INDICATIONS FOR CANCER GENETICS REFERRAL[1]

January 2024

In a given at-risk family it is more informative to initiate the process of genetic testing in the cancer-affected relative at greatest risk of carrying a genetic alteration. When it is not feasible to test the affected relative first, then an unaffected family member should be considered for genetic counseling and discussion of testing.

GENERAL GUIDANCE

Consider cancer genetics referral when there is/are:

- Three relatives on the same side of the family with similar or related cancers
- An individual or a close relative with two or more different cancers
- An individual or a close relative with cancer typically occurring in adulthood diagnosed at a younger age than expected (often less than age 50)
- Non-cancerous findings suggesting a recognized genetic condition (*e.g*., multiple colon polyps)
- A known cancer-related mutation in the family (*e.g*., *BRCA1, MLH1, MUTYH, TP53,* etc.)
- A rare cancer (*e.g*., medullary thyroid cancer, pheochromocytoma, etc.)
- A potential germline variant detected on tumor-based genomic testing
- An individual or a close relative with ovarian or pancreas cancer at any age
- An individual with a personal history of cancer suggestive of a hereditary cancer syndrome and an unknown or limited family history/structure, such as fewer than two first- or second-degree relatives having lived beyond age 45 in either lineage

Use the following checklists to aid in assessing whether a genetics referral is necessary for patients with the following:

[1]These referral checklists are designed as simplified tools to assist in the clinic-based evaluation of patients and families. They do not reflect all high-risk criteria. These documents are expected to change over time. For questions regarding specific patients or families, or updated versions of these checklists, please contact the Cancer Risk and Prevention Program: Phone 207-396-7270; Fax 207-800-4237.

Checklist for Breast Cancer Genetic Assessment
For use in individuals with a ***personal history of breast cancer***

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g., ATM, BRCA1, BRCA2, CHEK2, TP53, PALB2, PTEN*, etc.)
☐	Individual who previously tested negative with limited analysis testing (*e.g.*, *BRCA1/2* only testing)
☐	Potential germline variant detected on tumor-based genomic testing
☐	Breast cancer at or before age 50
☐	Triple negative breast cancer at any age
☐	Male breast cancer
☐	To aid in treatment decisions (*e.g.*, PARP inhibitors)
☐	Multiple primary breast cancers at any age
☐	Ashkenazi Jewish ancestry
☐	In individuals with a personal history of breast cancer at any age and family history of cancer: ☐ **One** or more relatives* with: o Breast cancer at or before age 50 o Metastatic prostate cancer o High- or very high-risk prostate cancer defined as stage T3a or greater, Gleason score of at least 8, or PSA >20 ng/mL o Male breast cancer, ovarian cancer or pancreatic cancer at any age ☐ **Two** or more relatives* with: o Breast cancer or prostate cancer (any grade) at any age o Breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, and/or leukemia *(suspicion for Li-Fraumeni syndrome—see NCCN for full criteria)* o Breast cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, macrocephaly, and/or GI hamartomatous polyps *(suspicion for Cowden syndrome—see NCCN for full criteria)* o Lobular breast cancer and/or diffuse gastric cancer *(suspicion for hereditary diffuse gastric cancer syndrome—see NCCN for full criteria)* o Breast cancer, GI cancer or polyps, ovarian sex cord tumors, pancreatic cancer, testicular Sertoli cell tumors, or childhood skin pigmentation *(suspicion for Peutz-Jeghers syndrome—see NCCN for full criteria)*

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd: cousins, great-grandparents, great-aunts/uncles, great-nieces/nephews, great-grandchildren. Affected relatives should be on the same side of the family to meet the criteria.

