Gene test interpretation: *APC*

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INTRODUCTION

This monograph summarizes the interpretation of germline testing of the *APC* gene. It does **not** discuss indications for testing and is not intended to replace clinical judgment in the decision to test or the care of the tested individual. These subjects are discussed separately [1].

OVERVIEW

How to read the report — An approach to reviewing a genetic test report is summarized in the checklist (table 1).

Testing involves two steps: determining the genotype and interpreting the pathogenicity of the variant(s).

- **Genotype –** Identifies variants. Should be repeated in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory if the results were obtained by direct-to-consumer testing or a research study and would impact clinical care (eg, positive finding, negative finding in an individual with a suspected cancer syndrome).
- **Interpretation –** Determines pathogenicity of the variants identified. May require updating, especially for variants of unknown significance (VUS). (See "Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Genetics'.)

The table provides a glossary of genetic testing terms (table 2).

Disease associations — Pathogenic and likely pathogenic variants in *APC* are associated with familial adenomatous polyposis (FAP), an autosomal dominant disorder. Individuals with FAP are at increased risk for developing gastrointestinal polyps and several cancers. The location of the variant within the *APC* gene can influence the severity of colonic polyposis, degree of cancer risk, age of cancer onset, and likelihood of extracolonic manifestations.

Variants associated with attenuated FAP (AFAP) are typically located at the far 5' or 3' ends of the *APC* gene.

A commonly reported *APC* variant, p.Ile1307Lys (p.I1307K; c.3920T>A), is found in approximately 8 percent of Ashkenazi Jewish individuals. This variant, often reported as a moderate or increased risk allele by laboratories, is not associated with colonic polyposis or FAP, but it increases the risk of colorectal cancer by 1.5- to twofold. Risks for other cancer types have not been established.

- **Intestinal tumors**
    - Classic FAP is characterized by the presence of multiple colorectal adenomas. In classic FAP, there are >100 adenomatous colorectal polyps. Polyposis typically develops in the second or third decade of life. Colorectal cancer occurs in essentially all untreated individuals.
    - AFAP is characterized by 10 to 100 adenomas. Individuals with AFAP have up to an 80 percent risk of developing colorectal cancer at an average age of 56 years.
    - Duodenal adenomas occur in 45 to 90 percent of individuals with FAP, most commonly at or adjacent to the ampulla. Patients with FAP have a 5 percent lifetime risk of duodenal cancer.
    - Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is characterized by >100 fundic gland polyps in the gastric body and fundus with antral sparing. Individuals with GAPPS have a high risk of gastric cancer. Colorectal polyposis generally does not occur.
- **Extraintestinal manifestations –** Individuals with FAP are at risk for follicular or papillary thyroid cancer, childhood hepatoblastoma, and central nervous system tumors, but these are much less common than colorectal and duodenal cancers.

  Other extraintestinal manifestations of FAP include congenital hypertrophy of the retinal pigment epithelium, cutaneous lesions (epidermoid cysts, fibromas, lipomas, pilomatricomas), and osteomas and dental abnormalities. (See "Clinical manifestations

and diagnosis of familial adenomatous polyposis", section on 'Extracolonic manifestations'.)

INDIVIDUALS WITHOUT CANCER

Implications of a pathogenic or likely pathogenic variant — We consider all individuals with a pathogenic or likely pathogenic variant in *APC* to be at risk for familial adenomatous polyposis (FAP), regardless of the initial reason for testing. Exceptions are noted above (see 'Disease associations' above). Information on the *APC* variant (eg, location within the gene) and personal and family history may help determine if the individual should be managed as having classic or attenuated FAP (AFAP).

Discussion should include the range of cancer risks, possible interventions for surveillance or risk reduction, and implications for family members. (See 'At-risk relatives' below.)

Counseling may require additional visits or referrals. Acting upon genetic test results is rarely an emergency; the individual can be reassured that management decisions can be deferred until questions are answered.

We adhere to National Comprehensive Cancer Network (NCCN) recommendations for surveillance and risk reduction [2]. Findings in family members (type of cancers, age of onset) may also inform surveillance (starting at an earlier age if a family member has an earlier age of onset).

In addition to annual physical examination, several evaluations and interventions are recommended to reduce the risk of FAP-associated cancers (algorithm 1).

