# A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

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Cancer genetic consultation is an important aspect of the care of individuals at increased risk of a hereditary cancer syndrome. Yet several patient, clinician, and system-level barriers hinder identification of individuals appropriate for cancer genetics referral. Thus, the purpose of this practice guideline is to present a single set of comprehensive personal and family history criteria to facilitate identification and maximize appropriate referral of at-risk individuals for cancer genetic consultation. To develop this guideline, a literature search for hereditary cancer susceptibility syndromes was conducted using PubMed. In addition, GeneReviews and the National Comprehensive Cancer Network guidelines were reviewed when applicable. When conflicting guidelines were identified, the evidence was ranked as follows: position papers from national and professional organizations ranked highest, followed by consortium guidelines, and then peer-reviewed publications from single institutions. The criteria for cancer genetic consultation referral are provided in two formats: (i) tables that list the tumor type along with the criteria that, if met, would warrant a referral for a cancer genetic consultation and (ii) an alphabetical list of the syndromes, including a brief summary of each and the rationale for the referral criteria that were selected. Consider referral for a cancer genetic consultation if your patient or any of their first-degree relatives meet any of these referral criteria.

*Genet Med* advance online publication 13 November 2014

**Key Words:** cancer genetics; cancer predisposition; genetic counseling; referral guidelines; referral indications

Cancer genetic consultation services include the evaluation of patients' personal and family history for concerning features of hereditary cancer predisposition syndromes, development of a differential diagnosis for one or more possible hereditary cancer syndromes, genetic testing if indicated and available, recommendations for management, cancer surveillance and prevention, and information regarding genetic counseling and genetic testing for at-risk relatives. This counseling is informed by the genetic

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Submitted 12 September 2014; accepted 12 September 2014; advance online publication 13 November 2014. doi:10.1038/gim.2014.147

risk assessment or diagnosis, which typically includes personal and family history, genetic and other laboratory results, results from procedures and imaging studies, and physical examination findings. Genetic counseling is an important component of the genetic consultation; it entails a discussion about the clinical and genetic aspects of a suspected diagnosis—including the mode of inheritance, identification of family members at risk, and discussion of the benefits, risks, and limitations of genetic testing and the alternative to not test—and helps patients make informed decisions about genetic testing considering their health-care needs, preferences, and values. Genetic testing performed without pre- and posttest genetic counseling by qualified clinicians has been associated with negative patient and societal outcomes such as misinterpretation of genetic test results, inappropriate medical management, lack of informed decision making, violation of established ethical standards, adverse psychosocial outcomes, and costly, unnecessary genetic testing.[1–3]

Cancer genetic consultation is an important aspect of the care of individuals at increased risk of a hereditary cancer syndrome.[4–8] Yet, several patient, clinician, and system-level barriers hinder the identification of individuals appropriate for cancer genetics referral. In addition to limited time for the clinician to collect family history necessary to trigger a referral[9–11] and limited patient awareness of their family cancer history,[12] identifying appropriate patients is complicated by an abundance of complex criteria and guidelines that often differ from each other.[13] Thus, the purpose of this practice guideline is to present a single set of comprehensive personal and family history criteria to facilitate identification and maximize appropriate referral of at-risk individuals for cancer genetic consultation. The criteria in this guidance statement are not designed to dictate what, if any, genetic testing is indicated or to recommend any specific cancer screening or treatment management.

Health-care providers have been encouraged to take a thorough family history from their patients and to refer them to genetic providers if the history is suspicious for a hereditary condition. Determining whom to refer is difficult for clinicians who do not specialize in cancer genetics, who may rarely encounter these syndromes, and who may not be familiar with the types of cancers known to be associated with a particular syndrome. These referral guidelines were developed in a table format so that the health-care provider can simply look up the cancer(s) that have been reported in a family and determine whether the personal or family history meets any of the criteria that warrant a referral. We include a short summary of each syndrome that explains the rationale behind the referral criteria in the Recommendations section of this guideline.

## MATERIALS AND METHODS

To develop this guideline, a literature search for each of the hereditary cancer susceptibility syndromes described below was conducted using PubMed. In addition, GeneReviews (http://www.genereviews.org) and the National Comprehensive Cancer Network guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp) were reviewed when applicable. The searches were conducted between 1 December 2012 and 20 June 2013 and included the following search terms: *hereditary cancer syndromes*, *referral criteria*, *guidelines*, *testing*, *mutation likelihood*, and each syndrome's specific name. When conflicting guidelines were identified, the following processes were used to select the referral criteria for inclusion in this practice guideline. We ranked the sources of the differing guidelines. Position papers from national and professional organizations ranked highest, followed by consortium guidelines and then peer-reviewed publications from single institutions. When guidelines from national and professional organizations differed, an attempt was made to select the least restrictive (i.e., most inclusive) set of referral criteria, as long as we felt it would not result in too many inappropriate referrals. For example, the National Comprehensive Cancer Network offers both evaluation criteria and genetic testing criteria for hereditary breast–ovarian cancer syndrome. We believe that the evaluation guidelines would result in an unmanageable number of referrals with little yield to patients and therefore chose the National Comprehensive Cancer Network genetic testing recommendations.