Checklist for Breast Cancer Genetic Assessment
For use in individuals with a ***family history of breast cancer***

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g., ATM, BRCA1, BRCA2, CHEK2, TP53, PALB2* or *PTEN*)
☐	Individual who previously tested negative with limited analysis testing *(e.g., BRCA1/2* only testing)
☐	Ashkenazi Jewish ancestry with a family history of breast cancer or prostate cancer, at any age
☐	In individuals with a family history of cancer in a first- or second-degree relative: ☐ **One** or more relatives with: ○ Breast cancer at 50 or younger ○ Triple negative breast cancer at any age ○ Multiple primary breast cancers ○ Metastatic prostate cancer ○ High- or very high-risk prostate cancer defined as stage T3a or greater, Gleason score of at least 8, or PSA >20 ng/mL ○ Male breast cancer, ovarian cancer or pancreatic cancer at any age ☐ **Three** or more relatives with: ○ Breast cancer or prostate cancer (any grade) at any age *(suspicion for hereditary breast and ovarian cancer syndrome—see NCCN for full criteria)* ○ Breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, and/or leukemia *(suspicion for Li-Fraumeni syndrome—see NCCN for full criteria)* ○ Breast cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, macrocephaly, and/or GI hamartomatous polyps *(suspicion for Cowden syndrome—see NCCN for full criteria)* ○ Lobular breast cancer and/or diffuse gastric cancer *(suspicion for hereditary diffuse gastric cancer syndrome—see NCCN for full criteria)* ○ Breast cancer, GI cancer or polyps, ovarian sex cord tumors, pancreatic cancer, testicular Sertoli cell tumors, or childhood skin pigmentation *(suspicion for Peutz-Jeghers syndrome—see NCCN for full criteria)*

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren. Affected relatives should be on the same side of the family to meet the criteria.

Checklist for Prostate Cancer Genetic Assessment
For use in individuals with a ***personal history of prostate cancer***

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g., ATM, BRCA1, BRCA2, CHEK2, TP53*)
☐	Individual who previously tested negative with limited analysis testing (*e.g.,* BRCA1/2 only testing)
☐	Potential germline variant detected on tumor-based genomic testing
☐	Metastatic prostate cancer
☐	Prostate cancer in the high- or very high-risk group
☐	Ashkenazi Jewish ancestry
☐	In individuals with a personal history of prostate cancer at any age and family history of cancer: ☐ **One** or more close blood relatives* with: ○ Metastatic prostate cancer ○ High- or very high-risk prostate cancer defined as stage T3a or greater, Gleason score of at least 8, or PSA >20 ng/mL ○ Breast cancer at 50 or younger ○ Triple-negative breast cancer at any age ○ Male breast cancer at any age ○ Ovarian cancer at any age ○ Pancreatic cancer at any age ☐ **Two** or more relatives* with: ○ Either breast or prostate cancer (any grade) at any age ☐ **Three** or more relatives* with: ○ Colorectal cancer, endometrial cancer, pancreatic cancer, gastric cancer, urothelial cancer, small intestine cancer (*suspicion for Lynch Syndrome- see NCCN for full criteria*)

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd: cousins, great-grandparents, great-aunts/uncles, great-nieces/nephews, great-grandchildren.
Affected relatives should be on the same side of the family to meet the criteria.

Checklist for Colorectal and Endometrial Cancer Genetic Assessment

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with any hereditary cancer predisposition (*e.g., MLH1, MSH2, MSH6, PMS2, EPCAM, MUTYH, APC*)
☐	Individual who previously tested negative with limited analysis testing (*e.g.,* Lynch syndrome only testing)
☐	Mismatch repair deficiency detected by tumor profiling (MSI-high or loss of expression on IHC), or potential germline variant detected on tumor-based genomic testing
☐	Individuals with colorectal, endometrial or other Lynch syndrome (LS)-related cancer**: ☐ Diagnosed before age 50 ☐ Another LS-related cancer** (*including a second colorectal cancer)* ☐ **One** or more first- or second-degree relatives* with a LS-related cancer** before age 50 ☐ **Two** or more first- or second-degree relatives* with LS-related cancers** at any age
☐	Individuals with polyps: ☐ 10 or more adenomas ☐ Two or more hamartomas ☐ Five or more serrated polyps, proximal to the rectum, with two or more being 1 cm or greater *(cumulative count over lifetime, includes hyperplastic polyps)* ☐ 20 or more serrated polyps of any size *(cumulative count over lifetime, includes hyperplastic polyps)* ☐ Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE) ☐ Desmoid tumor ☐ Osteoma or supernumerary teeth ☐ Hepatoblastoma ☐ Papillary thyroid cancer, cribiform-morular variant
☐	Individuals with family history of polyposis and affected family member unwilling/unable to have testing
☐	Individuals with a family history of: ☐ **One** or more first-degree relative(s)* with: ○ Colorectal or endometrial cancer before age 50, or ○ Colorectal or endometrial cancer at any age AND another LS-related cancer** ☐ **Two** or more first- or second-degree relatives* with LS-related cancer** with one or more diagnosed before age 50 ☐ **Three** or more first- or second-degree relatives* with LS-related cancer**, any age