- **Colorectal cancer**
  - Increased screening/surveillance:
    - Individuals with a pathogenic *APC* variant and/or clinical features of classic FAP should have annual colonoscopy starting around age 10 to 15 years. Patients should continue to undergo annual colonoscopy in the absence of an indication for colectomy.
    - Individuals with a pathogenic variant in *APC* and clinical features of AFAP should have a colonoscopy every one to two years starting in the late teens. Patients with colorectal polyps should undergo polypectomy when feasible, followed by annual colonoscopy.
  - Colectomy in patients with any of the following:

- Documented or suspected colorectal cancer
- Severe symptoms (eg, gastrointestinal bleeding)
- Adenomas with high-grade dysplasia or multiple adenomas >6 mm
- Marked increases in polyp number on consecutive examinations
- Inability to adequately survey the colon because of multiple diminutive polyps

- Endoscopic evaluation of the rectum and ileal pouch every six to 12 months depending on polyp burden (annually for end-ileostomies) following colectomy.

- **Upper gastrointestinal tract**

  - Individuals with FAP should have screening for gastric and duodenal polyps, with upper endoscopy and duodenoscopy. This is initiated at the onset of colonic polyposis or age 20 to 25 years, whichever comes first. Screening should be performed earlier if there is a history of early onset gastroduodenal cancer in the family.

  - Those without duodenal adenomas can have repeat upper endoscopy and duodenoscopy every four years (some expert groups suggest every five years).

  - Those with duodenal adenomas should have complete polypectomy or sampling of duodenal polyps at the time of initial discovery and on each subsequent examination. An abnormal-appearing papilla should be biopsied. The frequency of upper endoscopies varies based on the severity of duodenal polyposis as classified by the Spigelman score (table 3):

    - Stage 0: Every 3 to 5 years
    - Stage I: Every 2 to 3 years
    - Stage II: Every 1 to 2 years
    - Stage III: Every 6 to 12 months
    - Stage IV: Every 3 to 6 months (in the absence of duodenectomy)

- **Desmoid tumors**

  - Abdominal computed tomography to assess for intra-abdominal desmoid tumors in the following individuals:

    - Prior to colectomy if at increased risk for desmoids
    - Palpable abdominal mass
    - Symptoms suggestive of obstruction

- **Thyroid cancer**

- Individuals with classic or AFAP should have a thyroid ultrasound every two to five years, beginning in the late teens.

- **Hepatoblastoma**

  - Screening for hepatoblastoma is controversial. If there is a family history of hepatoblastoma, we screen with serum alpha-fetoprotein, liver palpation, and abdominal ultrasound every three to six months from infancy until age five years.

- **Other cancers**

  - Routine screening is not recommended for small bowel, pancreas, and central nervous system cancers. However, the decision should be individualized based on family history.

Additional details and supporting evidence are discussed separately. (See "Familial adenomatous polyposis: Screening and management of patients and families".)

Implications of a negative test — Negative testing means no pathogenic variants were identified (algorithm 1). However, some tests only evaluate a subset of variants; pathogenic variants might be present in other parts of the gene (if testing was not comprehensive) or in other genes.

- If the familial *APC* variant is known and the tested individual does not have that variant, usually they can be reassured that they are not at high risk for FAP-associated cancers, with caveats outlined above (see 'How to read the report' above). However, it is important provide an individualized risk assessment based on family history and other risk factors.

- If a familial *APC* variant is not known and results of genetic testing are negative, additional risk factors (genetic or acquired) may be present, and additional testing (for other *APC* variants or with a gene panel that includes other colorectal cancer genes) and/or surveillance is based on family history and other risk factors. Referral to a clinical geneticist, oncologist, or genetic counselor may be helpful to determine optimal testing in those with a strong family history of cancer. (See 'Locating a genetics expert' below.)

Implications of a VUS — Individuals with a variant of uncertain significance (VUS) should be managed based on their personal and family history and not the VUS (algorithm 1).

New information may become available; the testing laboratory or other resources should be consulted periodically for updates (eg, annually).

PATIENTS WITH COLORECTAL CANCER

The implications of genetic test results should be discussed with the individual's oncologist or surgeon; in some cases, referral to a specialist in hereditary colorectal cancer syndromes may be appropriate.

The presence of a pathogenic or likely pathogenic *APC* variant may impact several aspects of management; examples include:

- More extensive colectomy (eg, total colectomy with ileorectal anastomosis or proctocolectomy to reduce the risk of metachronous cancers based on patient age and rectal polyp burden.
- Additional screening and prophylactic measures. (See 'Implications of a pathogenic or likely pathogenic variant' above.)

