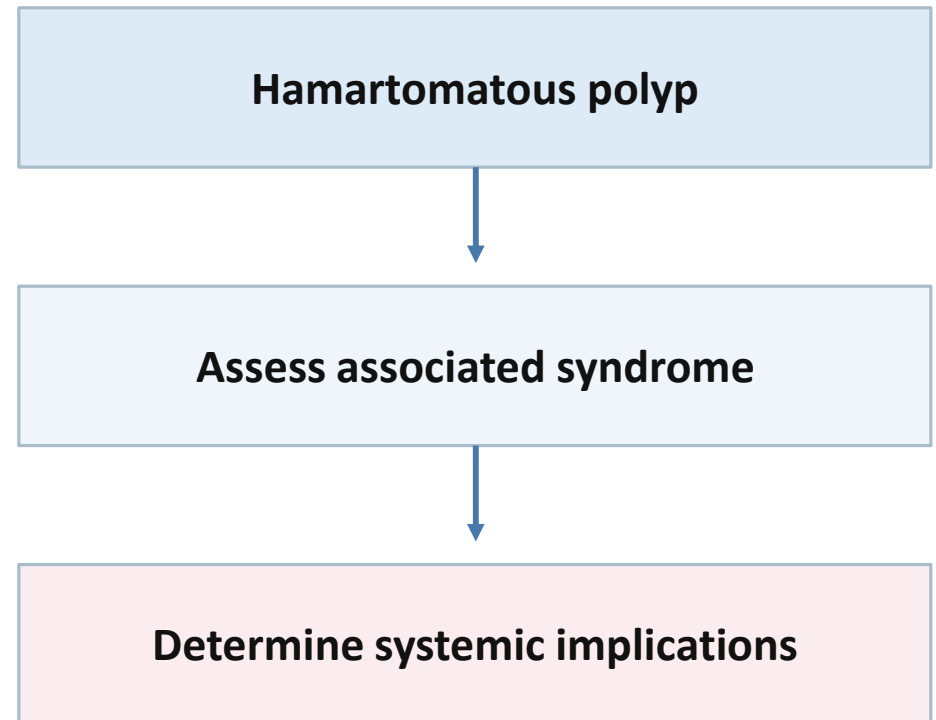
Three linked components define the syndrome

- Multiple gastrointestinal hamartomatous polyps.
- Characteristic mucocutaneous pigmented macules.
- An inherited predisposition to malignancies at several organ sites.



Hamartomatous polyps belong in a broader category

- Hamartomatous polyps may occur sporadically or in genetic syndromes.
- Some inherited hamartomatous polyposis syndromes carry increased cancer risk.
- Histologic appearance alone does not establish the full syndrome.



Autosomal dominant inheritance is a defining feature

- Peutz–Jeghers syndrome is a rare autosomal dominant condition.
- A germline alteration can be present in multiple tissue lineages.
- A positive family history is diagnostically informative.

AUTOSOMAL DOMINANT

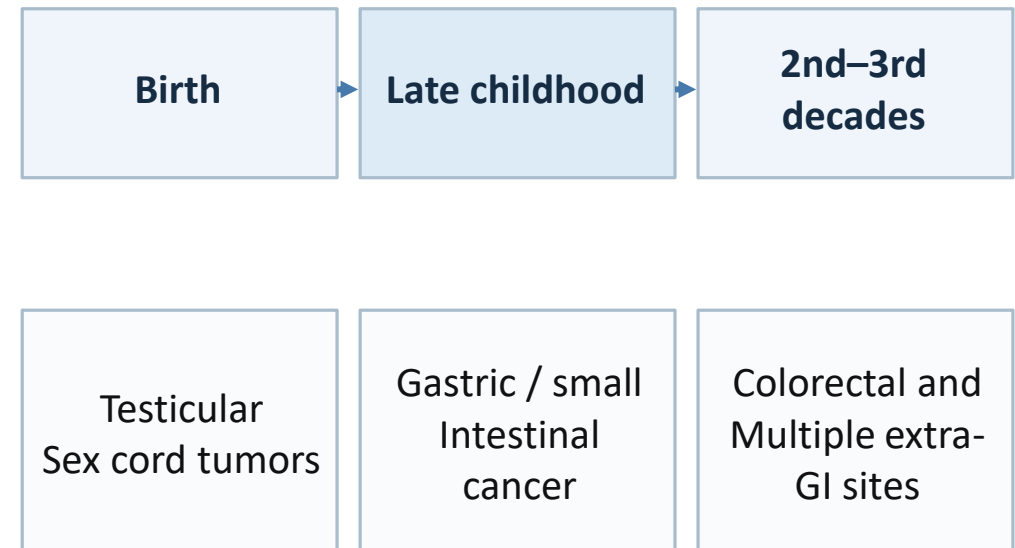
One inherited altered STK11 allele



Familial transmission is possible

Clinical recognition often begins in childhood

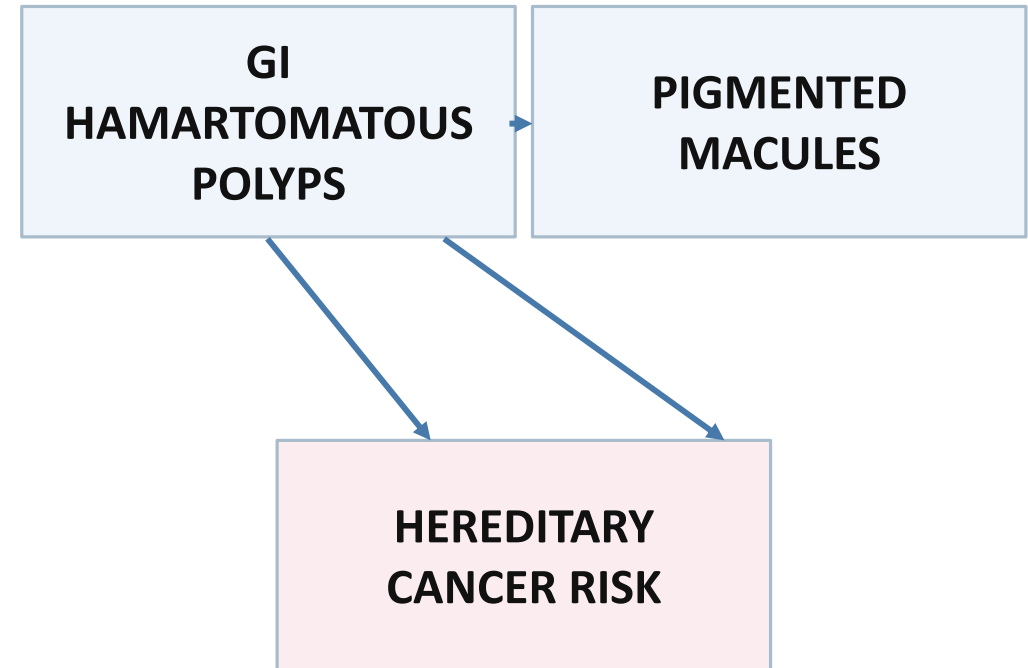
- A median age at presentation of approximately 11 years.
- The earliest important problem may be a gastrointestinal polyp complication.
- The pigmentation phenotype offers an additional clue before or during evaluation.



Teaching timeline; Surveillance windows are discussed separately.

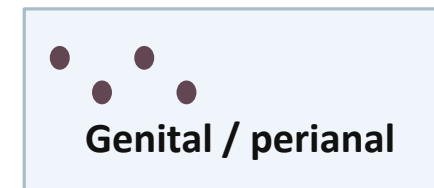
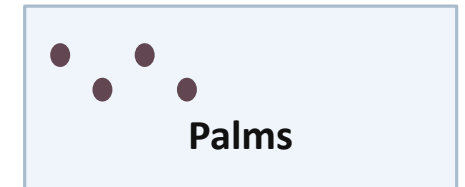
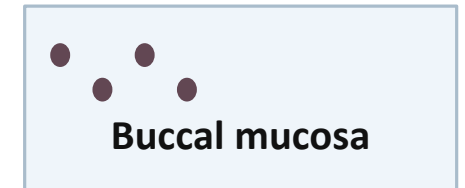
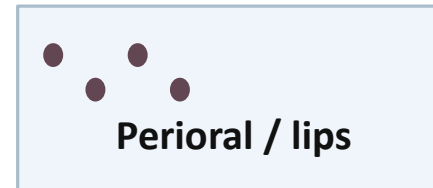
The syndrome links the skin and the gut

- Dark blue-to-brown macules accompany gastrointestinal polyposis.
- The pigment pattern is mucocutaneous rather than restricted to sun-exposed skin.
- Recognition should prompt integration with symptoms and family history.



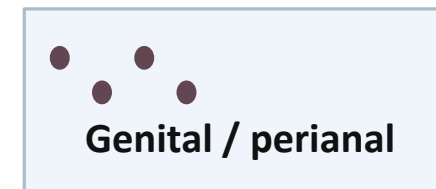
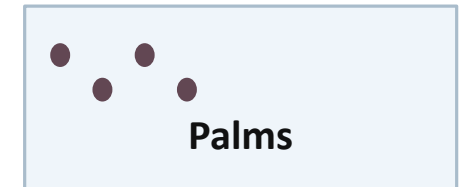
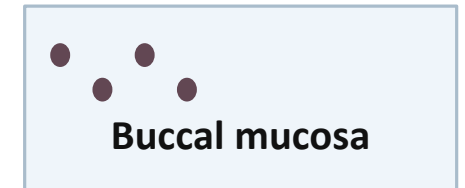
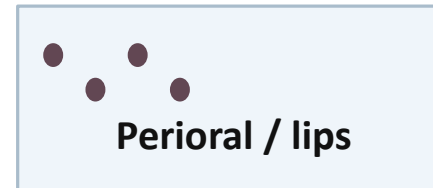
Typical pigment sites are diagnostically useful

- Lips, nostrils, and buccal mucosa are characteristic locations.
- Palmar surfaces may also contain pigmented macules.
- Genital and perianal sites can be involved.



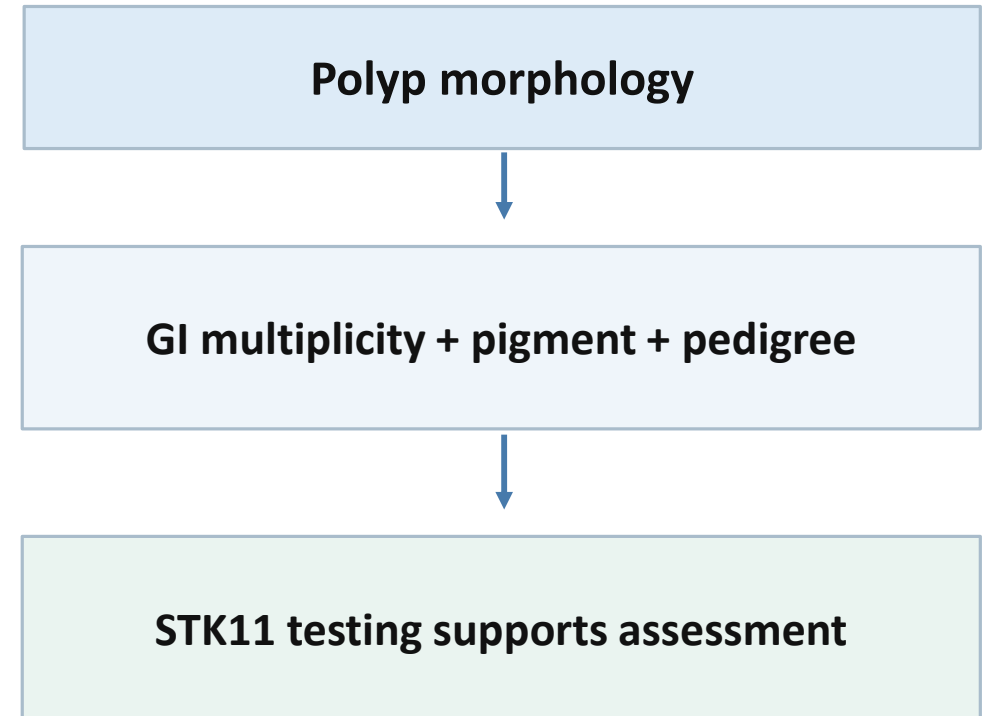
Buccal pigmentation helps distinguish freckles

- The macules may superficially resemble ordinary freckles.
- Involvement of the buccal mucosa is an especially useful discriminator.
- A mucosal inspection adds information beyond perioral observation.



Pigmentation is a phenotype, not a stand-alone test

- Pigmented macules contribute to the diagnostic pattern.
- Absence of pigmentation does not rule out Peutz–Jeghers syndrome.
- Polyp burden, anatomic location, pedigree, and molecular findings must be considered.



Peutz–Jeghers polyps favor the small intestine

- The small intestine is the most common polyp location.
- Lesions also occur in the stomach and colon.
- Site distribution is useful when the pathology resembles a sporadic hamartoma.

