Updates in Genetic Testing Guidelines

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Objectives

1. Identify patients with personal and/or family histories of breast, ovarian, pancreatic, and prostate cancer for whom referral for genetic counseling/testing is appropriate based on current guidelines
2. Identify patients with personal and/or family histories of colorectal cancer and/or polyposis for whom referral for genetic counseling/testing is appropriate based on current guidelines
3. Anticipate and apply future changes to guidelines for genetic counseling/testing

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NCCN Guidelines

- Gold standard
- Updated annually (if not more often)
- Recommendations based on evidence and consensus
- Closely followed by most insurance companies

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NCCN Guidelines & Genetics

Specific genetic guidelines

- Genetic/Familial High-Risk Assessment: Colorectal
- Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic

Summary of Genes and/or Syndromes Included/Mentioned in Other NCCN Guidelines

- BOP Version 2.2023 (first included in Version 1.2023)
  - SUMM-1

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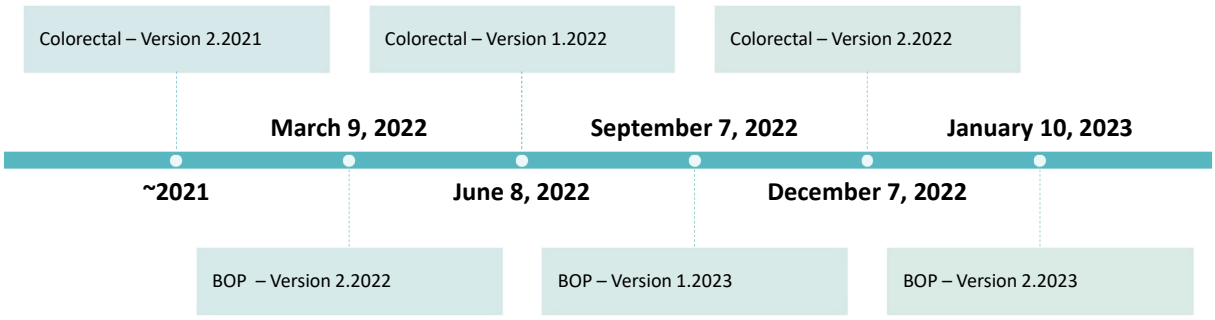
New Guidelines Published



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Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

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General Testing Criteria

- Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene
- Individuals meeting other criteria but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing
- A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline
- To aid in systemic therapy and surgical decision-making[b]
  - [b]Eg, PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer; and risk-reducing surgery.
- Individual who meets
  - Li-Fraumeni syndrome (LFS) testing criteria
  - Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS) testing criteria
  - Lynch syndrome

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General Testing Criteria

Testing *may be* considered:

- Ashkenazi Jewish ancestry w/o additional risk factors
- Personal history of serous endometrial cancer[d]

[d]This is a rare subtype of uterine cancer for which there is evolving evidence of an association with *BRCA1* P/LP variants

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Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes

Personal history of breast cancer with specific features:

≤50 y

Any age:

- Treatment indications
  - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
  - To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer
- Pathology/histology
  - Triple-negative breast cancer
  - Multiple primary breast cancers (synchronous or metachronous)
  - Lobular breast cancer with personal or family history of diffuse gastric cancer

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Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes

Personal history of breast cancer with specific features:

Any age (continued):

- Male breast cancer
- Ashkenazi Jewish ancestry
- Family history
  - ≥1 close blood relative with ANY:
    - breast cancer at age ≤50
    - male breast cancer
    - ovarian cancer
    - pancreatic cancer
    - prostate cancer with metastatic, or high- or very-high-risk group ~~or intraductal/cribriform histology~~
  - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
  - ≥2 close blood relatives with either breast or prostate cancer (any grade)

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Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes

Family history of breast cancer:

An affected individual (not meeting testing criteria listed above) or unaffected individual with a FDR or SDR meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).

- If the affected relative has pancreatic cancer or prostate cancer, only FDR should be offered testing unless indicated based on additional family history

An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)

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Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes

Testing *may be* considered:

Personal history of breast cancer <60 y not meeting other criteria may approach a 2.5% probability of having a PV. It is cautioned that the majority of those PVs will be in moderate penetrance genes . . . data on appropriate management are often lacking. Important to have access to an experienced genetic counseling team

Personal history of breast cancer diagnosed at any age with ≥1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology

An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of BRCA1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)

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Testing Criteria for High-Penetrance Ovarian Cancer Susceptibility Genes

Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age

Family history of cancer only

- An unaffected individual with a FDR or SDR with epithelial ovarian cancer at any age
- An unaffected individual who otherwise does not meet criteria above but has a probability of >5% of a BRCA1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)

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Testing Criteria for Pancreatic Cancer Susceptibility Genes