Counseling and testing of family members are also often appropriate. (See 'Considerations for family members' below.)

For individuals with a negative test or a variant of uncertain significance (VUS) who have reasons to be concerned about a genetic cause, additional genetic testing may be appropriate. The need for additional testing may be discussed with a genetic counselor, the primary oncologist, or other hereditary colorectal cancer specialists. (See 'Locating a genetics expert' below.)

CONSIDERATIONS FOR FAMILY MEMBERS

Preconception counseling — Preconception counseling is appropriate for individuals with a pathogenic or likely pathogenic *APC* variant who are considering childbearing.

Some may elect to conceive using donor gametes or in vitro fertilization (IVF) with preimplantation genetic testing (PGT). (See "Preimplantation genetic testing", section on 'Patients known to be at increased risk of offspring with a specific medically actionable condition'.)

At-risk relatives — Individuals with a pathogenic variant or likely pathogenic *APC* variant should inform their at-risk relatives about the importance of genetic counseling and possible testing.

- The risk of having inherited the variant is 50 percent for first-degree relatives. Others at-risk may include aunts, uncles, nieces, nephews, and cousins.

- Usually, the variant segregates on the side of the family with a history of cancer; however, if possible, it is recommended to test a parent or other relative with cancer.
- Genetic testing for at-risk relatives may be considered as early as 10 to 12 years for classic familial adenomatous polyposis (FAP) and the late teens for attenuated FAP (AFAP). Age of polyposis onset for relatives may help guide the timing.
- Families facing decisions to test minors should meet with a genetic counselor or other health care provider with genetics expertise. If genetic testing is deferred in a child at 50 percent risk, FAP screening is recommended until genetic testing is obtained. (See "Genetic testing", section on 'Ethical, legal, and psychosocial issues' and 'Implications of a pathogenic or likely pathogenic variant' above.)

RESOURCES

UpToDate topics

- Familial adenomatous polyposis (FAP):
  - Manifestations and cancer risks – (See "Clinical manifestations and diagnosis of familial adenomatous polyposis".)
  - Management – (See "Familial adenomatous polyposis: Screening and management of patients and families".)
- Genetics:
  - Variant classification – (See "Basic genetics concepts: DNA regulation and gene expression", section on 'Clinical classification of pathogenicity'.)
  - Terminology – (See "Genetics: Glossary of terms".)
  - Genetic testing – (See "Genetic testing".)
  - Genetic counseling – (See "Genetic counseling: Family history interpretation and risk assessment".)

Locating a genetics expert

- Clinical geneticists – American College of Medical Genetics and Genomics (ACMG)
- Genetic counselors – National Society of Genetic Counselors (NSGC)
- National Institutes of Health (NIH) Cancer Genetics Services Directory

REFERENCES

1. Supporting references are provided in the associated UpToDate topics, with selected cita tion(s) below.
2. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf (Accessed on October 24, 2022).

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GRAPHICS

Checklist for reviewing the accuracy and interpretation of genetic test results

Section of the report	Action(s)	Concern(s)
Patient identification	▪ Verify the patient identification with at least two independent identifiers. ▪ Repeat testing if clinically indicated* and the original testing does not have a proper "chain of evidence."	▪ Individuals may inadvertently provide the wrong name or date of birth on a test sample. ▪ Testing should be done by a laboratory that can ensure that the identification matches the tested individual.
Testing laboratory	▪ Verify that testing was done in a CLIA-certified laboratory (or other nationally certified laboratory). ▪ Repeat testing if clinically indicated and/or if original results are actionable and testing was not performed in a CLIA or other nationally certified laboratory.	▪ All actionable medical testing (eg, positive finding or negative finding in an individual suspected of having a genetic disorder) should be conducted in a CLIA-certified laboratory (or other nationally certified laboratory) that has met appropriate quality standards for performing the specific test. ▪ In the United States, most certification is performed by the College of American Pathologists (CAP) and a CAP number for the laboratory is listed. ▪ Some direct-to-consumer testing in some countries is not performed in certified laboratories and may lack appropriate quality controls.
Date of testing	▪ Review the testing date. ▪ Request reinterpretation of the results if the interpretation is inconclusive (eg, a variant of uncertain significance [VUS]).	▪ Germline variants do not change over time. However, as new data become available, the classification of variant pathogenicity may change, especially for variants classified as variant of uncertain significance (VUS). ▪ Repeat testing may be considered, as the technologies for exome sequencing may improve and may identify a variant missed on a prior test.
Gene(s) tested	▪ Verify which genes were tested. ▪ If testing was performed to evaluate a	▪ Not all genetic testing panels are comprehensive for the genes that can cause a particular health condition or for the