## RECOMMENDATIONS

The criteria for cancer genetic consultation referral are detailed in **Tables 1** and **2**. **Table 1** includes an alphabetical list of common cancers along with the criteria that, if met, would warrant a referral for a cancer genetic consultation. **Table 2** includes the same information based on an alphabetical list of rare cancers. Referring to the tables in the clinic when a cancer is noted in a family history may be helpful to quickly determine whether a referral is indicated. If the family or individual meets the referral guideline for a particular syndrome, a brief summary of the syndrome and the rationale for the referral criteria can be found listed alphabetically in the text below. More detailed information about these syndromes can be found elsewhere.[14]

Consider referral for a cancer genetic consultation if your patients or any of their first-degree relatives meet any of these criteria. All affected relatives must be on the same side of the family. For the purposes of these guidelines, close relatives include first-degree relatives such as parents, siblings, and children, and second-degree relatives such as aunts, uncles, nieces, nephews, grandparents, and grandchildren. Please note that all the syndromes described in this guideline are inherited in an autosomal dominant manner, except where otherwise noted. Finally, any individual in a family with a known mutation in a cancer susceptibility gene should be referred for cancer genetic consultation.

### Birt–Hogg–Dubé syndrome (OMIM 135150)

Birt–Hogg–Dubé syndrome is caused by mutations in the *FLCN* gene and is characterized by the presence of classic skin lesions (fibrofolliculomas, perifollicular fibromas, trichodiscomas or angiofibromas, and acrochordons), bilateral and multifocal renal tumors (chromophobe clear cell renal carcinoma, renal oncocytoma, oncocytic hybrid tumor, and less often, clear cell renal carcinoma), and multiple bilateral lung cysts often associated with spontaneous pneumothorax.[15]

**Table 1** Common benign and malignant tumors and the criteria that warrant assessment for cancer predisposition

| Cancer/feature (patient or FDR) | When to refer to genetic counseling | Syndrome(s) to consider |
|---|---|---|
| BCC | • >5 cumulative BCCs or BCC dx at age <30 and one additional NBCCS criterion (Table 7) in the same person | NBCCS, OMIM 109400 |
| Brain | • Brain tumor dx at age <18 if any of the following criteria are met:<br>–Café-au-lait macules and/or other signs of NF1, or hypopigmented skin lesions<br>–Consanguineous parents<br>–Family history of LS-associated cancer<br>–Second primary cancer<br>–Sibling with a childhood cancer | CMMRD,OMIM 276300 |
| | • Brain tumor and two additional cases of any LS-associated cancer (Table 6) in the same person or in relatives | LS, OMIM 120435, 120436 |
| | • Brain tumor and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45 | LFS, OMIM 151623 |
| | • Astrocytoma and melanoma in the same person or in two FDRs | MAS, OMIM 155755 |
| | • Subependymal giant cell astrocytoma and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| | • Medulloblastoma and ≥10 cumulative adenomatous colon polyps in the same person | FAP, OMIM 175100 |
| | • Medulloblastoma (PNET) dx at age <18 and one additional NBCCS criterion (Table 7) in the same person | NBCCS, OMIM 109400 |
| Breast cancer, female | • Breast cancer dx at age ≤50 | HBOC, OMIM: 604370, 612555; LFS, OMIM 151623 |
| | • Triple-negative breast cancer dx at age ≤60 | |
| | • ≥2 primary breast cancers in the same person | |
| | • Ashkenazi Jewish ancestry and breast cancer at any age | |
| | • ≥3 cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer in close relatives, including the patient | |
| | • Breast cancer and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45 | |
| | • Breast cancer and ≥1 PJ polyp in the same person | PJS, OMIM 175200 |
| | • Lobular breast cancer and diffuse gastric cancer in the same person | HDGC, OMIM 137215 |
| | • Lobular breast cancer in one relative and diffuse gastric cancer in another, one dx at age <50 | |
| | • Breast cancer and two additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| Breast cancer, male | • Single case present | HBOC, OMIM: 604370, 612555 |
| Colorectal cancer | • Colorectal cancer dx at age <50 | LS, OMIM 120435, 120436; CMMRD, OMIM 276300; MAP, OMIM 608456 |
| | • Colorectal cancer dx at age ≥50 if there is a FDR with colorectal or endometrial cancer at any age | |
| | • Synchronous or metachronous colorectal or endometrial cancers in the same person | |
| | • Colorectal cancer showing mismatch repair deficiency on tumor screening | |
| | • Colorectal cancer and two additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives | |
| | • Colorectal cancer and two additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Colorectal cancer and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45 | LFS, OMIM 151623 |
| | • Colorectal cancer with ≥10 cumulative adenomatous colon polyps in the same person | FAP, OMIM 175100; MAP, OMIM 608456 |

Refer for a cancer predisposition assessment if your patients or any of their first-degree relatives (FDRs) meet any of the criteria. All affected relatives must be on the same side of the family. For the purposes of these guidelines, close relatives include the patient's parents, siblings, children, aunts, uncles, nieces, nephews, grandparents, and grandchildren.

BCC, basal cell carcinoma; BHD, Birt–Hogg–Dubé syndrome; CMMRD, constitutional mismatch repair deficiency; dx, diagnosed; FAP, familial adenomatous polyposis; FP, familial prostate cancer; FPC, familial pancreatic cancer; GI, gastrointestinal; HBOC, hereditary breast–ovarian cancer syndrome; HDGC, hereditary diffuse gastric cancer; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HM, familial atypical mole and malignant melanoma; HMPS, hereditary mixed polyposis syndrome; HPRC, hereditary papillary renal cancer; JPS, juvenile polyposis syndrome; LFS, Li–Fraumeni syndrome; LS, Lynch syndrome; MAP, *MUTYH*-associated polyposis; MAS, melanoma astrocytoma syndrome; MEN2, multiple endocrine neoplasia type 2; NBCCS, nevoid basal cell carcinoma syndrome; NF1, neurofibromatosis type 1; PJ, Peutz–Jeghers; PJS, Peutz–Jeghers syndrome; RCC, renal cell carcinoma; SP, serrated polyp, which includes hyperplastic polyps, sessile serrated polyps/adenomas, and traditional serrated polyps; SPS, serrated polyposis syndrome; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau syndrome.