All individuals diagnosed with exocrine pancreatic cancer

FDR of individuals diagnosed with exocrine pancreatic cancer

Additional guidelines for neuroendocrine pancreatic tumors

- NCCN Guidelines for Neuroendocrine and Adrenal Tumors

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Testing Criteria for Prostate Cancer Susceptibility Genes

Personal history of prostate cancer with specific features:

By tumor characteristics (any age)

- Metastatic
- Histology:
  - high or very-high risk group
  - ~~Intraductal/cribriform histology~~

By family history and ancestry

- ≥1 close blood relative with:
  - Breast cancer at age ≤50 y
  - Triple-negative breast cancer at any age
  - Male breast cancer at any age
  - Ovarian cancer at any age
  - Pancreatic cancer at any age
  - Prostate cancer that is metastatic, high-, or very-high risk group at any age, ~~or intraductal/cribriform histology~~
- ≥2 close blood relatives with either breast or prostate cancer (any grade) at any age
- Ashkenazi Jewish ancestry

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Testing Criteria for Prostate Cancer Susceptibility Genes

Family history of cancer:

An affected (not meeting testing criteria) or unaffected individual with a FDR meting any of the criteria above (except individuals whose relatives meet criteria only for systemic therapy decision-making)

Testing *may be* considered:

Personal history of prostate cancer with intermediate-risk prostate cancer with intraductal/cribriform histology at any age

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Testing Criteria for Li-Fraumeni Syndrome

Individuals with a familial *TP53* P/LP variant

Classic LFS criteria:

- Combination of an individual diagnosed <45 with a sarcoma ***AND***
  - A FDR diagnosed <45 years with cancer ***AND***
  - An additional FDR or SDR in the same lineage with cancer diagnosed <45, or a sarcoma at any age

Chompret criteria:

- Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), <46, **AND** at least one FDR or SDR with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) <56 or with multiple primaries at any age **OR**
- Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring <46 **OR**
- Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history **OR**
- Breast cancer <31

Pediatric hypodiploid acute lymphoblastic leukemia

Affected individual with P/LP variant identified on tumor genomic testing that may have implications if also identified on germline testing

*Other cancers associated with LFS but not in the testing criteria include: melanoma, colorectal, gastric, and prostate.

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Testing Criteria for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome

Individuals with a familial *PTEN* P/LP variant

Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)

Individual meeting clinical diagnostic criteria for CS/PHTS

Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of:

- Adult Lhermitte-Duclos disease (cerebellar tumors); or
- Autism spectrum disorder and macrocephaly; or
- Two or more biopsy-proven trichilemmomas; or
- Two or more major criteria (one must be macrocephaly); or
- Three major criteria, without macrocephaly; or
- One major and ≥3 minor criteria; or
- ≥4 minor criteria

At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed

- The at-risk individual must have the following:
  - Any one major criterion or
  - Two minor criteria

PTEN P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

*Other cancers associated with *PTEN* but not in the testing criteria include: colorectal, kidney cancer, and melanoma.

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Genetic/Familial High-Risk Assessment: Colorectal

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Assessment for Hereditary CRC Syndromes

Family history of a germline pathogenic variant in a colorectal polyposis or cancer gene

Personal history of CRC

Personal or family history of a Lynch syndrome-related cancer or a personal history of a tumor with deficient mismatch repair (dMMR)

Personal or family history of:

- ≥10 adenomatous polyps
- ≥ 2 hamartomatous polyps
- ≥ 5 serrated polyps/ lesions proximal to the rectum

Patients who had limited genetic testing in the past may benefit from repeat genetic testing using a larger MGPT

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Personal history of CRC

Germline multigene panel test (MGPT) evaluation for LS and other hereditary cancer syndromes

<50 at age of diagnosis	Known MMR deficiency in tumor •**OR** consider additional tumor-based testing

None of the above

Utilize tumor and family history-based criteria for evaluation of LS **OR**	Consider germline MGPT evaluation for LS and other hereditary cancer syndromes for all individuals with CRC aged ≥50 years at diagnosis (category 2B recommendation*)

*Category 2B = consensus, but not uniform

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Criteria for Evaluation of Lynch Syndrome

- Known LS pathogenic variant in the family
- Personal history of colorectal or uterine cancer
- Family history of cancer
- Increased model-predicted risk for LS
- Tumor with MMR deficiency[cc]
  - Additional tumor-based testing **OR**
  - Germline MGPT evaluation for LS and other hereditary cancer syndromes[o]

[cc]Consider tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis.