	medical condition or a familial disorder, ensure that the correct gene(s), and variant(s), if applicable, were included. ▪ If new research has identified new disease genes, additional testing may be appropriate.	variants in those genes that the panel evaluates. ▪ New disease genes or clinically important variants in existing genes may be identified through further research.
Testing method	▪ Review whether the gene(s) were evaluated using genome sequencing, exome sequencing, panel testing, or other methods such as Sanger sequencing for a specific variant.	▪ Not all methods will identify all variants. ▪ In some cases such as *HFE* testing, only one or two variants are clinically relevant, and sequencing of the entire coding region of the gene is not required, whereas in other conditions, limited testing for one or two variants may miss clinically important findings. ▪ Gene panels may be especially useful when multiple genes could potentially be responsible for a clinical phenotype.
Classification of pathogenicity	▪ Review the category of pathogenicity that was assigned to each variant. ▪ For a variant of uncertain significance (VUS; or any variant for which interpretation is inconclusive), consider requesting reinterpretation annually and/or before making a final decision on interventions.	Interpretation of pathogenicity incorporates many data sources including laboratory research, research databases, population studies, and pedigree analyses. ▪ In some cases, pathogenicity is well established (eg, the known variant that causes sickle cell disease); in others, it is more subjective and incomplete. The designation of a variant of uncertain significance (VUS) refers to the lack of available information on pathogenicity for the variant; further information may eventually allow pathogenicity to be determined. ▪ Variants of uncertain significance (VUS), likely benign, or benign are generally not considered actionable and should not impact medical interventions, which would typically be based on personal and family history of disease. ▪ Consulting a publicly curated database such as ClinVar (or other disease-specific specialty database), discussing the results with an expert in the specific disease, or referral to a

		clinical geneticist, genetic counselor, or disease expert may be helpful.

Clinicians should view the report themselves and should not make clinical decisions based on a verbal report or written summary of the results. Refer to UpToDate for additional information about genetic testing. Details of variant nomenclature (DNA and protein) are available from the Human Genome Variation Society (HGVS) at https://varnomen.hgvs.org/.

CLIA: Clinical Laboratory Improvement Amendments (the national certification standard in the United States); PCR: polymerase chain reaction.

* Indications for testing vary according to the individual's medical history, family history, and other factors such as desire for preconception counseling. In some cases, an individual who did not have a clinical indication for testing may have an unexpected finding from genetic testing that, if accurate, would indicate the need for an intervention, and such findings may be actionable regardless of the initial reasons for testing.

Graphic 122437 Version 10.0

Glossary of terms in the genetic test report

Term	Definition
Allele	A genetic locus or the genotype (base sequence) at a specific genetic locus. When used to refer to pathogenic variants, biallelic refers to a pathogenic variant affecting both alleles (homozygous for the same pathogenic variant at both alleles, or compound heterozygous with a different pathogenic variant at each allele). Monoallelic refers to a genotype affecting only one allele (heterozygous).
Autosomal dominant	Pattern of inheritance that requires only one affected variant allele (a variant inherited from one parent or that arises de novo) to transmit the trait or risk of disease. Not sex-linked. First-degree relatives (siblings, children) have a 50% chance of sharing (or inheriting) the variant allele.
Autosomal recessive	Pattern of inheritance that generally requires variants on both alleles (one from each parent) in order to transmit the trait or risk of disease. Not sex-linked. Individuals with one variant are sometimes called carriers.
Carrier	Individual who has a specific variant in one allele of the gene in their germline DNA (inherited from one parent or arising de novo). For recessive disorders, refers to a heterozygote who is generally (or mostly) unaffected. For dominant disorders, carriers are generally considered at risk for the disorder.
Compound heterozygote	Also called "double heterozygote"; refers to an individual who is heterozygous for two different variants of the same gene, one from each parent. Typically refers to pathogenic variants.
Expressivity	Differences in the severity of disease manifestations in individuals who share the same genotype (eg, cystic fibrosis is said to have variable expressivity because two individuals with the same genotype may have differences in the degree of pancreatic or lung dysfunction).
Genotyping	Determining the DNA sequence of a particular gene or portion of a gene in an individual. Can be done on DNA from sources such as nucleated epithelial cells from saliva, tumor cells from a biopsy, or WBCs from peripheral blood. Can be used to determine germline or somatic sequence, depending on the source of the cells.
Germline	Derived from the gametes (sperm or egg cells) and present in the early embryo; germline variants are typically present in all body cells and do not change. Germline variants can be passed down to subsequent generations.
Heterozygous	Having a genetic variant on one, but not both, of a pair of genes.
Homozygous	Having the same genetic sequence or the same allele on both chromosomes. A person can be homozygous for a pathogenic variant or for the wildtype allele.
Mosaicism	Having two populations of genetically distinct cells that arose from a single fertilized egg. Mosaicism that arises later during embryonic development affects a smaller proportion of cells and a more limited number of cell lineages. Individuals with mosaicism can only transmit a genetic variant to the next generation if it is present in the gametes. If an individual with mosaicism for a disease trait harbors