Small intestine

Most common

Stomach

Possible

Colon

Possible

Bladder / lung

Much less common

Extraintestinal polyps are uncommon

- The Robbins morphology section also describes much rarer polyps in bladder and lung.
- These sites are not the defining distribution of gastrointestinal polyposis.
- Distinguish occasional ectopic polyp locations from the spectrum of cancer susceptibility.

Small intestine

Most common

Stomach

Possible

Colon

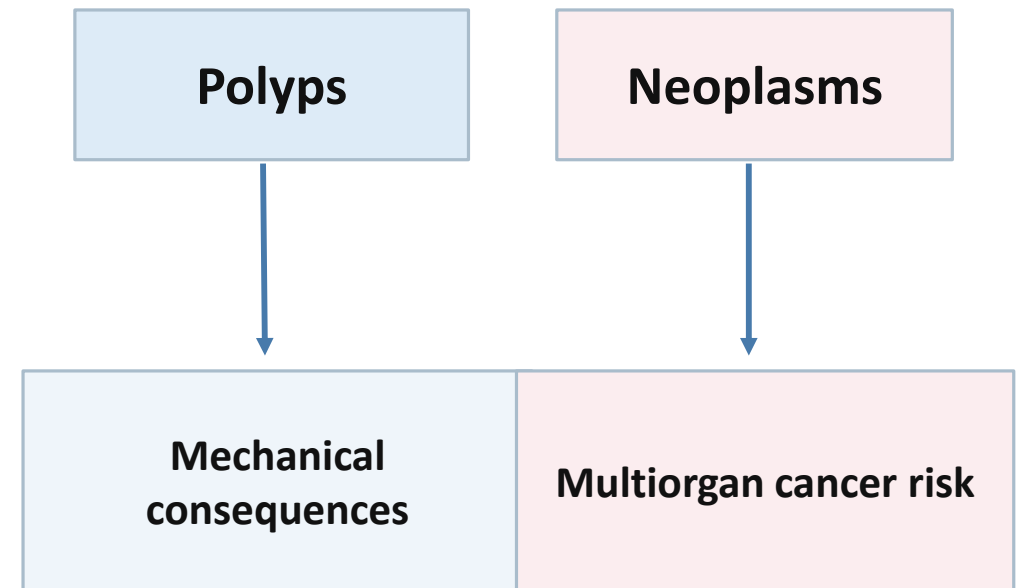
Possible

Bladder / lung

Much less common

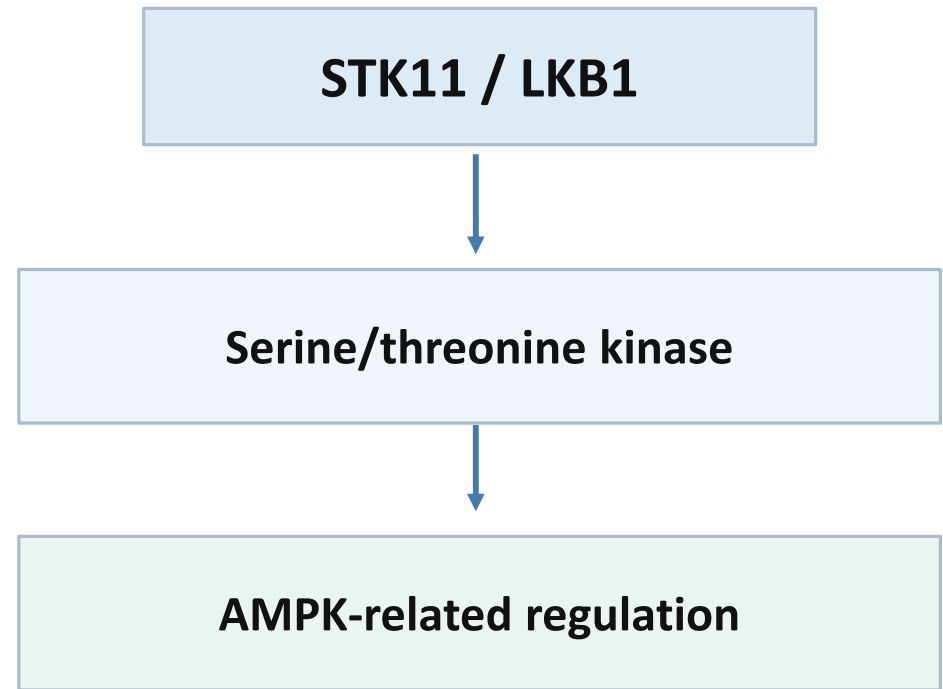
A polyp has two distinct clinical dimensions

- Local mass effect can create acute gastrointestinal complications.
- Systemic predisposition creates a separate, long-term oncologic problem.
- A benign-appearing individual polyp does not eliminate hereditary cancer risk.



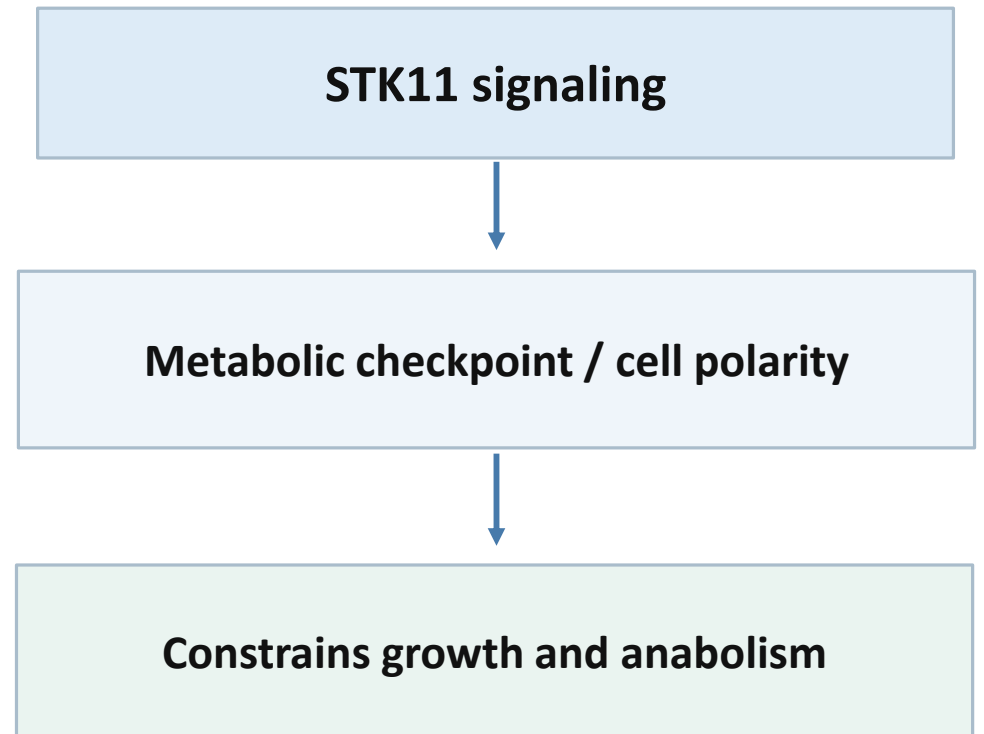
STK11 is the major molecular link

- Heterozygous germline loss-of-function STK11 alterations occur in affected families.
- STK11 is also known as LKB1.
- It encodes a serine/threonine kinase with tumor-suppressive functions.



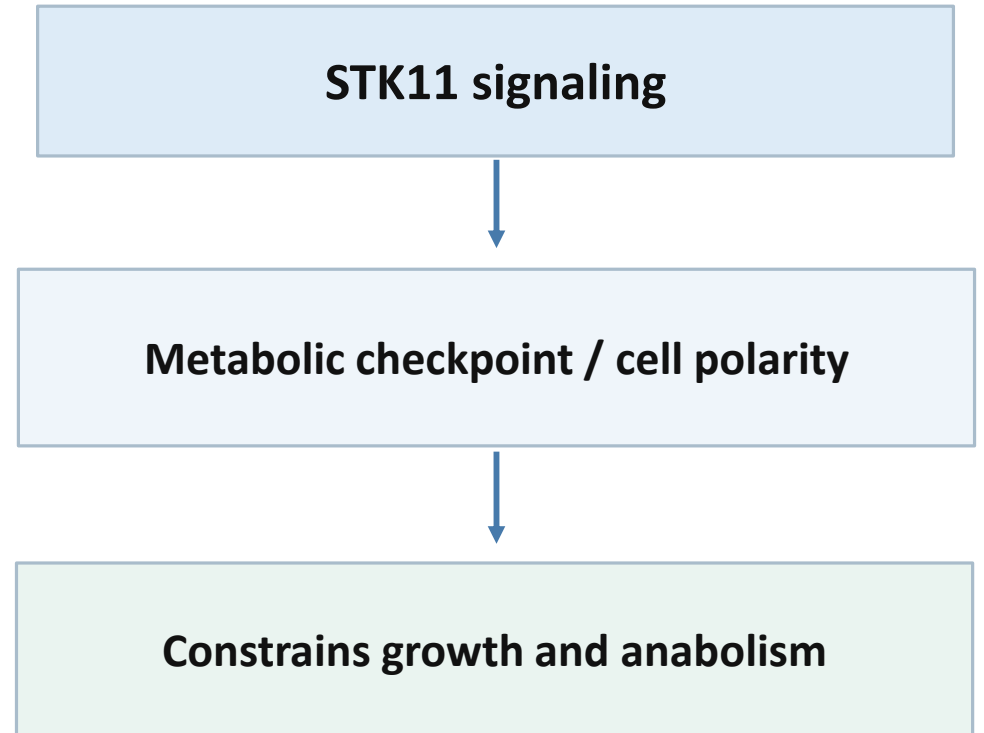
STK11 acts through metabolic regulation

- The STK11 kinase regulates AMP-activated protein kinase–related pathways.
- These pathways participate in control of cellular growth and anabolic metabolism.
- Loss of regulation can favor the metabolic conditions that support neoplasia.



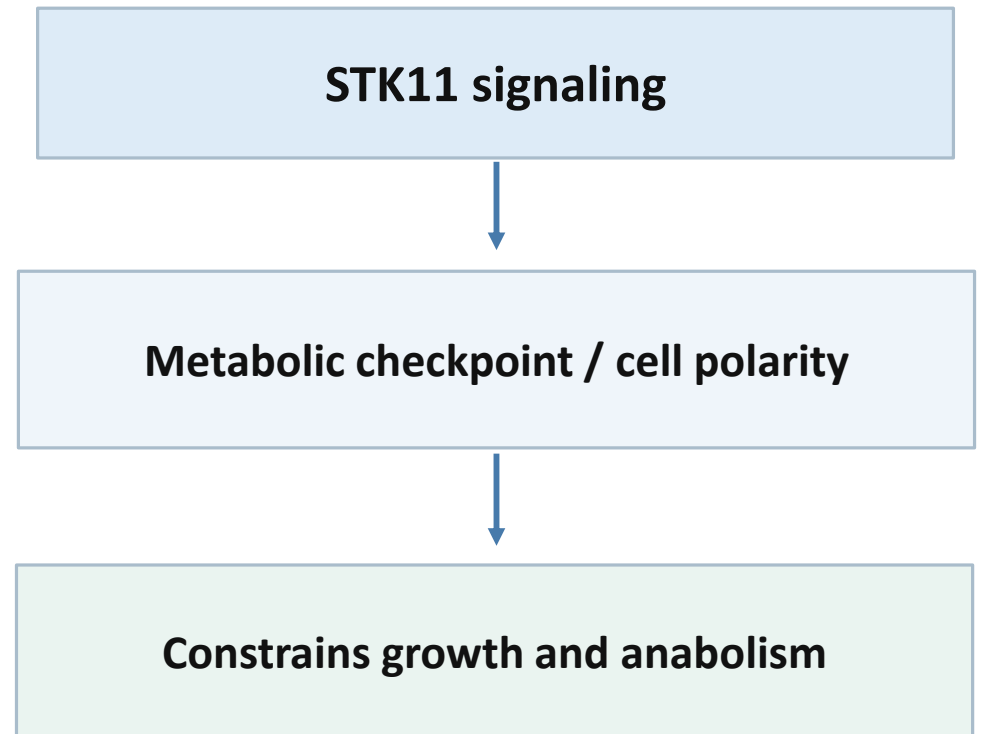
Cell polarity is part of the STK11 phenotype

- Cell polarization among the cellular processes regulated by STK11–AMPK signaling.
- Polarity controls how cells organize their structural axes and tissue architecture.
- This connects a molecular tumor suppressor to broader cellular organization.