**Table 1** Continued on next page

**Table 1** Continued

| Cancer/feature (patient or FDR) | When to refer to genetic counseling | Syndrome(s) to consider |
|---|---|---|
| Colorectal polyposis, adenomatous | • ≥ 10 cumulative adenomatous colon polyps in the same person | FAP, OMIM 175100; MAP, OMIM 608456 |
| Colorectal polyposis, hamartomatous | • 3–5 cumulative histologically proven juvenile polyps in the same person | JPS, OMIM 174900 |
| | • Multiple juvenile polyps throughout the GI tract in the same person | |
| | • Any number of juvenile polyps with a positive family history of JPS | |
| | • ≥2 cumulative histologically proven PJ polyps in the same person | PJS, OMIM 175200 |
| | • ≥1 PJ polyp and mucocutaneous hyperpigmentation in the same person | |
| | • Any number of PJ polyps and a positive family history of PJS | |
| | • GI hamartoma or ganglioneuroma and two additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Rectal hamartomatous polyps and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| | • Diffuse ganglioneuromatosis of the GI tract | MEN2, OMIM 171400 |
| Colorectal polyposis, serrated | • ≥5 SPs proximal to the sigmoid colon, two of which are >1 cm in diameter, in the same person | SPS, not in OMIM |
| | • >20 SPs at any site in the large bowel in the same person | |
| | • Any number of SPs proximal to the sigmoid colon and a positive family history of SPS | |
| Colorectal polyposis, mixed | • ≥ 10 cumulative polyps with >1 histology in the same person | HMPS, OMIM 201228, 610069 |
| Endometrial cancer | • Endometrial cancer dx at age <50 | LS, OMIM 120435, 120436 |
| | • Endometrial cancer dx at age ≥50 if there is a FDR with colorectal or endometrial cancer at any age | |
| | • Synchronous or metachronous colorectal or endometrial cancer in the same person | |
| | Endometrial cancer showing mismatch repair deficiency on tumor screening | |
| | • Endometrial cancer and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives | |
| | • Epithelial endometrial cancer and two additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| Gastric cancer | • ≥2 cases of gastric cancer, one dx at age <50 in close relatives | HDGC, OMIM 137215 |
| | • ≥3 cases of gastric cancer in close relatives | |
| | • Diffuse gastric cancer dx at age <40 | |
| | • Diffuse gastric cancer and lobular breast cancer in the same person | |
| | • Diffuse gastric cancer in one relative and lobular breast cancer in another, one dx at age <50 | |
| | • Gastric cancer and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives | LS, OMIM 120435, 120436 |
| Leukemia | • Leukemia dx at age <18, if any of the following criteria are met: | CMMRD, OMIM 276300 |
| | –Café-au-lait macules and/or other signs of NF1, or hypopigmented skin lesions | |
| | –Consanguineous parents | |
| | –Family history of LS-associated cancers | |
| | –Second primary cancer | |
| | –Sibling with a childhood cancer | |
| | • Leukemia and one additional LFS tumor (Table 5) in the same person or in 2 close relatives, one dx at age ≤45 | LFS, OMIM 151623 |

Refer for a cancer predisposition assessment if your patients or any of their first-degree relatives (FDRs) meet any of the criteria. All affected relatives must be on the same side of the family. For the purposes of these guidelines, close relatives include the patient's parents, siblings, children, aunts, uncles, nieces, nephews, grandparents, and grandchildren.

BCC, basal cell carcinoma; BHD, Birt–Hogg–Dubé syndrome; CMMRD, constitutional mismatch repair deficiency; dx, diagnosed; FAP, familial adenomatous polyposis; FP, familial prostate cancer; FPC, familial pancreatic cancer; GI, gastrointestinal; HBOC, hereditary breast–ovarian cancer syndrome; HDGC, hereditary diffuse gastric cancer; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HM, familial atypical mole and malignant melanoma; HMPS, hereditary mixed polyposis syndrome; HPRC, hereditary papillary renal cancer; JPS, juvenile polyposis syndrome; LFS, Li–Fraumeni syndrome; LS, Lynch syndrome; MAP, *MUTYH*-associated polyposis; MAS, melanoma astrocytoma syndrome; MEN2, multiple endocrine neoplasia type 2; NBCCS, nevoid basal cell carcinoma syndrome; NF1, neurofibromatosis type 1; PJ, Peutz–Jeghers; PJS, Peutz–Jeghers syndrome; RCC, renal cell carcinoma; SP, serrated polyp, which includes hyperplastic polyps, sessile serrated polyps/adenomas, and traditional serrated polyps; SPS, serrated polyposis syndrome; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau syndrome.