*First-, second-, and third-degree relative(s) on the same side of the family. 1st= parents, siblings, children; 2nd= grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd= first cousins, great-grandparents, great-aunts, great-uncles, great-nieces, great-nephews, great-grandchildren.
Affected relatives should be on the same side of the family to meet the criteria.
**LS-associated tumors= colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, small intestine, and sebaceous adenoma, carcinoma or keratoacanthoma

Checklist for Hereditary Melanoma Genetic Assessment

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g., BAP1, BRCA1, BRCA2, CDKN2A,* etc)
☐	Individual who previously tested negative with limited analysis testing (*e.g., BRCA1/2* only testing)
☐	Potential germline variant detected on tumor-based genomic testing
☐	**Three** or more invasive cutaneous melanomas (in an individual or family)
☐	A mix of **three** of the following in an individual or family: ☐ Invasive melanoma ☐ Pancreatic cancer ☐ Astrocytoma
☐	Although formal guidelines do not exist, *BAP1* tumor predisposition syndrome (*BAP1*-TPDS) should be suspected if the individual has two or more *BAP1*-TPDS associated tumors[1], with the exception of two basal cell cancers and/or cutaneous melanomas[2] [1] In descending order of likelihood, *BAP1*-TPDS associated tumors include: *BAP1*-inactivated melanocytic tumor (i.e., atypical Spitz tumor), uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell cancer, basal cell cancer, hepatocellular carcinoma, cholangiocarcinoma and meningioma. [2] GeneReviews website, accessed 1/16/24

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd: cousins, great-grandparents, great-aunts/uncles, great-nieces/nephews, great-grandchildren. Affected relatives should be on the same side of the family to meet the criteria.

Checklist for Renal Cancer Genetic Assessment

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g., BAP1, FH, FLCN, VHL,* etc.)
☐	Individual who previously tested negative with limited analysis testing
☐	Potential germline variant detected on tumor-based genomic testing
☐	Individual with kidney cancer with any of the following: ☐ Diagnosed at 46 or younger ☐ Bilateral or multifocal tumors at any age ☐ Has **one** or more first or second degree* relative with kidney cancer
☐	Individual whose tumors have the following features: ☐ Multifocal papillary histology ☐ Type 2 papillary kidney cancer with fumarate hydratase (FH) deficiency (*suspicion for Hereditary Leiomyomatosis and Renal Cell Carcinoma- see NCCN for full criteria*) ☐ Multiple chromophobe, onocytoma, or oncocytic hybrid (*suspicion for Birt-Hogg-Dube- see NCCN for full criteria*) ☐ Angiolipomas of the kidney*** (*suspicion for tuberous sclerosis complex (TSC)- see NCCN for full criteria*) ☐ Succinate dehydrogenase (SDH) deficiency (*suspicion for Hereditary Pheochromocytoma and Paraganglioma Syndrome- see NCCN for full criteria*)
☐	Family history of **two** or more first or second degree* relatives with kidney cancer
☐	Family history of one first degree relative with kidney cancer meeting criteria above and family member is unwilling/unable to have testing

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd: cousins, great-grandparents, great-aunts/uncles, great-nieces/nephews, great-grandchildren.
Affected relatives should be on the same side of the family to meet the criteria.
***Referral to MMP Pediatric Specialty Care – Genetics (Pediatric and Adult Genetics)