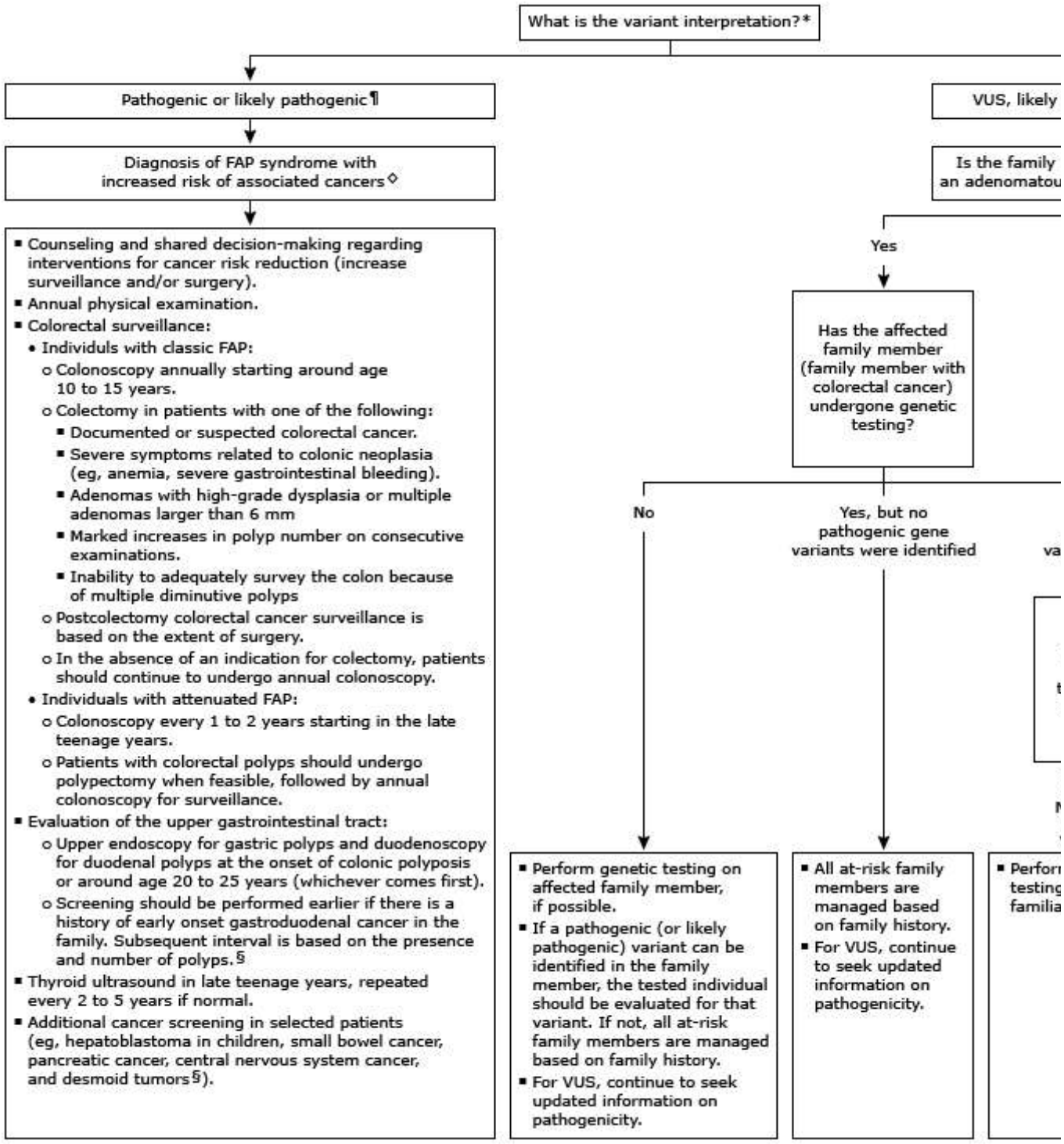
	the associated variant in the germline, the trait may present as a new finding in children who inherit the variant.
Mutation	Term that may be used to describe changes in DNA or protein sequence compared with a reference sequence. The American College of Genetics and Genomics (ACMG) has expressed concern that this term can cause confusion or incorrect assumptions regarding pathogenicity, and the ACMG recommends that findings from genetic testing be described using the term "variant" with a qualifier regarding pathogenicity (or lack thereof).
Pathogenicity	Likelihood that a specific variant is capable of causing disease or conferring disease risk. Does not determine the likelihood that disease will occur (which depends on other factors such as disease penetrance). Refer to separate table in UpToDate for the categories.
Pedigree	Diagram of a family showing relationships among family members, sex of each family member, presence or absence of one or more genetic disorders, and often the age at which they manifested. Used in genetic counseling to identify possible inherited causes of disease and their inheritance patterns.
Penetrance	Likelihood that a person with a disease-associated variant will manifest one or more features of the disease. Many disease variants have incomplete or variable penetrance, meaning that not all individuals with the variant will manifest the associated disorder.
Somatic	Referring to tissues that are not within the germline. Variation that arises in somatic tissues is not passed from parent to offspring. Somatic mutations are common in cancer.
Variant	Change in the sequence of DNA compared with a reference sequence. Variants can be benign (associated with normal gene function), pathogenic (associated with altered gene function and/or clinical disease), or of uncertain significance (VUS). Two other categories are "likely pathogenic" and "likely benign." The term polymorphism is often (but not exclusively) used for benign variants. Refer to a separate table in UpToDate that defines the categories.
VUS	Variant of uncertain significance (or unknown significance). Refers to a variant for which insufficient information is available to classify as benign or pathogenic.