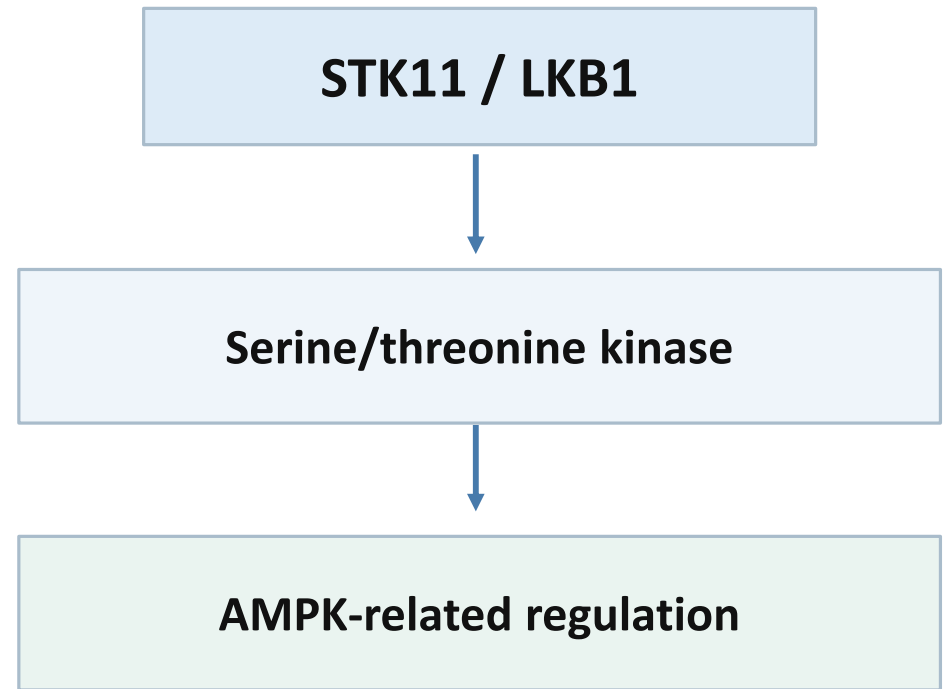
Normal STK11 signaling restrains anabolism

- Growth requires energy use and synthesis of proteins, lipids, and other components.
- STK11-related signaling acts as a brake on growth and anabolic metabolism.
- Loss of a brake is a conceptual mechanism of tumor-suppressor dysfunction.



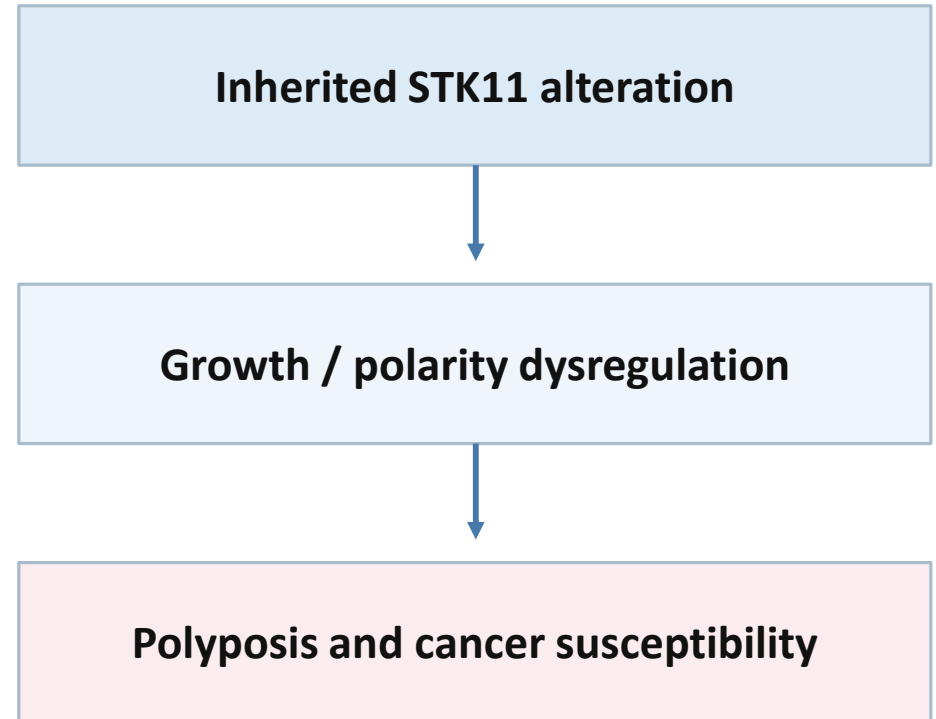
STK11 influences multiple metabolic functions

- Chapter 7 identifies roles in glucose uptake and gluconeogenesis.
- Protein synthesis and mitochondrial biogenesis are also affected.
- Lipid metabolism is another regulated process.



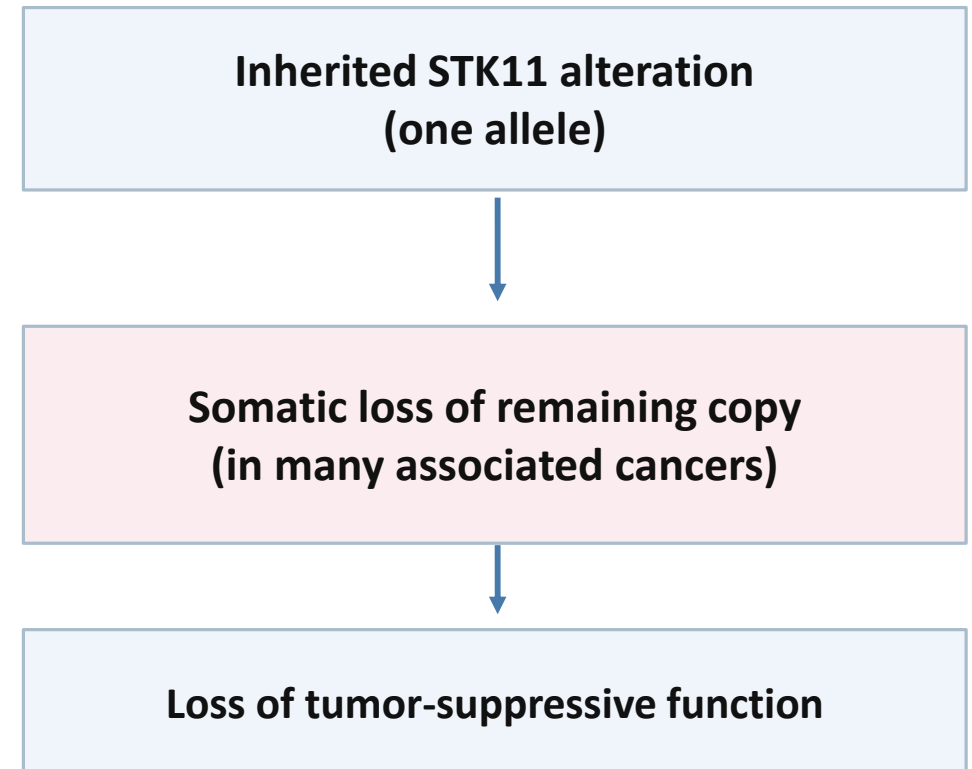
A multistep model connects genotype to phenotype

- A germline STK11 loss-of-function alteration creates inherited susceptibility.
- Abnormal growth regulation is linked to hamartomatous polyposis.
- Additional somatic events can contribute to development of an associated cancer.



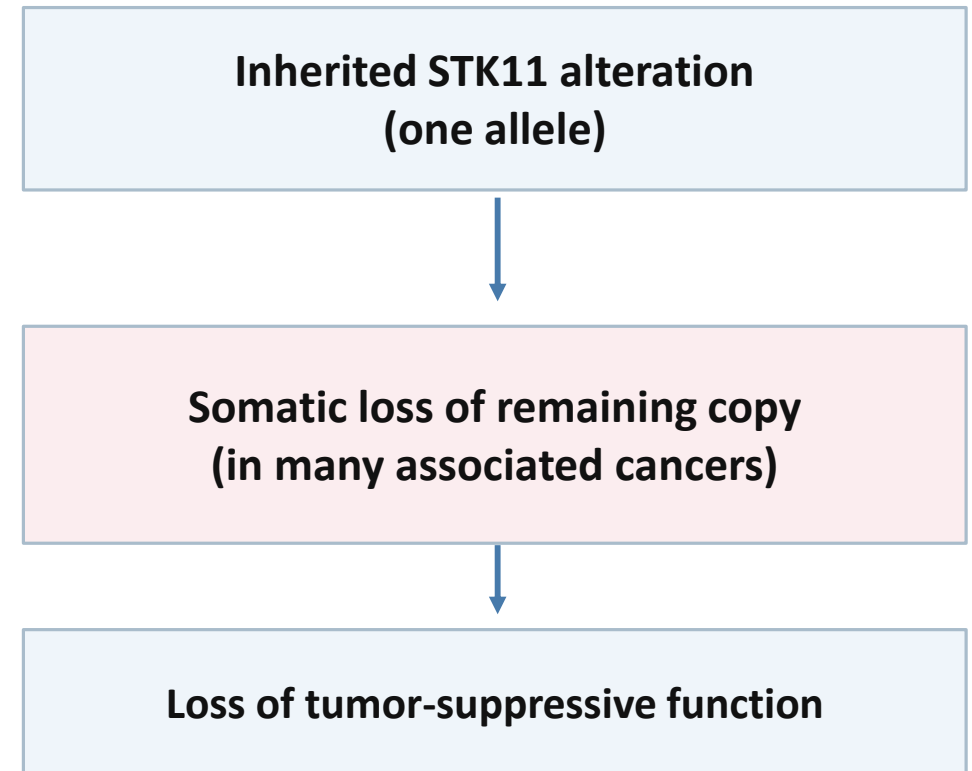
STK11 behaves as a tumor-suppressor gene

- A tumor suppressor constrains processes that otherwise permit uncontrolled growth.
- Peutz–Jeghers syndrome begins with inherited alteration of one STK11 copy.
- A second somatic event may abolish the remaining normal copy in a tumor.



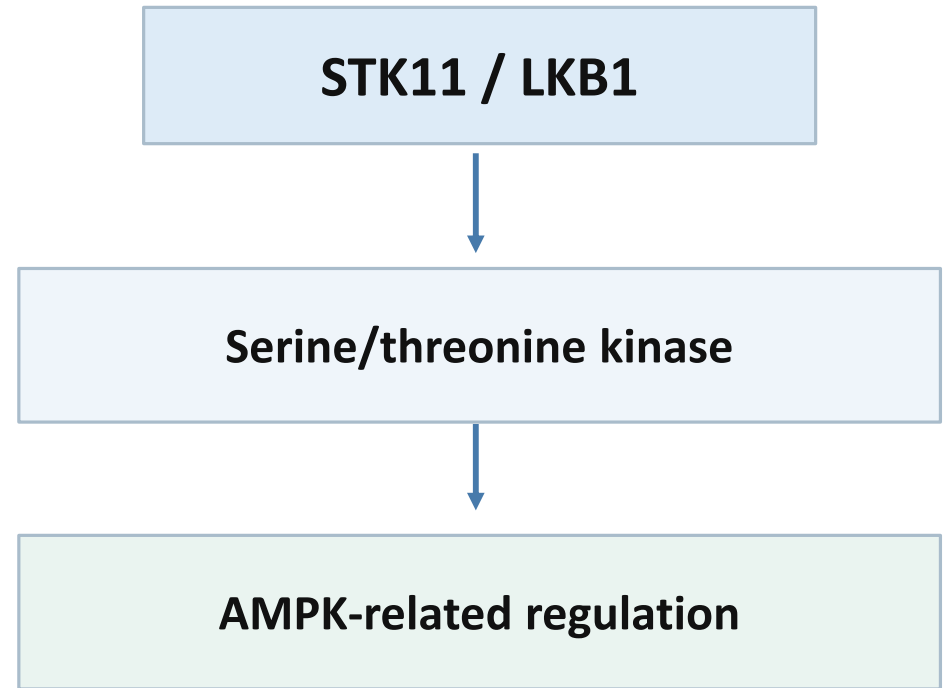
The two-hit model applies to associated cancers

- A germline variant represents the inherited first alteration.
- The second, previously functional allele is often lost somatically in associated cancers.
- Not every polyp or tumor is asserted to follow an identical molecular sequence.



