MaineHealth CANCER CARE NETWORK SUPPORTED BY THE HAROLD ALFOND FOUNDATION	Indications for Cancer Genetics Referral	
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	Cancer Risk and Prevention Clinic	

INDICATIONS FOR CANCER GENETICS REFERRAL[1]

BREAST CANCER

Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- An individual at any age with a known *BRCA1* or *BRCA2* pathogenic/likely pathogenic variant in the family
- An individual diagnosed at any age with any of the following:
  - Ovarian, fallopian tube or primary peritoneal cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - Breast cancer or high-grade (Gleason score ≥ 7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer at or before age 50
  - Triple negative breast cancer at or before age 60
  - Two breast cancer primaries
  - Breast cancer at any age and (any of below)
    - One or more relatives*with:
      - breast cancer at or before age 50
      - ovarian cancer
      - male breast cancer
      - pancreatic cancer
      - high-grade (Gleason score ≥7) or metastatic prostate cancer
    - Two or more relatives* with breast cancer at any age
- An individual who does not meet the above criteria but has a first-or second-degree relative with any of the following:
  - Breast cancer at or before age 45
  - Ovarian cancer
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer
  - 2 or more breast cancer primaries in a single individual
  - 2 or more individuals with breast cancer primaries on the same side of family with at least one diagnosed at or before age 50
- Breast cancer at any age with limited family history**

*First-, second-, and third-degree relative(s) on the same side of the family

**Such as fewer than 2 first- or second-degree female relatives or female relatives not surviving beyond 45 years in either lineage

Li-Fraumeni Syndrome (LFS)

- Confirmed *TP53* pathogenic/likely pathogenic variant in family
- Breast cancer before age 31
- Individual diagnosed with an LFS-associated cancer (breast, CNS, osteogenic sarcoma, soft tissue sarcoma, adrenocortical cancer) before age 46 & relative with LFS-associated cancer (other than breast cancer if proband has breast cancer) before age 56 or with multiple primary tumors at any age
- Individual with multiple tumors (except multiple breast tumors), two of which are LFS-associated cancers, with the initial cancer before age 46
- Individual with adrenocortical carcinoma, choroid plexus carcinoma, rhabdomyosarcoma of embryonal or anaplastic subtype at any age
- Individuals with an LFS-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years in either lineage

Cowden Syndrome

- Confirmed *PTEN* pathogenic/likely pathogenic variant in family
- Breast cancer in individual & one of the following in individual:
  - Endometrial cancer

  - Non-medullary thyroid cancer

- Breast cancer in individual & family history of the cancers listed below*
- Individuals with a Cowden syndrome-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years in either lineage

*Major criteria for Cowden syndrome include: breast cancer, endometrial cancer, follicular thyroid cancer, multiple GI hamartomas/ganglioneuromas, macrocephaly (58 cm in adult women/60 cm in adult men), macular pigmentation of glans penis, and benign skin growths (facial and mucosal). Minor criteria for Cowden Syndrome include: autism spectrum disorder, colon cancer, esophageal glycogenic acanthosis (at least 3), lipomas, mental handicap, papillary/follicular variant of papillary thyroid cancer, thyroid lesions (i.e. adenoma, nodules, goiter), renal cell carcinoma, single GI hamartoma/ganglioneuroma, testicular lipomatosis, vascular anomalies (including multiple intracranial developmental venous anomalies)

COLORECTAL CANCER

HNPCC/Lynch Syndrome

- Confirmed *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* pathogenic/likely pathogenic variant in family
- Colorectal cancer before age 50
- Endometrial cancer before age 50
- Colorectal or endometrial cancer at any age & first-degree or second-degree relative with an HNPCC-associated cancer* diagnosed before age 50
- Colorectal or endometrial cancer at any age & 2 or more first-degree or second-degree relatives with HNPCC-associated cancers* regardless of age
- 2 or more HNPCC-associated cancers* in individual
- MSI-H and/or IHC for mismatch repair proteins (MLH1, MSH2, MSH6, or PMS2) demonstrating absence of one or more proteins in tumor
- Unaffected individual with a first-degree or second-degree relative meeting any of the above criteria
- Individuals with an HNPCC-associated cancer* that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years in either lineage

* colorectal, endometrial, stomach, ovary, small bowel, pancreas, ureter or renal pelvis, biliary tract, brain (glioblastoma) as seen in HNPCC syndrome variant (Turcot syndrome), sebaceous gland adenomas and keratoacanthomas as seen in HNPCC syndrome variant (Muir-Torre syndrome). Evidence supports consideration of prostate cancer as part of Lynch syndrome. *Cancer Epidemiol Biomarkers Prev; 23(3); 437–49. ©2014 AACR.*

Polyposis Syndromes

- Confirmed polyposis-related pathogenic/likely pathogenic variant in family
- > 10 adenomas
- ≥ 2 hamartomatous polyps
- ≥ 5 serrated polyps proximal to sigmoid

MUTYH Associated Polyposis (also relevant to Serrated Polyposis Syndrome)

- Confirmed *MUTYH* pathogenic/likely pathogenic variant in family
- > 10 adenomas
- At least five serrated polyps proximal to the sigmoid colon with two or more of these larger than 10mm, with at least some adenomas
- More than 20 serrated polyps of any size throughout the colon with some adenomas