**Table 1** Continued on next page

**Table 1** Continued

| Cancer/feature (patient or FDR) | When to refer to genetic counseling | Syndrome(s) to consider |
|---|---|---|
| Melanoma | • ≥3 cases of melanoma and/or pancreatic cancer in close relatives | HM, OMIM 155600; MAS, OMIM 155755 |
| | • ≥3 primary melanomas in the same person | |
| | • Melanoma and pancreatic cancer in the same person | |
| | • Melanoma and astrocytoma in the same person or in 2 FDRs | |
| Ovarian/Fallopian tube/ primary peritoneal cancer | • Single case present in the patient or a FDR | HBOC, OMIM: 604370, 612555; LS, OMIM 120435, 120436 |
| Pancreatic cancer | • Pancreatic cancer dx at any age, if any of the following criteria are met: | HBOC, OMIM: 604370, 612555; FPC, OMIM 260350 |
| | –≥2 cases of pancreatic cancer in close relatives | |
| | –≥2 cases of breast, ovarian, and/or aggressive prostate cancer in close relatives | |
| | –Ashkenazi Jewish ancestry | |
| | • Pancreatic cancer and ≥1 PJ polyp in the same person | PJS, OMIM 175200 |
| | • Pancreatic cancer and two additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives | LS, OMIM 120435, 120436 |
| | • ≥3 cases of pancreatic cancer and/or melanoma in close relatives | HM, OMIM 155600 |
| | • Pancreatic cancer and melanoma in the same person | |
| Prostate cancer | • ≥2 cases of prostate cancer dx at age ≤55 in close relatives | FP, OMIM 176807, 601518, 602759, 300147, 603688, 608656, 153622 |
| | • ≥3 FDRs with prostate cancer | |
| | • Aggressive (Gleason score >7) prostate cancer and ≥2 cases of breast, ovarian, and/or pancreatic cancer in close relatives | HBOC, OMIM 604370, 612555 |
| Renal cancer | • RCC with clear cell histology, if any of the following criteria are met: | VHL, OMIM 193300; BHD, OMIM 135150 |
| | –dx at age <50 | |
| | –Bilateral or multifocal tumors | |
| | –≥1 close relative with clear cell RCC | |
| | • RCC with papillary type 1 histology | HPRC, OMIM 605074 |
| | • RCC with papillary type 2 histology | HLRCC, OMIM 605839, 150800 |
| | • RCC with collecting duct histology | HLRCC, OMIM 605839, 150800 |
| | • RCC with tubulopapillary histology | HLRCC, OMIM 605839, 150800 |
| | • RCC with BHD-related histology (chromophobe, oncocytoma, oncocytic hybrid) | BHD, OMIM 135150 |
| | • Urothelial carcinoma (or transitional cell carcinoma) and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in relatives | LS, OMIM 120435, 120436 |
| | • RCC and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Angiomyolipomas of the kidney and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Thyroid cancer | • Medullary thyroid cancer | MEN2, OMIM 171400, 155240, 162300 |
| | • Nonmedullary thyroid cancer and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| | • Nonmedullary thyroid cancer and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Papillary thyroid cancer (cribriform-morular variant) | FAP, OMIM 175100 |

Refer for a cancer predisposition assessment if your patients or any of their first-degree relatives (FDRs) meet any of the criteria. All affected relatives must be on the same side of the family. For the purposes of these guidelines, close relatives include the patient's parents, siblings, children, aunts, uncles, nieces, nephews, grandparents, and grandchildren.

BCC, basal cell carcinoma; BHD, Birt–Hogg–Dubé syndrome; CMMRD, constitutional mismatch repair deficiency; dx, diagnosed; FAP, familial adenomatous polyposis; FP, familial prostate cancer; FPC, familial pancreatic cancer; GI, gastrointestinal; HBOC, hereditary breast–ovarian cancer syndrome; HDGC, hereditary diffuse gastric cancer; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HM, familial atypical mole and malignant melanoma; HMPS, hereditary mixed polyposis syndrome; HPRC, hereditary papillary renal cancer; JPS, juvenile polyposis syndrome; LFS, Li–Fraumeni syndrome; LS, Lynch syndrome; MAP, *MUTYH*-associated polyposis; MAS, melanoma astrocytoma syndrome; MEN2, multiple endocrine neoplasia type 2; NBCCS, nevoid basal cell carcinoma syndrome; NF1, neurofibromatosis type 1; PJ, Peutz–Jeghers; PJS, Peutz–Jeghers syndrome; RCC, renal cell carcinoma; SP, serrated polyp, which includes hyperplastic polyps, sessile serrated polyps/adenomas, and traditional serrated polyps; SPS, serrated polyposis syndrome; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau syndrome.

Skin lesions typically occur in the 30s and 40s and increase with age. The median age at diagnosis of renal cell tumors is 48 years, with a range of 31–71 years.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) ≥5 Birt–Hogg–Dubé–associated facial or truncal papules; (ii) early-onset (<50