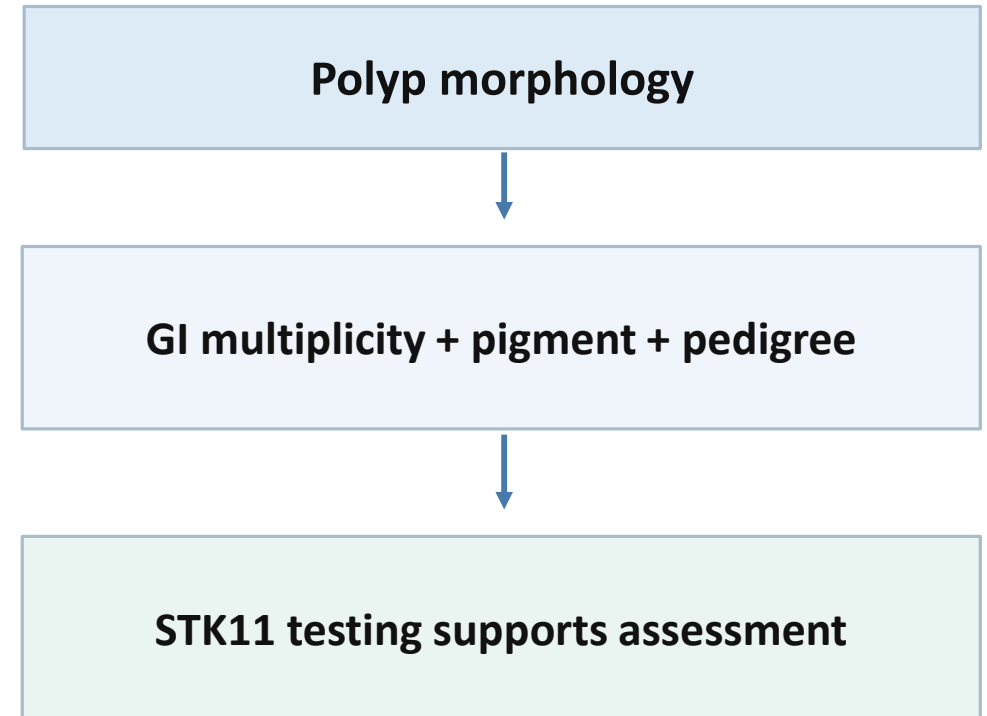
The detectable mutation fraction is incomplete

- Germline STK11 loss-of-function mutations in approximately half of familial cases.
- These mutations are also observed in a subset of apparently sporadic cases.
- A negative test must therefore be interpreted in the context of phenotype.



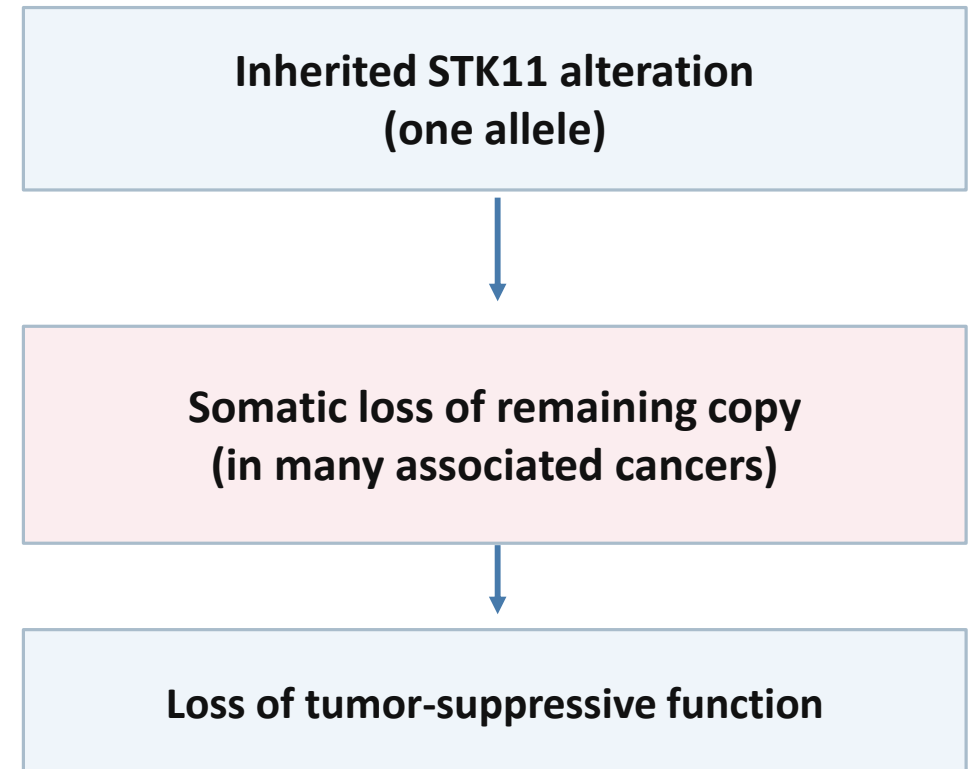
Negative STK11 testing cannot exclude the syndrome

- Not all clinically affected patients have a detectable STK11 alteration in the cited source.
- An informative tissue diagnosis and classic pigment phenotype remain relevant.
- Molecular testing supports rather than replaces clinicopathologic judgment.



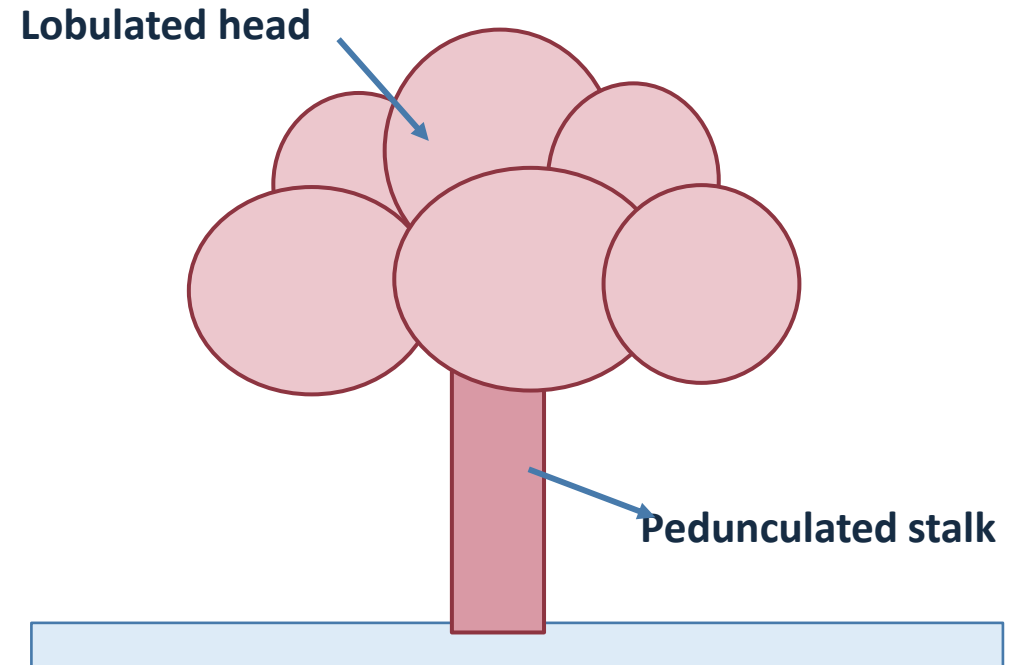
STK11 loss also occurs in sporadic malignancies

- Somatic STK11 loss-of-function variants are identified in diverse carcinomas.
- That finding supports its broader tumor-suppressor role.
- Somatic tumor STK11 loss by itself does not establish inherited Peutz–Jeghers syndrome.



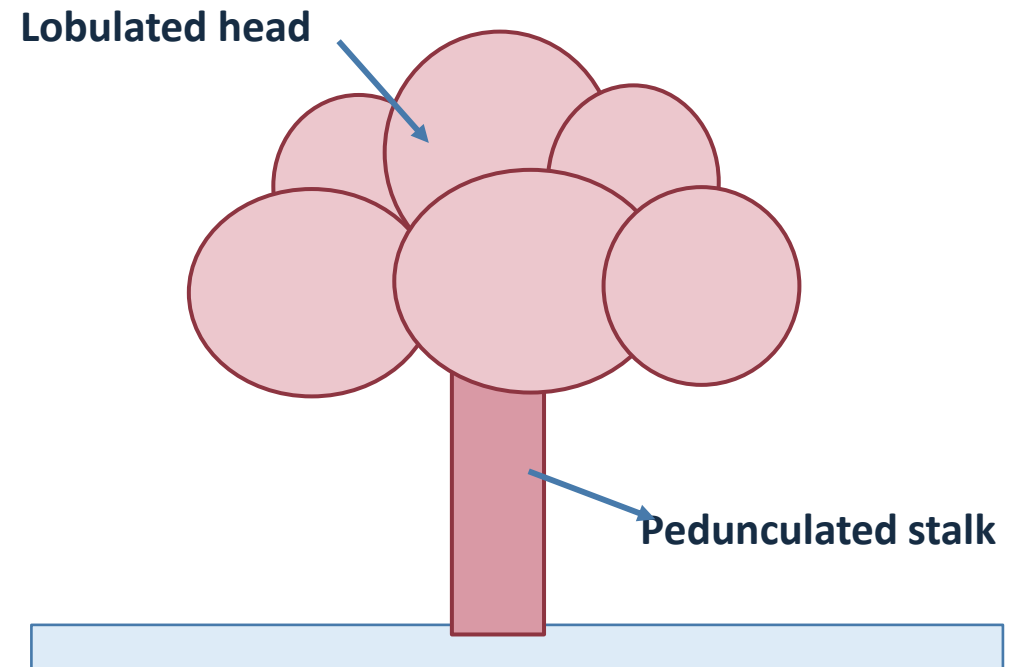
Grossly, polyps are often large and pedunculated

- A prominent stalk connects the lesion to the mucosal surface.
- The polyp head may be sizeable.
- Gross shape alone cannot establish a specific hereditary syndrome.



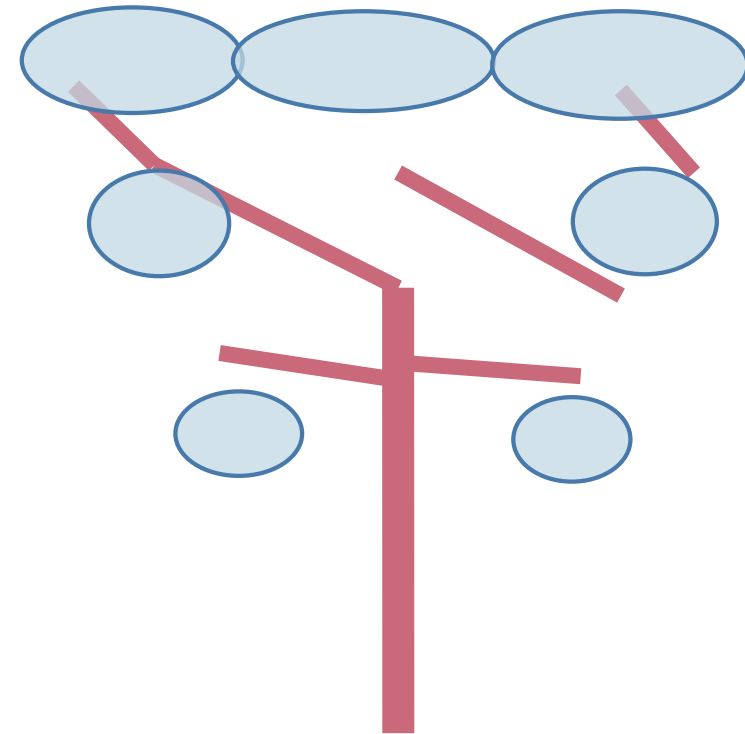
A lobulated head is a classic gross feature

- The polyp contour is characteristically lobulated.
- Lobulation corresponds to the complex internal architecture.
- The decisive microscopic feature is the branching stromal framework.



Arborizing architecture is the microscopic hallmark

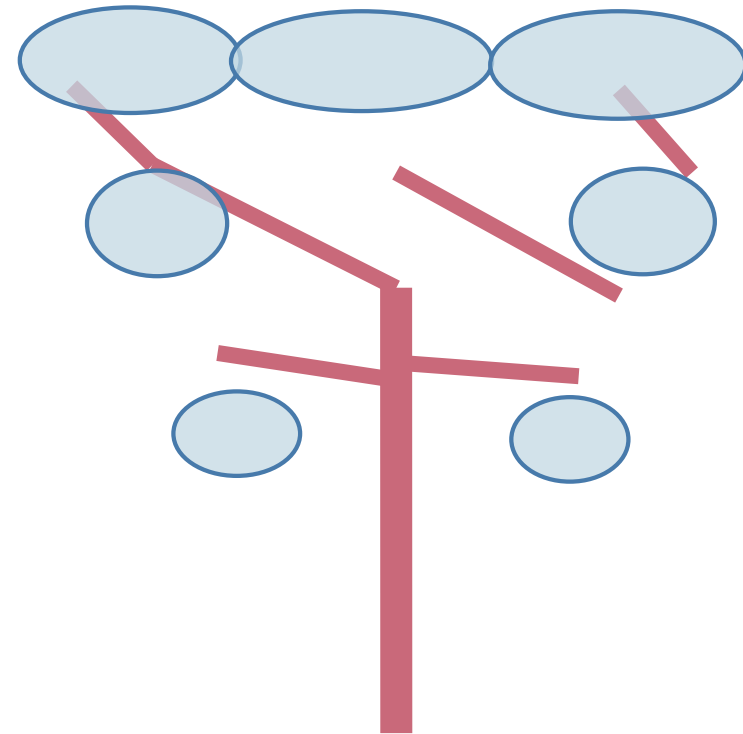
- The stroma branches in a tree-like pattern through the polyp.
- Smooth muscle bundles are integral to the arborizing core.
- The appearance is more specific than simple polyp size or pedunculation.