[o] Biallelic MUTYH gene mutations have been shown to lead to dMMR tumors; therefore, MUTYH should be included in the testing at a minimum with consideration of other base-excision repair genes (NTHL1) and DNA polymerase genes (POLE and POLD1), which have the potential to also lead to biallelic somatic MMR gene inactivation

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Lynch Syndrome Criteria – Personal History

Personal history of **colorectal** or **endometrial** cancer and any of the following:

Diagnosed <50 years

A synchronous or metachronous LS-related cancer regardless of age

1 FDR or SDR with a LS-related cancer diagnosed <50

≥2 FDR or SDR with a LS-related cancer regardless of age

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Lynch Syndrome Criteria – Family History

Family history of any of the following:

- ≥1 FDR with a colorectal or endometrial cancer diagnosed <50y
- ≥1 FDR with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age
- ≥2 FDR or SDR with LS-related cancers, including ≥1 diagnosed <50y
- ≥3 FDR or SDR with LS-related cancers regardless of age

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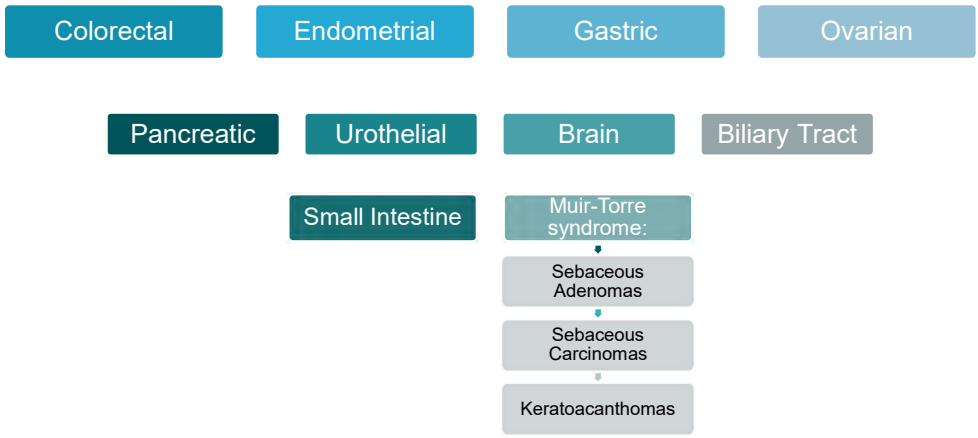
Lynch Syndrome Cancers



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Increased Model-Predicted Risk for LS

≥5% risk of pathogenic MMR variant based on predictive models

Personal hx of CRC and/or endometrial cancer	No personal hx of CRC and/or endometrial cancer
• PREMM score of ≥2.5% should be considered for MGPT	• Some data have suggested using a PREMM score threshold of ≥2.5% rather than ≥5% for MMR gene testing

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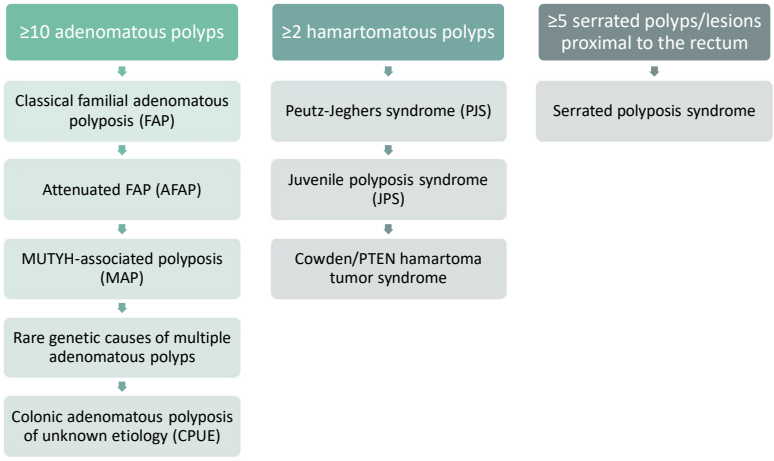
Assessment for Polyposis Syndromes



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Adenomatous Polyposis Testing Criteria (*APC* and *MUTYH* genes)

Personal history of ≥20 cumulative adenomas

Known pathogenic variant in adenomatous polyposis gene in family

Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)

Consider testing if a personal history of

- Between 10–19 cumulative adenomas
- Desmoid tumor
- Hepatoblastoma
- Cribriform-morular variant of papillary thyroid cancer
- Unilateral CHRPE
- Individual meets criteria for SPS with at least some adenomas

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Other Causes of Adenomatous Polyps

- *AXIN2*
- *GREM1*
- *MSH3*
- *NTHL1*
- *POLE*
- *POLD1*

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Peutz-Jeghers Syndrome Testing Criteria (*STK11* gene)

Clinical diagnosis of at least 2 of the following:

- ≥2 Peutz-Jeghers-type hamartomatous polyps of the GI tract
- Mucocutaneous hyperpigmentation
  - Mouth
  - Lips
  - Nose
  - Eyes
  - Genitalia
  - Fingers

Family history of PJS

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Juvenile Polyposis Syndrome Testing Criteria (*BMPR1A* and *SMAD4* genes)

≥5 juvenile polyps of the colon
Multiple juvenile polyps found throughout the GI tract
Any number of juvenile polyps in an individual with a family history of JPS
Family history of JPS

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Questions

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