**Table 2** Rare benign and malignant tumors and the criteria that warrant assessment for cancer predisposition

| Cancer/feature (patient or FDR) | When to refer to genetic counseling | Syndrome(s) to consider |
|---|---|---|
| Adrenocortical tumor | • Single case present in the patient or a FDR | LFS, OMIM 151623 |
| Adrenal tumor | • Adrenal tumor and pancreatic neuroendocrine tumor, parathyroid adenoma, thymic or bronchial carcinoid tumor, or pituitary tumor in the same person | MEN1, OMIM 131100 |
| Brain | • Cortical tuber, subependymal nodule, or cerebral white matter "migration lines" and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| | • Choroid plexus carcinoma (single case present) in the patient or a FDR | LFS, OMIM 151623 |
| | • Lhermitte–Duclos (dysplastic gangliocytoma of the cerebellum) dx at age >18 | Cowden, OMIM 158350 |
| Breast | • Myxomatosis and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| | • Multiple ductal adenomas and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| Bone cysts | • Bone cysts and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Carcinoid tumor of foregut (e.g., thymic, bronchial) | • Foregut carcinoid tumor and parathyroid adenoma, pancreatic neuroendocrine tumor, anterior pituitary tumor, or adrenal tumor in the same person | MEN1, OMIM 131100 |
| Cardiac fibromas | • Cardiac fibroma and one additional NBCCS criterion (Table 7) in the same person | NBCCS, OMIM 109400 |
| Cardiac myxoma | • Cardiac myxoma and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| Cardiac rhabdomyoma | • Cardiac rhabdomyoma (especially prenatal/newborn) and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Cervix, adenoma malignum | • Single case present in the patient or a FDR | PJS, OMIM 175200 |
| Dental pitting | • Pitting in dental enamel and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Desmoid tumor | • Single case present in the patient or a FDR | FAP, OMIM 175100 |
| Endolymphatic sac tumor | • Single case present in the patient or a FDR | VHL, OMIM 193300 |
| Gastrinoma | • Single case present in the patient or a FDR | MEN1, OMIM 131100 |
| GIST | • ≥3 close relatives with GIST | Familial GIST, OMIM 606764 |
| | • Wild-type GIST | |
| | • ≥3 primary GISTs in the same person | |
| Hemangioblastoma (CNS or retinal) | • Single case present in the patient or a FDR | VHL, OMIM 193300 |
| Hepatoblastoma | • dx at age <5 | FAP, |
| Lung cysts | • Lung cysts leading to multiple pneumothoraces | BHD, OMIM; 135150 |
| Lymphangiomyomatosis | • Lymphangiomyomatosis and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Osteochondromyxoma | • Osteochondromyxoma and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| Ovarian fibromas | • Ovarian fibroma and one additional NBCCS criterion (Table 7) in the same person | NBCCS, OMIM 109400 |
| Ovarian sex cord tumor with annular tubules | • Single case present in the patient or a FDR | PJS, OMIM 175200 |
| Ovarian small cell carcinoma, hypercalcemic type | • Single case present in the patient or a FDR | RPS, OMIM 613325 |
| Pancreatic neuroendocrine tumor (e.g., gastrinoma, insulinoma, glucagonoma, VIPoma) | • Pancreatic neuroendocrine tumor and parathyroid adenoma, thymic or bronchial carcinoid tumor, pituitary tumor, or adrenal tumor in the same person | MEN1, OMIM 131100 |
| | • Multiple primary neuroendocrine tumors in the same person | |
| | • Gastrinoma in the patient or a FDR | |
| Parathyroid adenoma | • Parathyroid adenoma dx at age <30 | MEN1, OMIM 131100; MEN2, OMIM 171400, 155240, 162300 |
| | • Parathyroid adenoma with multiple glands involved | |
| | • Parathyroid adenoma and thymic or bronchial carcinoid, pancreatic neuroendocrine tumor, pituitary tumor, or adrenal tumor in the same person | |
| | • Parathyroid adenoma and a family history of hyperparathyroidism, pituitary adenoma, pancreatic islet cell tumor, or foregut carcinoid tumor | |

BHD, Birt–Hogg–Dubé syndrome; CNS, central nervous system; dx, diagnosed; FAP, familial adenomatous polyposis; FDR, first-degree relative; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HPPS, hereditary paraganglioma–pheochromocytoma syndrome; LFS, Li–Fraumeni syndrome; LS, Lynch syndrome; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; NBCCS, nevoid basal cell carcinoma syndrome; PJS, Peutz–Jeghers syndrome; PMS, psammomatous melanotic schwannoma; RB, retinoblastoma; RP, rhabdoid predisposition; RPS, rhabdoid predisposition syndrome; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau syndrome; VIP, vasoactive intestinal peptide.

**Table 2** Continued on next page

**Table 2** Continued

| Cancer/feature (patient or FDR) | When to refer to genetic counseling | Syndrome(s) to consider |
|---|---|---|
| Pheochromocytoma/ paraganglioma | • Single case present in the patient or a FDR | HPPS, OMIM 115310, 168000, 605373, 601650, 154950, 613403; VHL, OMIM 193300; MEN2, OMIM 171400, 155240, 162300 |
| Pituitary adenoma | • Pituitary adenoma and parathyroid adenoma, pancreatic neuroendocrine tumor, thymic or bronchial carcinoid, or adrenal tumor in the same person | MEN1, OMIM 131100 |
| | • Growth hormone–producing adenoma with acromegaly and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| Primary pigmented nodular adrenocortical dysplasia | • Single case present in the patient or a FDR | Carney, OMIM 160980 |
| Psammomatous melanotic schwannoma | • PMS and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| Renal cysts | • Renal cysts and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Retinal achromic patch | • Retinal achromic patch and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Retinal hamartoma | • Retinal hamartoma and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |
| Retinoblastoma | • Single case present in the patient or a FDR | Hereditary RB, OMIM 180200 |
| Rhabdoid tumors | • Single case present in the patient or a FDR | RP, OMIM 609322, 613325 |
| Sarcoma (non-Ewing sarcoma) | • Sarcoma and one additional LFS tumor (Table 5) in the same person or in 2 close relatives, one dx at age ≤45<br>• Sarcoma dx at age <18 | LFS, OMIM 151623 |
| Sertoli cell tumor | • Single case present in the patient or a FDR | PJS, OMIM 175200 |
| | • Large cell calcifying histology and one additional Carney complex criterion (Table 3) in the same person or a FDR | Carney, OMIM 160980 |
| Skin (rare) | • Spotty skin pigmentation on lips, conjunctiva and inner or outer canthi, and/or vaginal or penile mucosa, and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| | • Cutaneous or mucosal myxoma and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| | • Epithelioid blue nevus and one additional Carney complex criterion (Table 3) in the same person | Carney, OMIM 160980 |
| | • Trichilemmoma (≥3) and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Acral keratoses (≥3) and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Oral papillomas and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Oral or ocular neuromas (lip, tongue, eyelid, or sclera) | MEN2, OMIM 171400, 155240, 162300 |
| | • Mucocutaneous neuromas and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Macular pigmentation of glans penis and 2 additional Cowden syndrome criteria (Table 4) in the same person | Cowden, OMIM 158350 |
| | • Cutaneous leiomyoma | HLRCC, OMIM 605839, 150800 |
| | • Sebaceous adenoma/carcinoma and one additional case of any LS-associated cancer (Table 6) in the same person or in relatives | LS, OMIM 120435, 120436 |
| | • Palmar or plantar pitting and one additional NBCCS criterion (Table 7) in the same person | NBCCS, OMIM 109400 |
| | • Mucocutaneous pigmentation and ≥1 PJ polyp in the same person | PJS, OMIM 175200 |
| | • Fibrofolliculomas, perifollicular fibromas, trichodiscomas/angiofibromas, and acrochordons (≥5) | BHD, OMIM; 135150 |
| | • Hypomelanotic macules, shagreen patch, ungual fibromas, facial angiofibromas, gingival fibroma, or "confetti" skins lesions and one additional TSC criterion (Table 8) in the same person | TSC, OMIM 191100 |