Branching smooth muscle

Smooth muscle extends among the glands

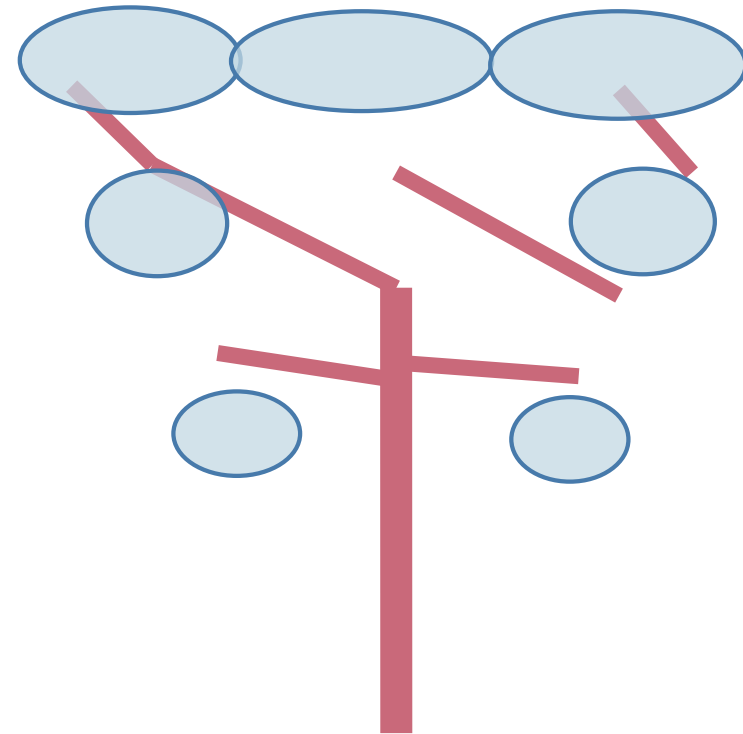
- Bundles of smooth muscle are intermixed with lamina propria.
- Branching smooth muscle helps separate Peutz–Jeghers from juvenile polyps.
- Recognition should be at the architectural level, not from a single crypt.



Branching smooth muscle

Lamina propria and connective tissue form the core

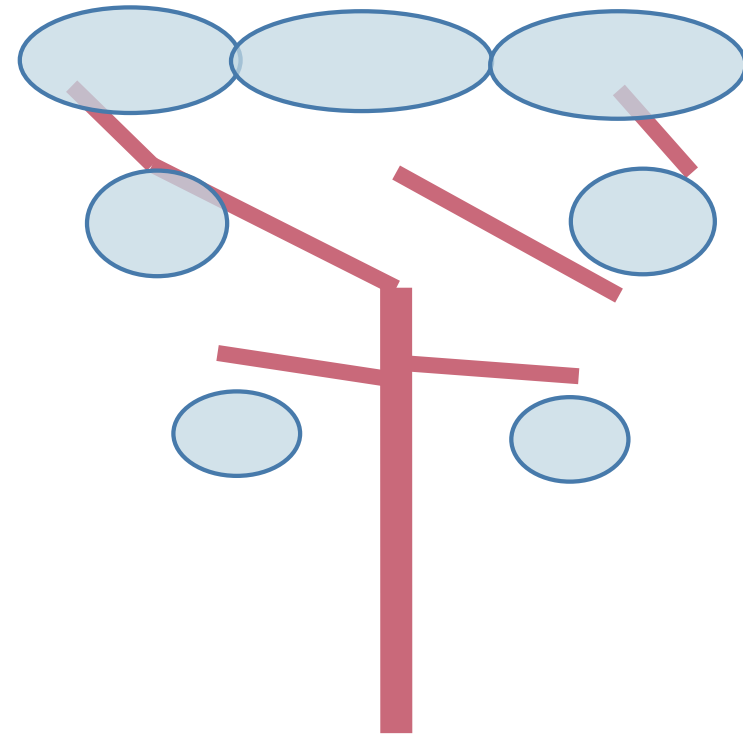
- The arborizing scaffold includes connective tissue and lamina propria.
- Smooth muscle forms a conspicuous branching component.
- The glandular structures remain embedded within that framework.



Branching smooth muscle

The glandular epithelium may look normal

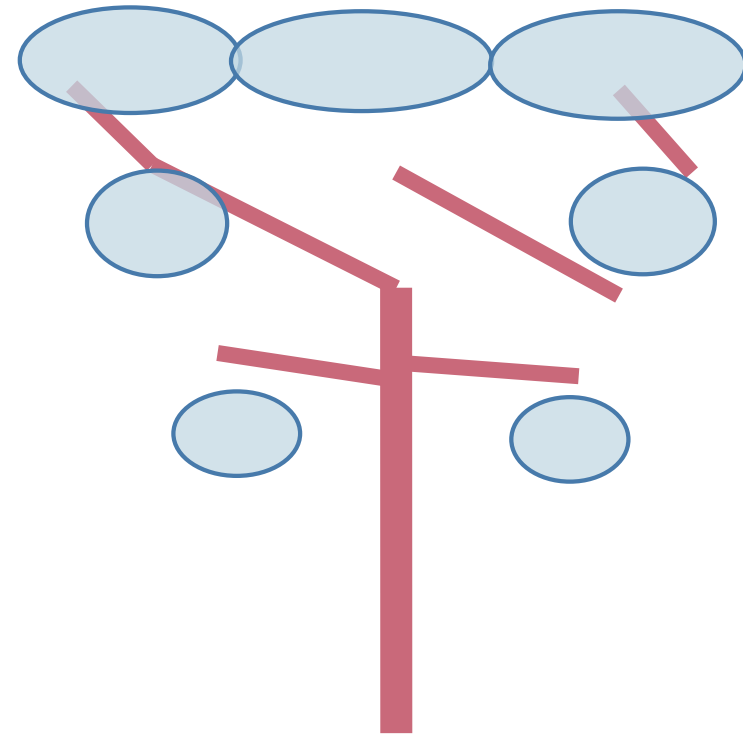
- Glands lined by normal-appearing intestinal epithelium.
- Architectural complexity need not imply cytologic malignancy.
- The polyp is assessed together with the broader cancer-predisposition syndrome.



Branching smooth muscle

Read a Peutz–Jeghers polyp from low to high power

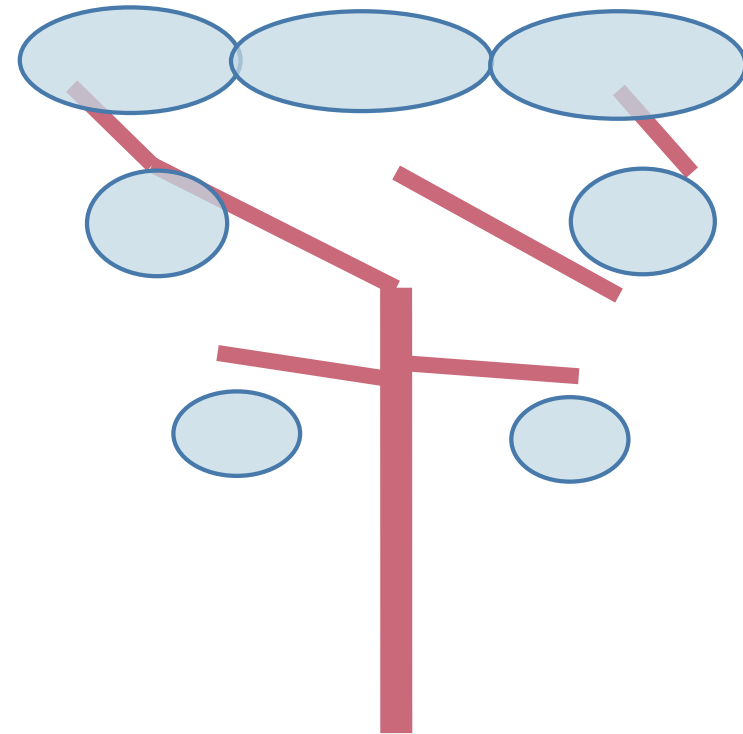
- First identify the overall polyp configuration and its lobules.
- Then trace a branching smooth-muscle–stromal axis.
- Finally assess the epithelium lining the glands and correlate with the clinical phenotype.



Branching smooth muscle

The diagnostic feature is an organized branch pattern

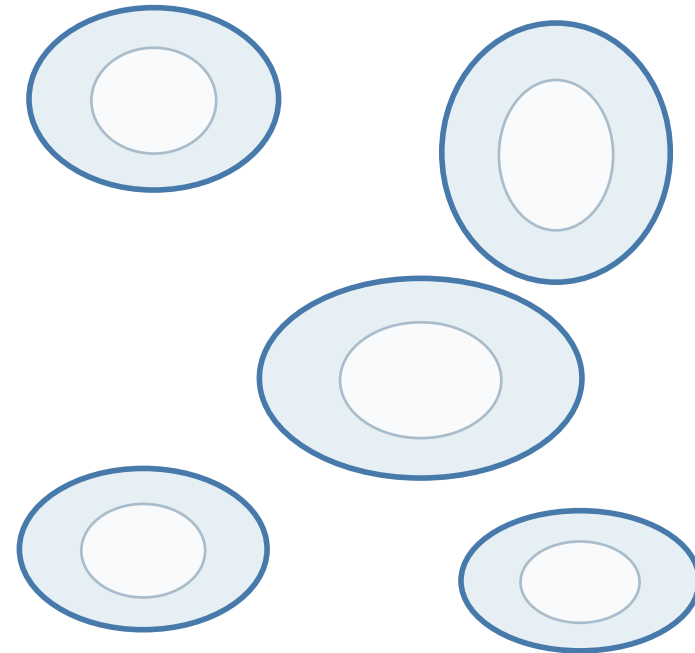
- The smooth muscle is not merely scattered between unrelated glands.
- Arborization creates a coherent branching internal architecture.
- This distinction matters when comparing other hamartomatous polyps.



Branching smooth muscle

Juvenile polyps provide the key histologic contrast

- A juvenile polyp typically contains cystically dilated glands.
- Those glands often contain mucin and inflammatory debris.
- The lamina propria is expanded by an inflammatory infiltrate.



Cystically dilated glands

Peutz–Jeghers versus juvenile polyp

Feature	Peutz–Jeghers polyp	Juvenile polyp
Core architecture	Arborizing smooth-muscle stroma	Cystically dilated glands
Epithelium	Often normal-appearing intestinal lining	Mucin-filled, dilated glands
Intervening stroma	Smooth muscle plus lamina propria	Inflammation-expanded lamina propria
Most useful clue	Tree-like smooth muscle branching	Cystic gland pattern

Juvenile polyposis has different genetic drivers

- Juvenile polyposis syndrome may involve SMAD4 mutations.
- BMPR1A is another established gene in the TGF- β superfamily pathway.
- This differs mechanistically from the STK11–AMPK axis of Peutz–Jeghers.