Refer to UpToDate for additional information on genetic testing, a separate table on the classification of pathogenicity, and a more extensive glossary of genetic terms.

WBCs: white blood cells; VUS: variant of uncertain significance, also called variant of unknown significance.

Graphic 122429 Version 14.0

Algorithm for a germline FAP (*APC* gene) genetic test result in a person with



This algorithm is only intended for individuals without a personal diagnosis of cancer. Interpretations of revised as more data become available. It is especially important to seek this updated information perio Discussion with a genetic counselor and/or an expert in hereditary syndromes is likely to be appropriate a pathogenic or likely pathogenic variant in the *APC* gene and/or a strong family history of FAP-associate

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FAP: familial adenomatous polyposis; VUS: variant of uncertain significance.

* Ensure that the genetic testing is performed properly, the patient identification is correct, and the inter pathogenicity is accurate based on the most recent data analysis.

¶ Pathogenic and likely pathogenic variants are treated the same for purposes of surveillance and risk re
these interventions are independent of family history.

Δ VUS lack sufficient information from clinical and bench research to be classified as pathogenic or benig
updated interpretation of pathogenicity periodically (eg, annually).

◇ Examples of FAP-associated cancers include colorectal, small bowel, gastric, thyroid, and brain. Refer t
FAP for the age at which interventions are initiated, the frequency at which they are performed, and the
these interventions.

§ Refer to related UpToDate content on FAP for additional information.

Graphic 129520 Version 4.0

Modified Spigelman score and classification of duodenal polyposis

Factor	Score		
	1 point	2 points	3 points
Number of polyps	1-4	5-20	>20
Polyp size, mm	1-4	5-10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	--	High grade

Classification: no polyp: stage 0; 1 to 4 points: stage I; 5 to 6 points: stage II; 7 to 8 points: stage III; 9 to 12 points: stage IV.

Contributor Disclosures

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