BHD, Birt–Hogg–Dubé syndrome; CNS, central nervous system; dx, diagnosed; FAP, familial adenomatous polyposis; FDR, first-degree relative; GIST, gastrointestinal stromal tumor; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; HPPS, hereditary paraganglioma–pheochromocytoma syndrome; LFS, Li–Fraumeni syndrome; LS, Lynch syndrome; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; NBCCS, nevoid basal cell carcinoma syndrome; PJS, Peutz–Jeghers syndrome; PMS, psammomatous melanotic schwannoma; RB, retinoblastoma; RP, rhabdoid predisposition; RPS, rhabdoid predisposition syndrome; TSC, tuberous sclerosis complex; VHL, Von Hippel–Lindau syndrome; VIP, vasoactive intestinal peptide.

years old), bilateral or multifocal clear cell renal carcinoma; (iii) renal cancers with Birt–Hogg–Dubé histology (chromophobe, oncocytoma, or oncocytic hybrid); or (iv) lung cysts associated with multiple spontaneous pneumothoraxes.[16,17]

**Carney complex (OMIM 160980)**

Carney complex is caused by mutations in the *PRKAR1A* gene and is characterized by pale brown to black lentigenes; myxomas of the heart, skin, and breast; primary pigmented nodular adrenocortical disease; and large cell calcifying Sertoli cell tumors. Psammomatous melanotic schwannoma, a rare nerve sheath tumor, can also occur. At least 50% of individuals with isolated primary pigmented nodular adrenocortical disease have a *PRKAR1A* mutation.[18–20] Thus, isolated primary pigmented nodular adrenocortical disease is sufficient for referral to genetic consultation. *PRKAR1A* mutations are found in 71% of individuals with at least two major diagnostic criteria for Carney complex[18] (**Table 3**).

Referral should be considered for any individual with a personal history of or first-degree relative with (i) primary pigmented nodular adrenocortical disease or (ii) two or more diagnostic criteria[21] (**Table 3**).

**Constitutional mismatch repair deficiency (OMIM 276300)**

Constitutional mismatch repair deficiency is a recessive condition caused by biallelic mutations in the mismatch repair genes (*MLH1*, *MSH2* (including methylation due to an *EPCAM* deletion), *MSH6*, and *PMS2*) and is characterized by a high risk of developing cancers during childhood, including Lynch syndrome (LS)–associated cancers, hematologic malignancies, and embryonic tumors.[22] Individuals with constitutional mismatch repair deficiency have neurofibromatosis type 1–like features, with café-au-lait macules observed in most cases[23] and skinfold freckling, Lisch nodules, neurofibromas, and tibial pseudoarthosis reported in fewer cases. Individuals with constitutional mismatch repair deficiency do not always have a family history of cancer.

**Table 3** Carney complex criteria[21]

- Spotty skin pigmentation on lips, conjunctiva and inner or outer canthi, and/or vaginal or penile mucosa
- Myxoma (cutaneous and mucosal)
- Cardiac myxoma
- Breast myxomatosis or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
- Acromegaly due to growth hormone–producing adenoma
- Large cell calcifying Sertoli cell tumor or characteristic calcification on testicular ultrasonography
- Primary pigmented nodular adrenocortical dysplasia
- Thyroid carcinoma (nonmedullary) or multiple hypoechoic nodules on thyroid ultrasonography in a young patient
- Psammomatous melanotic schwannoma
- Blue nevus, epithelioid blue nevus (multiple)
- Breast ductal adenoma (multiple)
- Osteochondromyxoma

Referral should be considered for any individual with a personal history of or first-degree relative with (i) an LS-associated cancer in childhood or (ii) another type of childhood cancer *and* one or more of the following features: (i) café-au-lait macules, skinfold freckling, Lisch nodules, neurofibromas, tibial pseudoarthrosis, or hypopigmented skin lesions; (ii) family history of LS-associated cancer; (iii) a second primary cancer; (iv) a sibling with a childhood cancer; or (v) consanguineous parents.