PJS: STK11

**Juvenile: SMAD4 /
BMPR1A**

**AMPK-related
growth control**

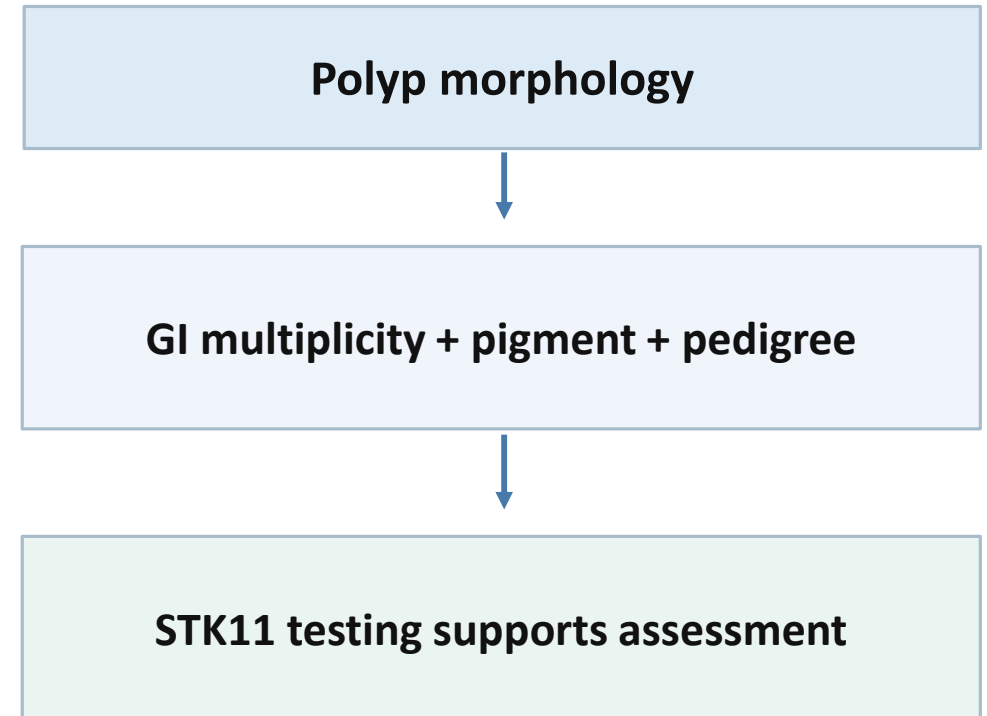
**TGF- β family
signaling**

Hamartomatous syndromes: Pathway comparison

Syndrome	Gene / pathway	Characteristic emphasis
Peutz–Jeghers	STK11; AMPK-related	Arborizing polyps; Pigmented macules
Juvenile polyposis	SMAD4 / BMPR1A; TGF- β	Cystic glands; GI cancer susceptibility
PTEN hamartoma-tumor	PTEN; PI3K/AKT	Mixed polyp phenotypes; Thyroid / breast lesions
Tuberous sclerosis	TSC1 / TSC2; MTOR	Hamartomas with multisystem findings

Sporadic hamartomatous polyps can overlap

- Morphologic overlap exists between Peutz–Jeghers and sporadic hamartomatous lesions.
- Multiple small-intestinal polyps increase the clinical suspicion of syndromic disease.
- Pigmentation and positive family history add discriminatory information.



Pathologic diagnosis benefits from anatomic context

- A solitary histologic specimen cannot show the whole gastrointestinal distribution.
- Location in the small intestine supports the characteristic syndrome pattern.
- The pathology report should be interpreted alongside clinical and family information.

Small intestine

Most common

Stomach

Possible

Colon

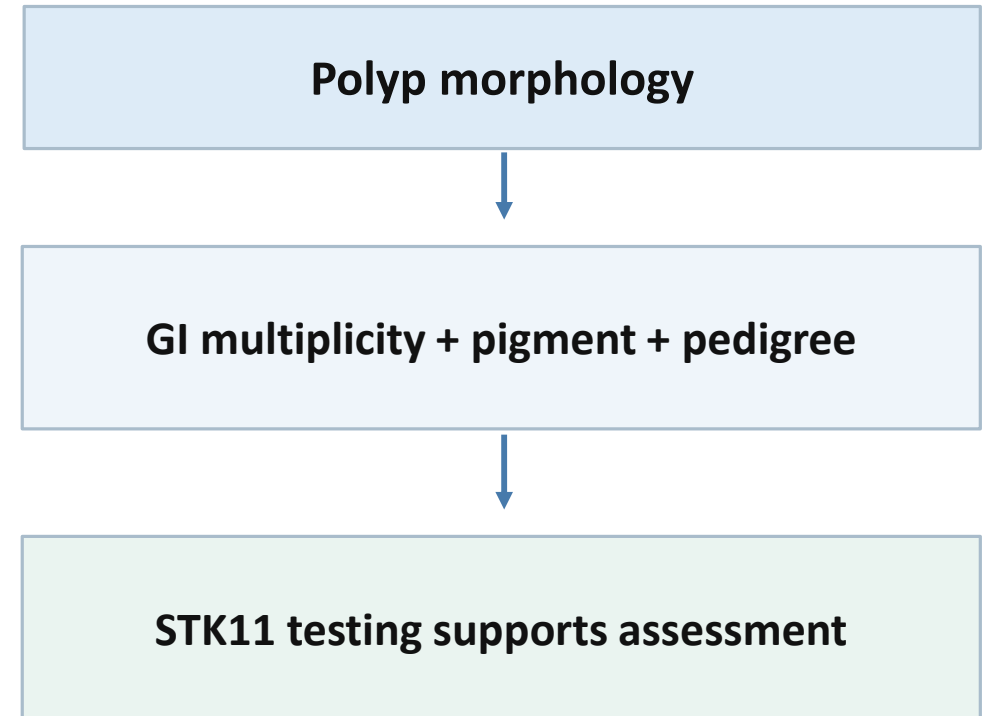
Possible

Bladder / lung

Much less common

An integrated phenotype is more useful than one sign

- Multiple gastrointestinal hamartomatous polyps are a major finding.
- Mucocutaneous hyperpigmentation is a characteristic associated clue.
- A compatible family history and STK11 result can strengthen the assessment.



Familial adenomatous polyposis has a different lesion type

- Classic familial adenomatous polyposis is characterized by multiple adenomas.
- It is linked to APC and Wnt-pathway dysregulation.
- Peutz–Jeghers instead has characteristic arborizing hamartomatous polyps with STK11 dysfunction.

Peutz–Jeghers

Classic FAP

**Hamartomatous
arborizing polyps**

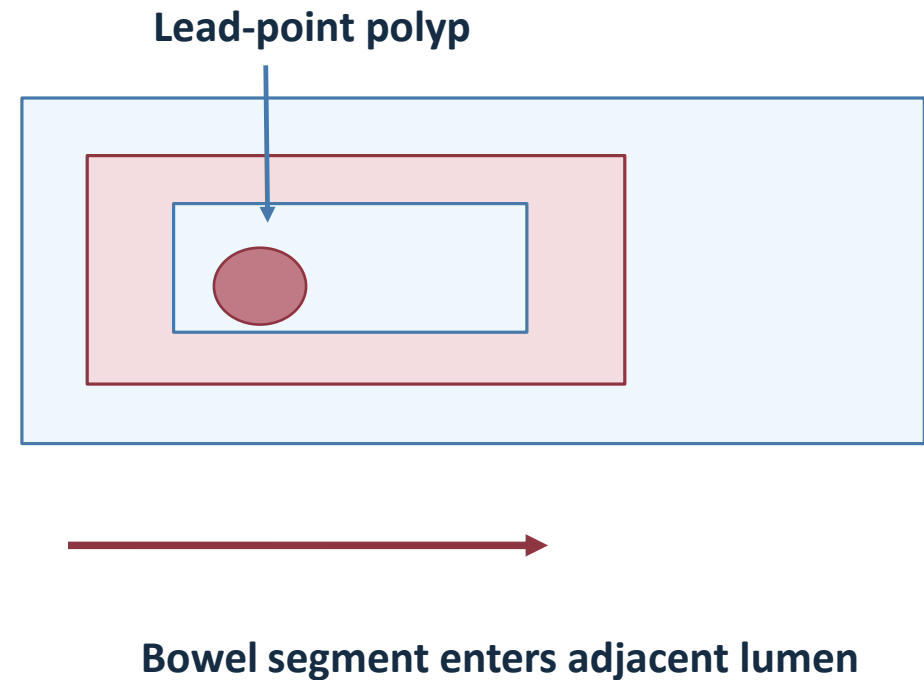
**Multiple epithelial
adenomas**

Syndrome-level discriminators in polyposis

Syndrome	Principal GI finding	Associated diagnostic clue
Peutz–Jeghers	Arborizing hamartomatous polyps	Mucocutaneous pigmented macules
Juvenile polyposis	Hamartomatous polyps with cystic glands	Family history; SMAD4/BMPR1A
Classic FAP	Numerous adenomatous polyps	APC-associated Wnt dysregulation
PTEN-associated	Hamartomatous / inflammatory polyps	Benign skin, thyroid, breast lesions

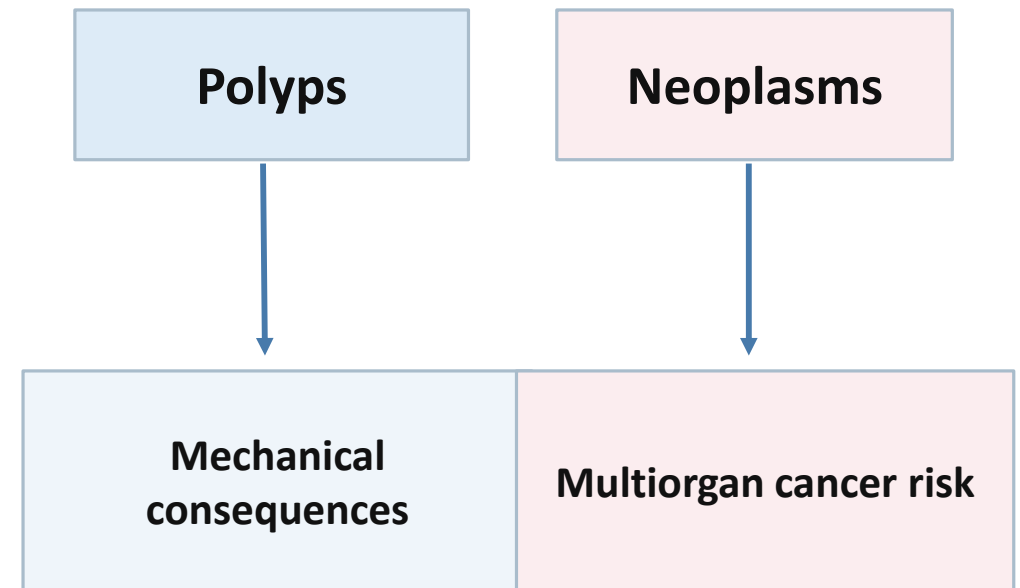
Intussusception is a polyp-related emergency

- A prominent polyp can act as a lead point for bowel telescoping.
- One segment of intestine enters the adjacent segment.
- This complication can occasionally be fatal.



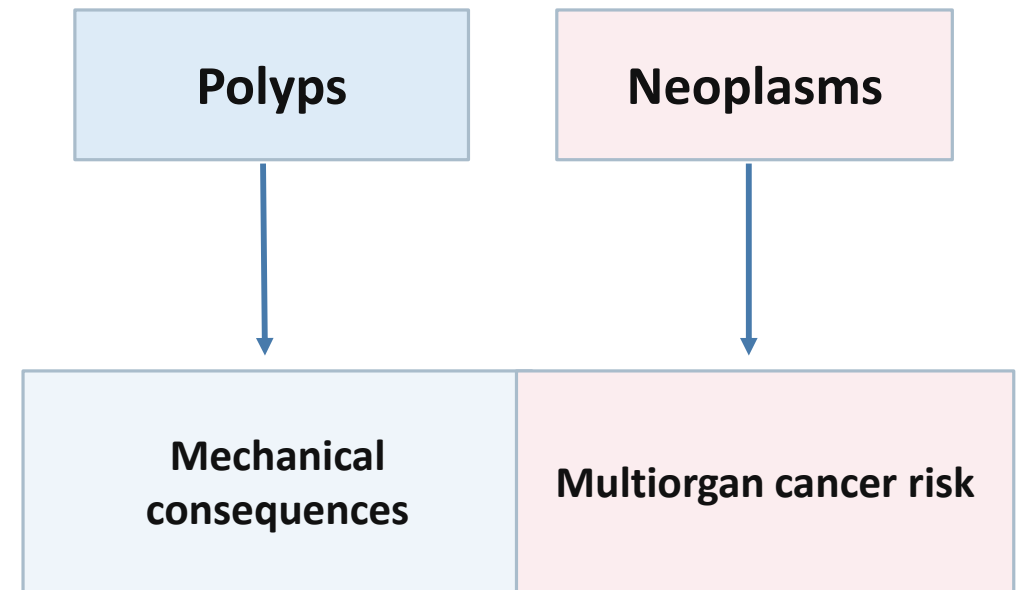
Mechanical effects differ from malignant progression

- Intussusception is a mechanical complication of a polyp.
- Cancer risk reflects inherited tumor susceptibility at multiple sites.
- Both require attention, but their pathophysiology and clinical urgency differ.



A hamartomatous label does not imply a harmless patient

- Histologically bland gland lining may coexist with a strong hereditary cancer predisposition.
- Long-term oncologic assessment is required irrespective of one polyp's appearance.
- Avoid equating “hamartomatous” with “no cancer risk”.



The cancer burden extends beyond the intestine

- A markedly increased lifetime malignancy risk.
- Gastrointestinal and extraintestinal malignancies both contribute.
- Surveillance therefore cannot be limited to the colon.

Gastrointestinal tract

Pancreas

Breast

Lung

Ovary

Uterus

Testis

Gastrointestinal malignancy sites include several organs

- Colon, stomach, and small intestine are relevant to the gastrointestinal spectrum.
- Pancreatic cancer is a particularly important extraintestinal-organ cancer.
- Site-specific surveillance is a central part of the clinical implications.