Checklist for Gastric Cancer Genetic Assessment

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g., APC, CDH1, MLH1, MSH2,* etc.)
☐	Individual who previously tested negative with limited analysis testing
☐	Potential germline variant detected on tumor-based genomic testing
☐	Gastric cancer before age 50
☐	Gastric cancer at any age AND: ☐ **Two** or more first- or second-degree relatives* with gastric cancer ☐ **One** or more relatives with gastric cancer; one confirmed diffuse gastric cancer ☐ Family history of breast cancer in a first-or second-degree relative diagnosed before age 50 ☐ Family history of juvenile polyps or gastrointestinal polyposis ☐ Family history of cancers associated with Lynch syndrome (LS)**
☐	Gastric cancer and breast cancer in individual, with one diagnosed before age 50
☐	Family history of gastric cancer: ☐ In a first- or second-degree relative diagnosed before age 40 ☐ In two first- or second-degree relatives with one diagnosis before age 50 ☐ In three first- or second-degree relatives regardless of age ☐ And breast cancer in the same relative, with one diagnosis before age 50 ☐ And a relative with juvenile polyps or gastrointestinal polyposis

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd: cousins, great-grandparents, great-aunts/uncles, great-nieces/nephews, great-grandchildren. Affected relatives should be on the same side of the family to meet the criteria.

**LS-associated tumors= colorectal, endometrial, gastric, ovarian, pancreas, urothelial, brain (usually glioblastoma), biliary tract, small intestine, and sebaceous adenoma, carcinoma or keratoacanthoma

Checklist for Neuro-oncology Cancer Genetic Assessment

Consider genetic assessment (to include consideration of genetic testing) for any patient who meets one or more of the following criteria:

✔ if present	Criteria
☐	A family member* with any germline pathogenic/likely pathogenic variant in a gene associated with hereditary cancer predisposition (*e.g.*, *NF2, PTCH1, PTEN, TP53,* etc.)
☐	Individual who previously tested negative with limited analysis testing
☐	Potential germline variant detected on tumor-based genomic testing
☐	Individuals with the following tumor types related to risk: ☐ Adrenocortical carcinoma ☐ Choroid plexus carcinoma ☐ Rhabdomyosarcoma of embryonal anaplastic subtype *** ☐ Adult Lhermitte Duclos disease (dysplastic gangliocytoma of the cerebellum) ☐ CNS or retinal hemangioblastoma ☐ Multiple cortical tubers and/or radial migration lines *** ☐ Subependymal giant cell astrocytoma (SEGA) and/or two or more subependymal nodules *** ☐ Optic pathway glioma *** ☐ Bilateral vestibular schwannoma/acoustic neuroma or unilateral vestibular schwannoma/acoustic neuroma with other NF2 features
☐	Individuals with a medulloblastoma or glioblastoma **AND** colorectal cancer or multiple colorectal adenomas *(suspicion for Familial Adenomatous Polyposis or Lynch syndrome-see NCCN for full criteria)*
☐	Individuals with a medulloblastoma and: ☐ Multiple nevoid basal cell carcinomas (more than 5 lifetime or a BCC before age 30 y), jaw keratocysts, congenital skeletal abnormalities *(suspicion for Gorlin syndrome)*
☐	Individuals with a brain tumor diagnosed under age 50, or brain tumor diagnosed at any age **AND** a personal or family history of any **two** of the following cancers: ☐ Colon, endometrial, ovarian, pancreatic, urothelial, biliary tract, and small intestine *(suspicion for Lynch syndrome-see NCCN for full criteria)*
☐	Individual with personal and/or family history of a mix of the following tumor types: astrocytoma, melanoma or pancreas cancer *(suspicion for Familial Atypical Multiple Mole Melanoma Syndrome - see NCCN for criteria)*
☐	**Two** or more relatives with: ☐ Brain tumor, breast cancer, sarcoma, adrenocortical carcinoma, and/or leukemia *(suspicion for Li-Fraumeni syndrome—see NCCN for full criteria)*

*1st: parents, siblings, children; 2nd: grandparents, aunts, uncles, nieces, nephews, half-siblings, grandchildren; 3rd: cousins, great-grandparents, great-aunts/uncles, great-nieces/nephews, great-grandchildren.

Affected relatives should be on the same side of the family to meet the criteria.

***Referral to MMP Pediatric Specialty Care – Genetics (Pediatric and Adult Genetics)