**Cowden syndrome, also known as PTEN hamartoma tumor syndrome (OMIM 158350)**

Cowden syndrome is caused by mutations in the *PTEN* gene and is characterized by benign skin findings, increased lifetime risks for breast (30–85%; often early-onset), follicular thyroid (10–38%), renal cell (34%), endometrial (5–28%), and colorectal cancers (9%), and possibly melanoma (6%).[24–28] Clinical diagnostic criteria involve combinations of major and minor criteria[29] (**Table 4**). We recommend referral for anyone meeting any three criteria from the major or minor diagnostic criteria.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) Lhermitte–Duclos disease diagnosed after age 18 (ref. 30) or (ii) any three

**Table 4** Cowden syndrome criteria (National Comprehensive Cancer Network, 2013)

| Major criteria |
|---|
| • Breast cancer |
| • Endometrial cancer (epithelial) |
| • Thyroid cancer (follicular) |
| • Gastrointestinal hamartomas (including ganglioneuromas but excluding hyperplastic polyps; ≥3) |
| • Lhermitte–Duclos disease (adult) |
| • Macrocephaly (≥97th percentile: 58 cm for adult women, 60 cm for adult men) |
| • Macular pigmentation of the glans penis |
| • Multiple mucocutaneous lesions (any of the following): |
| –Multiple trichilemmomas (≥3, at least 1 proven by biopsy) |
| –Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) |
| –Mucocutaneous neuromas (≥3) |
| –Oral papillomas (particularly on tongue and gingival), multiple (≥3) OR biopsy proven OR dermatologist diagnosed |
| **Minor criteria** |
| • Autism spectrum disorder |
| • Colon cancer |
| • Esophageal glycogenic acanthosis (≥3) |
| • Lipomas (≥3) |
| • Intellectual disability (i.e., intelligence quotient ≤75) |
| • Renal cell carcinoma |
| • Testicular lipomatosis |
| • Thyroid cancer (papillary or follicular variant of papillary) |
| • Thyroid structural lesions (e.g., adenoma, multinodular goiter) |
| • Vascular anomalies (including multiple intracranial developmental venous anomalies) |

criteria from the major or minor diagnostic criteria list in the same person[31] (**Table 4**).

### Familial adenomatous polyposis and attenuated familial adenomatous polyposis (OMIM 175100)

Familial adenomatous polyposis (FAP) and attenuated FAP are caused by mutations in the *APC* gene and are characterized by adenomatous colon polyps and increased lifetime risk for colorectal cancer (nearly 100% for individuals with FAP and 70% for individuals with attenuated FAP).[32] A clinical diagnosis of classic FAP is made when an individual has >100 adenomatous polyps in his or her colon. Attenuated FAP is characterized by 30–100 adenomatous polyps. Individuals with FAP are also at increased risk for duodenal (4–12%), pancreatic (~2%), and papillary thyroid (cribriform morular variant)[33,34] (1–2%)[29,30] cancers, as well as hepatoblastoma by age 5 (1–2%)[35,36] and medulloblastoma (<1%).[32] Extracolonic manifestations can include congenital hypertrophy of the retinal pigmented epithelium, osteomas, dental abnormalities, benign cutaneous lesions such as epidermoid cysts and fibromas, and desmoid tumors. *APC* mutations are found in 80% of patients with 1,000 or more adenomas, 56% of patients with 100–999 adenomas, 10% of patients with 20–99 adenomas, and 5% of patients with 10–19 adenomas.[37]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) a total of ≥10 adenomatous colon polyps with or without a colorectal or other FAP-associated cancer[38]; (ii) a cribriform morular variant of papillary thyroid cancer; (iii) a desmoid tumor; or (iv) hepatoblastoma diagnosed before age 5.

### Familial gastrointestinal stromal tumor (OMIM 606764)

Familial gastrointestinal stromal tumor (GIST) is a rare condition associated with mutations in the *KIT*, *PDGFRA*, *SDHB*, and *SDHC* genes. Individuals with germline mutations in *KIT* can have hyperpigmentation, mast cell tumors, or dysphagia. Large hands have been associated with *PDGFRA* mutations. Individuals with neurofibromatosis type 1 can also develop GISTs. Wild-type GISTs are defined as GISTs that do not have detectable mutations in *KIT*, *PDGFRA*, or *BRAF*. Of patients with sporadic wild-type GIST, 12% had *SDHB* or *SDHC* mutations,[39] and in another series, 12% of wild-type GISTs had an *SDHA* mutation (all of which exhibited loss of the SDHA protein by immunohistochemistry).[40] There are no published referral guidelines for this condition; recommendations were made based on expert opinion.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) three or more close relatives with GIST; (ii) wild-type GIST; or (iii) individuals with three or more GISTs.

### Familial pancreatic cancer (OMIM 260350)

Pancreatic cancer risk is increased in several known hereditary cancer syndromes such as Lynch syndrome, Peutz–Jeghers syndrome, FAP, hereditary melanoma, and hereditary breast–ovarian cancer syndrome. The most common cause of familial pancreatic cancer are mutations in the *BRCA2* gene. Published studies of families with two or more pancreatic cancer diagnoses demonstrate that 2.8–17% of these families have a *BRCA2* gene mutation.[41–44] Because of increased prevalence of *BRCA* mutations, unselected individuals of Ashkenazi Jewish ancestry with pancreatic cancer have a 5.5–31% chance of having one of the three Ashkenazi Jewish founder mutations.[45–47] Some families with familial pancreatic cancer also have mutations in the *CDKN2A*, *PALB2*, or *ATM* genes. *PALB2* mutations occur in 0.9–3.7% of pancreatic cancer patients with at least one additional relative affected with pancreatic cancer.[48–50] *ATM* mutations were found in 2.4% (4/166) of patients with familial pancreatic cancer and in 4.6% (4/87) of families with three or more affected individuals.[51]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) Ashkenazi Jewish ancestry and pancreatic cancer at any age; (ii) pancreatic cancer and a close relative with pancreatic cancer; (iii) three or more cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer; or (iv) three or more cases of pancreatic cancer and/or melanoma.