Gastrointestinal tract

Pancreas

Breast

Lung

Ovary

Uterus

Testis

Important extra-GI tumor sites are diverse

- Breast and lung cancers are included's risk spectrum.
- Ovarian and uterine cancers also warrant attention.
- Sex cord tumors of the testes are relevant to early-life surveillance.

Gastrointestinal tract

Pancreas

Breast

Lung

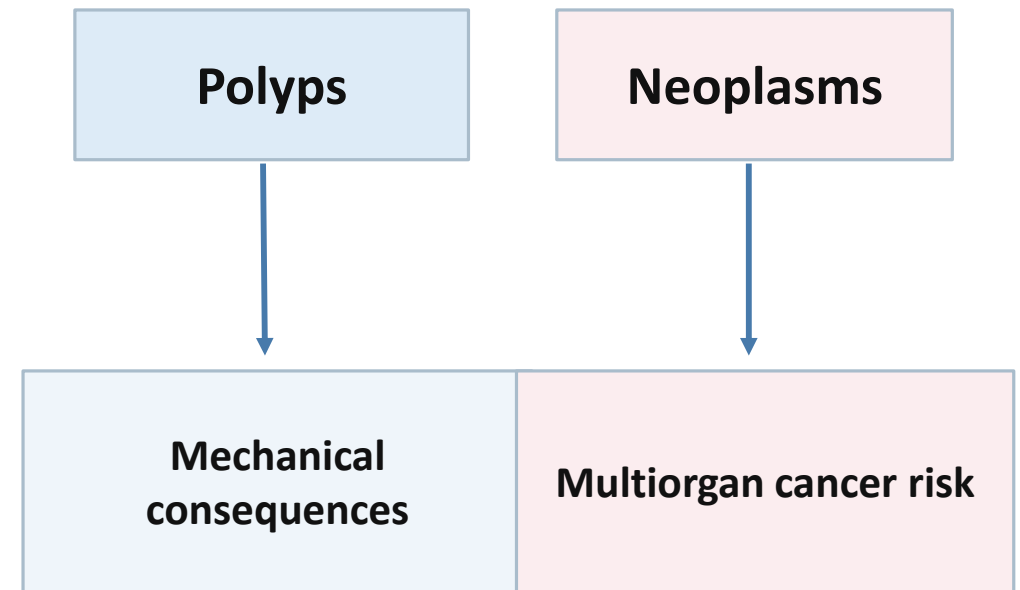
Ovary

Uterus

Testis

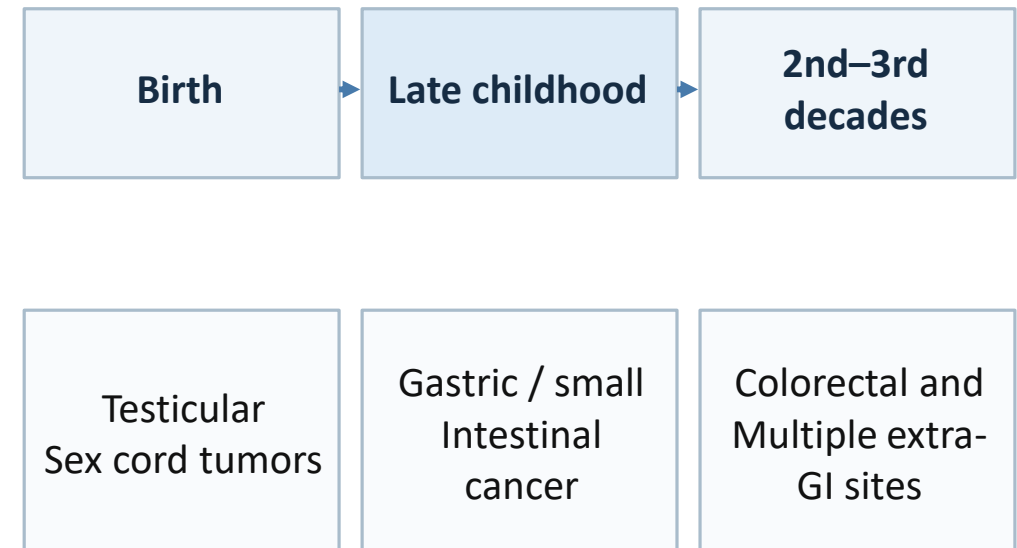
Interpreting the textbook lifetime-risk estimate

- Robbins gives an approximately 40% lifetime cancer risk figure for Peutz–Jeghers syndrome.
- The estimate is presented as a textbook summary rather than a site-specific risk model.
- Do not distribute this figure across organ systems or infer individual prognosis from it.



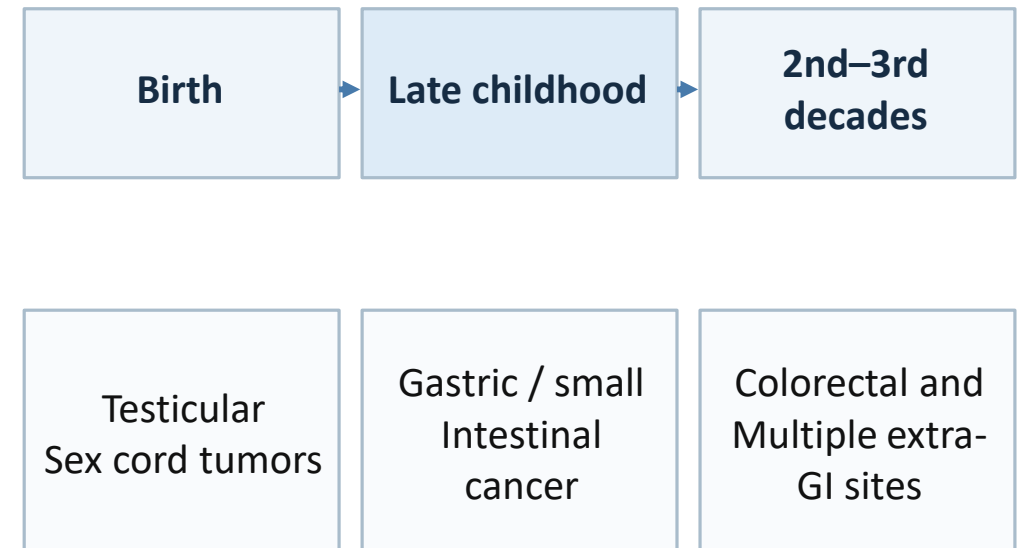
Surveillance spans successive life stages

- Surveillance beginning in early life.
- Different malignancy types become surveillance priorities at different ages.
- Exact tests and intervals are not specified by the source excerpt.



Testicular sex cord tumors are an early concern

- Surveillance for testicular sex cord tumors from birth.
- This is a distinctive component of a multisystem predisposition phenotype.
- The textbook excerpt does not provide a detailed testicular monitoring protocol.



Gastric and small-bowel surveillance begins in childhood

- Surveillance for gastric and small-intestinal cancers in late childhood.
- The small bowel is also the predominant site of hamartomatous polyps.
- Clinical plans must address both local polyp complications and malignant risk.

Small intestine

Most common

Stomach

Possible

Colon

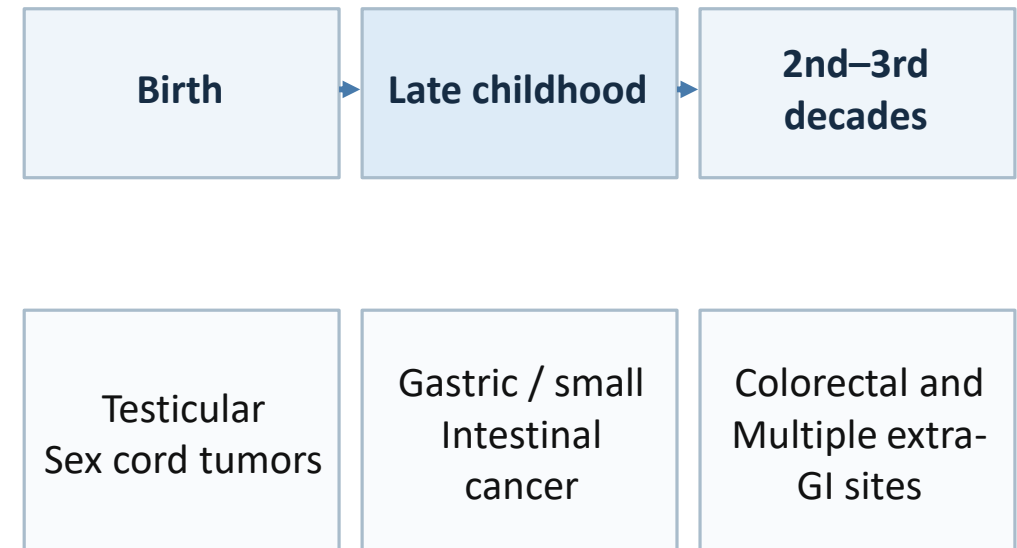
Possible

Bladder / lung

Much less common

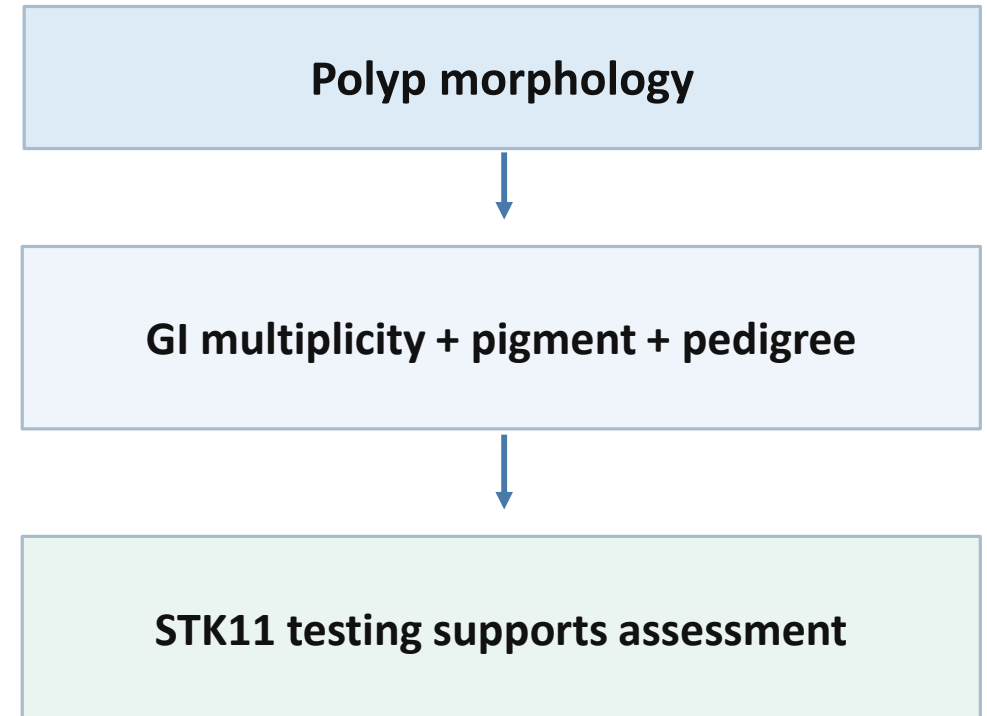
Adult surveillance broadens across organ systems

- The text places surveillance for colorectal, pancreatic, breast, lung, ovarian, and uterine cancers in the second and third decades.
- The affected sites differ by sex and other individual characteristics.
- Detailed modalities and frequencies require dedicated clinical guidelines beyond this excerpt.



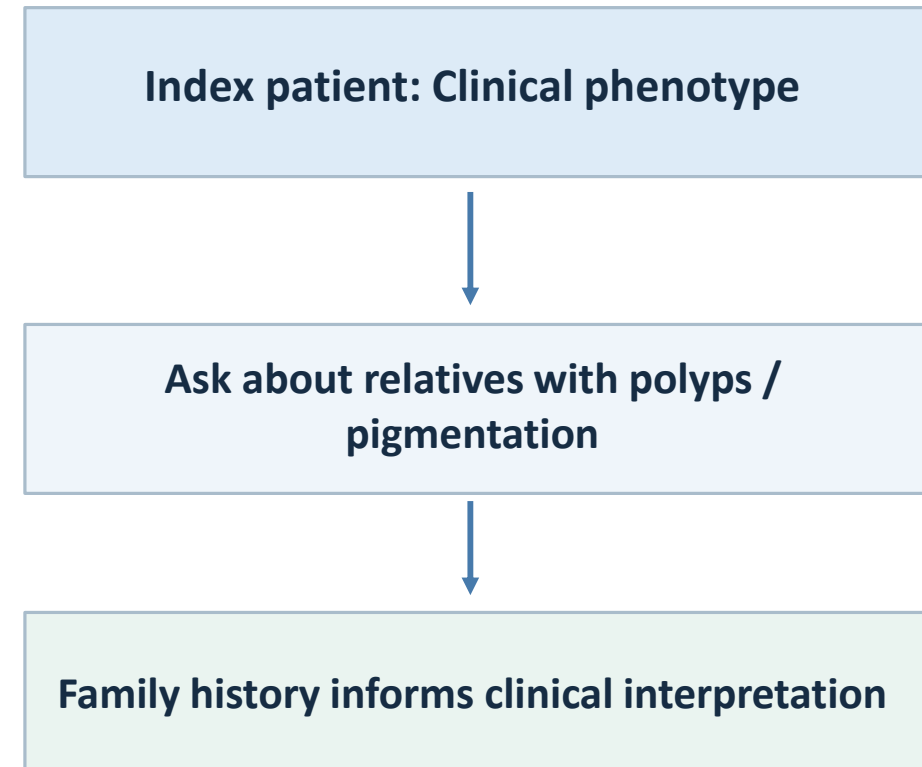
Surveillance advice requires source specificity

- The Robbins overview establishes the importance of routine surveillance.
- It supplies broad life-stage windows, not a prescriptive procedure-by-procedure schedule.
- No additional intervals or modality-specific recommendations are implied by this lecture.