OTHER

Prostate Cancer (from J Clin Oncol. 2018 Feb 1; 36(4):414-424)

- Confirmed prostate cancer-associated pathogenic/likely pathogenic variant in family
- Personal history of prostate cancer at any age with families meeting established testing or syndromic criteria for the following*:
    - Hereditary breast and ovarian cancer syndrome
    - Lynch syndrome
- Personal history of prostate cancer with at least two relatives on the same side of the family with a cancer associated with the following syndromes:
    - Hereditary breast and ovarian cancer syndrome (i.e., breast, ovary, pancreas, prostate, melanoma)
    - Hereditary prostate cancer (i.e., prostate)
    - Lynch syndrome (i.e., colorectal, uterus, upper GI tract, ovary, pancreas, upper urinary tract, sebaceous adenoma)
- Personal history of prostate cancer with tumor genomic analysis showing mutations in cancer-risk genes, in the absence of previous germline testing
- Personal history of metastatic castration-resistant prostate cancer

*See associated *Indications for Cancer Genetics Referral* Breast Cancer and Colorectal Cancer sections

Hereditary Melanoma (from GenoMEL.org)

- Confirmed melanoma-associated pathogenic/likely pathogenic variant in family
- 2 first-degree relatives with melanoma
- 2 cases (even if more distant relatives) if one or more have had multiple primaries or the cases have atypical mole syndrome (dysplastic nevi)
- 3 or more cases of melanoma in the family

Renal Cancer (from Can Urol Assoc J. 2013;7(9-10):319-23)

- Confirmed renal cancer-associated pathogenic/likely pathogenic variant in family
- Confirmed clinical diagnosis in family of any of the following:
    - Von Hippel Lindau syndrome
    - Birt-Hogg-Dube syndrome
    - Hereditary leiomyomatosis and renal cell cancer
    - Hereditary papillary renal cell cancer
    - Hereditary paraganglioma/pheochromocytoma
    - Tuberous sclerosis
- Individuals with a personal history of any renal tumor (benign or malignant) with one of the following:
    - Bilateral or multifocal tumors
    - Diagnosed before age 46
    - 1 or more first- or second-degree relatives with any renal tumor, regardless of age
    - Personal history or first-degree relative with a history of one of the following:
        - Pneumothorax

        - Skin leiomyomas
        - Skin fibrofolliculomas/trichodisomas
        - Pheochromocytoma/paraganglioma
        - Hemangioblastoma of the retina, brainstem, cerebellum, or spinal cord
        - Multiple uterine fibroids before age 30
        - Lymphangiomyomatosis
        - Childhood seizure disorder
        - Endolymphatic sac tumor*
    - Individuals with non-clear cell histologies including chromophobe, oncocytic, papillary types 1 and 2*, or hybrid tumors

*from ACMG/NSGC Practice Guideline (Hampel et al. 2015)

Neuro-oncology

- Confirmed CNS cancer-associated pathogenic/likely pathogenic variant in family
- Individual with primary brain/neuroaxis tumor and one FDR with primary brain/neuroaxis tumor
- Two or more CNS or retinal hemangioblastomas
- Single CNS or retinal hemangioblastomas and personal or family history of renal, hepatic, or pancreatic cysts; pheochromocytoma; renal cell carcinoma; endolymphatic sac tumor; cystadenoma of the epididymis/broad ligament; or neuroendocrine tumor of the pancreas
- Bilateral vestibular schwannoma/acoustic neuroma
- Unilateral vestibular schwannoma/acoustic neuroma with personal or family history of meningioma, schwannoma, glioma, neurofibroma, or juvenile posterior subcapsular lens opacity

Hereditary Diffuse Gastric Cancer (HDGC) (GeneReviews)

- Confirmed *CDH1* pathogenic/likely pathogenic variant in family
- An individual with diffuse gastric cancer before 40 years of age
- An individual with gastric cancer and one or more relatives with gastric cancer; one confirmed diffuse gastric cancer
- Personal and/or family history of diffuse gastric cancer and lobular breast cancer, one diagnosed before age 50
- An individual with diffuse gastric cancer and a family history of two first- or second-degree relatives with diffuse gastric cancer or lobular breast cancer
- An individual with diffuse gastric cancer and a personal or family history of cleft lip/palate
- An individual with diffuse gastric cancer and pathologically confirmed in situ signet ring cells and/or pagetoid spread of signet ring cells adjacent to diffuse gastric cancer
- Individuals with an HDGC-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years in either lineage

Consider cancer genetics referral if:

- 3 relatives on the same side of the family with similar or related cancers
- Individual or a family member had 2 or more different cancers

- Individual or a family member had a cancer typically occurring in adulthood at a younger age than expected (often less than age 50)
- Non-cancerous findings suggesting a recognized genetic condition (i.e., multiple colon polyps)
- A known cancer-related mutation in family
- Rare cancer (i.e., medullary thyroid cancer)
- Potential germline variant detected on tumor-based genomic testing (see http://www.acmg.net/docs/ACMGSFv202016UpdateGIMFeb2017.pdf)

[1]These referral guidelines are designed as simplified tools to assist in the clinic-based evaluation of patients and families. They do not reflect all high-risk criteria. For questions regarding individual patients or families, contact staff of the Cancer Risk and Prevention Clinic at 207-396-7788.