Family history is integral to diagnostic reasoning

- Autosomal dominant inheritance makes affected relatives clinically informative.
- A family history may add confidence when polyp morphology is not specific.
- A negative molecular test should not automatically erase a strong phenotype or pedigree.



Case 1: Intestinal obstruction in a child

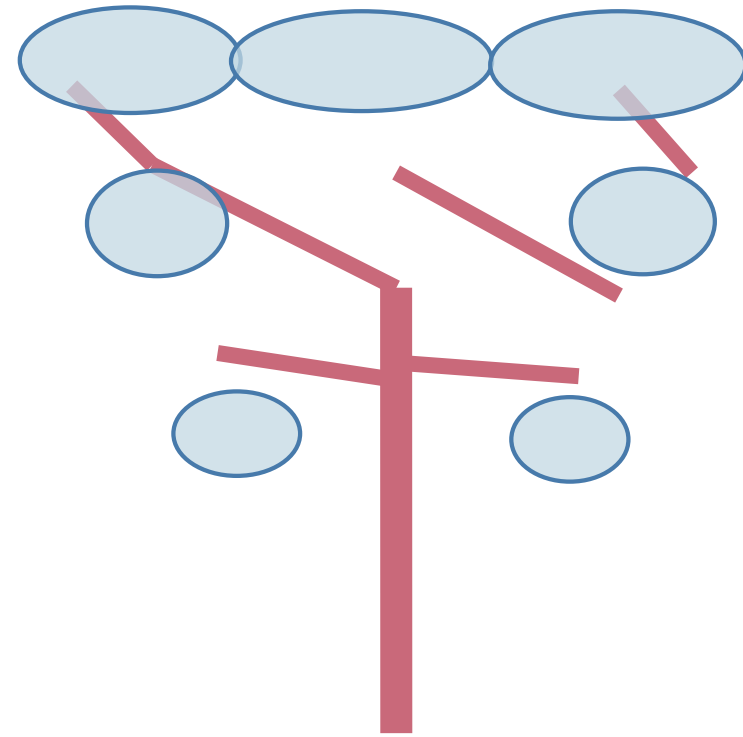
- A child has a small-intestinal polyp and an episode suggestive of intussusception.
- The lesion is pedunculated with a lobulated head.
- What additional tissue and clinical features would support Peutz–Jeghers syndrome?

Clinical vignette

What is the most discriminating microscopic feature?
What other systems should be examined?

Case 1: Connect morphology and phenotype

- Search for branching smooth-muscle bundles and normal-appearing glandular lining.
- Inspect for characteristic mucocutaneous pigmentation, especially oral mucosa.
- Ask about additional polyps and an affected family member.



Branching smooth muscle

Case 2: A juvenile-type polyp differential

- A hamartomatous intestinal polyp contains large mucin-filled dilated glands.
- Inflammatory debris is present within cystic spaces.
- How does this morphology differ from a typical Peutz–Jeghers lesion?

Clinical vignette

Cystically dilated glands with inflammatory debris: Which polyp family is favored?

Case 2: Resolve the histologic differential

- A juvenile polyp favors cystic gland dilatation with inflamed lamina propria.
- A Peutz–Jeghers polyp favors arborizing smooth-muscle architecture.
- The associated syndromic diagnosis still needs clinical correlation.

Juvenile type

Peutz–Jeghers

**Cystic glands +
inflammation**

**Branching smooth-
muscle scaffold**

Case 3: A negative molecular result

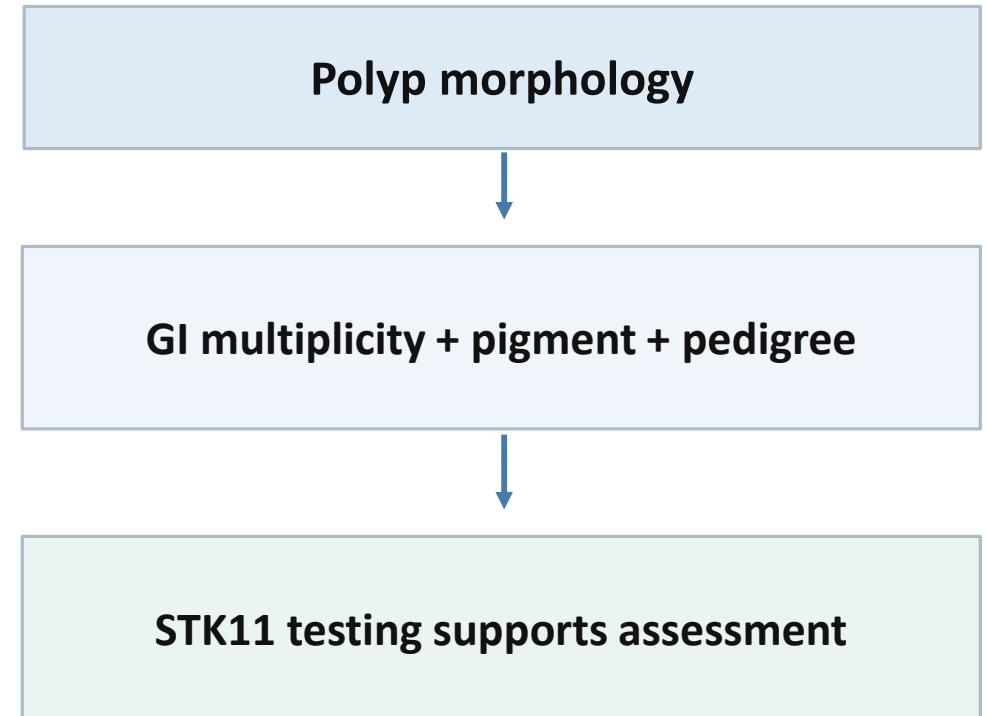
- A patient has multiple small-intestinal polyps with arborizing smooth muscle.
- Buccal macules and a relevant family history are also present.
- A clinical STK11 test is negative: Is the diagnosis excluded?

Clinical vignette

Would a negative STK11 result
invalidate a strong clinicopathologic
pattern?

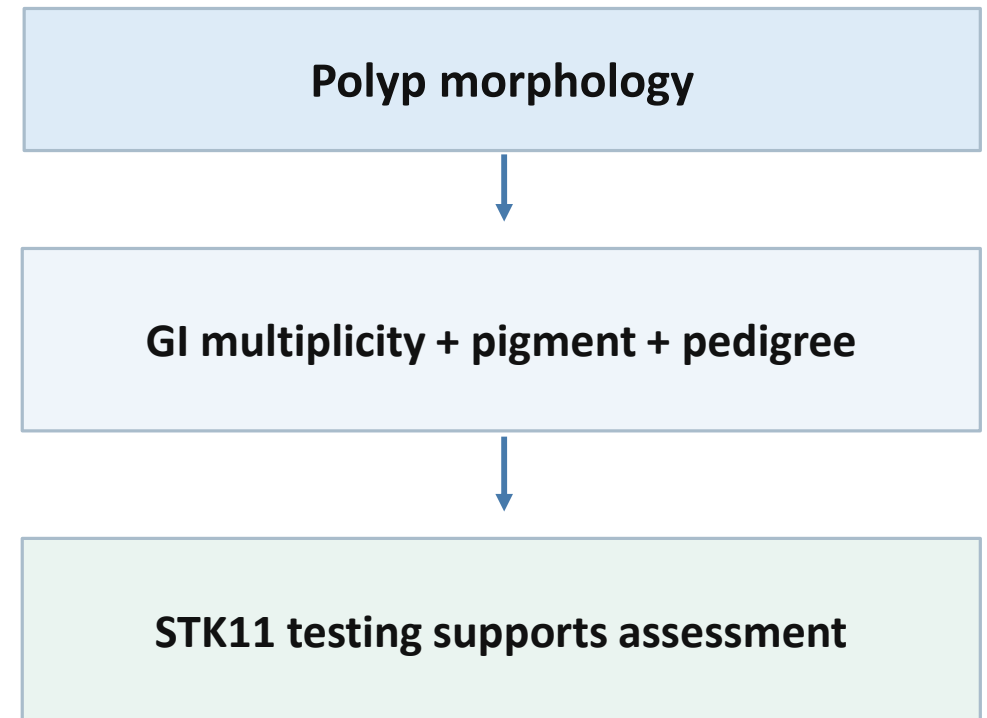
Case 3: Integrate molecular limitations

- No: Detectable STK11 variants are absent in some affected individuals.
- The phenotype remains clinically important.
- A negative result should be interpreted rather than equated with absence of the syndrome.



A practical pathology assessment pathway

- Recognize a hamartomatous polyp and define its architecture.
- Assess extent and distribution of polyposis.
- Integrate mucocutaneous findings and family history.
- Use molecular findings as supportive, not infallible, evidence.



Four mechanisms unify the clinical picture

- Inherited STK11 dysfunction connects the disorder to growth regulation.
- Arborizing polyps explain the characteristic intestinal histology.
- Polyp mass effect explains intussusception risk.
- Multiorgan tumor susceptibility explains lifelong surveillance.

Phenotype

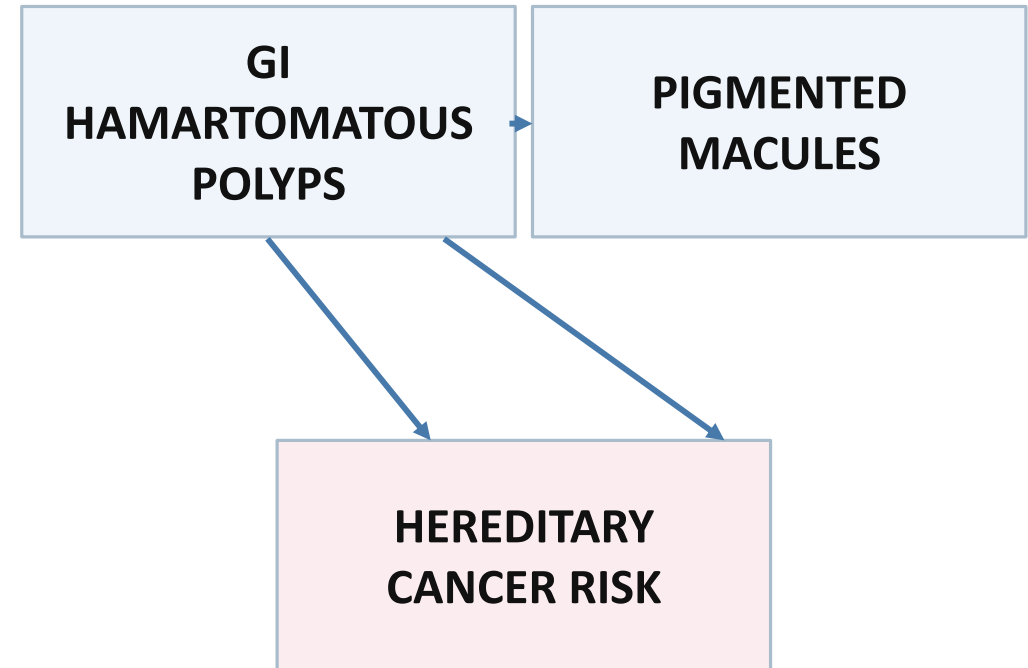
STK11 biology

Arborizing histology

Cancer surveillance

High-yield take-home summary

- Autosomal dominant STK11-associated hamartomatous polyposis.
- Dark mucocutaneous macules, particularly oral, are useful clues.
- Pedunculated polyps show a characteristic arborizing smooth-muscle core.
- Intussusception and multiorgan malignancy risk are separate essential outcomes.



Source and scope of this lecture

- Primary text: Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Source sections: Peutz–Jeghers syndrome and adjacent juvenile/hamartomatous polyps; STK11 tumor suppressor.
- Conceptual tissue drawings are original schematics, not actual photomicrographs.
- This source-based lecture does not substitute for updated clinical surveillance guidelines.