### Familial prostate cancer (OMIM 176807, 601518, 602759, 300147, 603688, 608656, and 153622)

The genetic etiology of familial prostate cancer has proven difficult to characterize. Autosomal dominant, recessive, and X-linked patterns of inheritance have been demonstrated in families with multiple cases of prostate cancer.[14] For these guidelines, the Hopkins criteria[52] have been adopted to define familial prostate cancer. Several studies have identified a specific *HOXB13* mutation in 1.4–4.6% of individuals (primarily of Northern European ancestry) meeting these criteria.[53–55] Identifying the basis of familial prostate cancer is ongoing, and genes found to date account for a small portion of families. However, referral may be appropriate for these families to help address concerns and provide screening recommendations.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) three or more first-degree relatives with prostate cancer; (ii) two or more cases of prostate cancer diagnosed before age 55; or (iii) aggressive prostate cancer (Gleason score ≥7) and two or more cases of breast, ovarian, or pancreatic cancer.

### Hereditary breast–ovarian cancer syndrome (OMIM 604370 and 612555)

Hereditary breast–ovarian cancer (HBOC) syndrome is caused by mutations in the *BRCA1* and *BRCA2* genes and is characterized by increased risks for early-onset breast, multiple breast primaries, male breast, and epithelial ovarian, Fallopian tube, or primary peritoneal cancers. In addition, cancers of the pancreas, prostate, and melanoma are more common in individuals with HBOC syndrome. The pathology of "triple-negative phenotype" breast cancer (estrogen receptor–negative, progesterone receptor–negative, and HER2/neu–negative) has been strongly associated with *BRCA1* mutations.[56–59] The likelihood of identifying a *BRCA1*/2 mutation in a woman with ovarian cancer at any age is around 13–18%.[60–62] Of males with breast cancer,

15–20% have a *BRCA1/2* mutation.[63] The overall prevalence of *BRCA1* mutations is estimated at 1 in 300 and that of *BRCA2* mutations is estimated at 1 in 800, but founder mutations in many populations (e.g., Ashkenazi Jewish,[64–67] Icelandic,[68] and Mexican Hispanic[69] populations) lead to increased mutation prevalence in these populations.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) breast cancer diagnosed at or before age 50; (ii) triple-negative breast cancer diagnosed at or before age 60; (iii) two or more primary breast cancers in the same person; (iv) ovarian, Fallopian tube, or primary peritoneal cancer; (v) Ashkenazi Jewish ancestry and breast or pancreatic cancer at any age; or (vi) male breast cancer. Individuals with a family history of three or more cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer (Gleason score ≥7) (refs. 70,71) should also be referred. Note that this should not include families in which all three cases are aggressive prostate cancer.

**Hereditary diffuse gastric cancer (OMIM 137215)**

Hereditary diffuse gastric cancer is caused by mutations in the *CDH1* gene and is characterized by an increased risk for diffuse gastric cancer, lobular breast cancer, and signet ring colorectal cancer. *CDH1* mutations occur in 25–50% of individuals who meet the hereditary diffuse gastric cancer criteria.[72] The International Gastric Cancer Linkage Consortium's most recent consensus guidelines for the clinical management of hereditary diffuse gastric cancer include indications for *CDH1* testing and have been adopted below.[73]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) diffuse gastric cancer diagnosed before age 40; (ii) lobular breast cancer and diffuse gastric cancer in the same person; (iii) lobular breast cancer in one relative and diffuse gastric cancer in another, one diagnosed before age 50; or (iv) two cases of gastric cancer in family, one of which is a confirmed diffuse gastric cancer diagnosed before age 50. Individuals with a family history of three or more relatives with gastric cancer should also be referred.

**Hereditary leiomyomatosis and renal cell cancer (OMIM 605839 and 150800)**

Hereditary leiomyomatosis and renal cell cancer is caused by mutations in the *FH* gene and is characterized by increased risks for renal cancer and cutaneous and uterine leiomyomas. Individuals with cutaneous leiomyoma and renal cell tumors of one of three types (papillary type 2 (refs. 74–78)), collecting duct,[71,74,75] and tubulopapillary[78]) should receive genetic counseling referral.[79,80] Although studies of the proportion of isolated cases of cutaneous leiomyomas with an *FH* mutation are not available, 85% of individuals with cutaneous leiomyomas (some of whom were isolated cases and some of whom had a family history of uterine leiomyoma or renal cell tumors) had an *FH* mutation in several studies.[74–77,81] A *FH* mutation was found in 17% of patients with papillary type 2 renal cell carcinoma (RCC).

Referral should be considered for any individual with a personal history of or first-degree relative with (i) cutaneous leiomyomas or (ii) RCC with histology characteristic of hereditary leiomyomatosis and renal cell cancer.

**Hereditary melanoma, also known as familial atypical mole and malignant melanoma (OMIM 155600)**

Hereditary melanoma is caused by mutations in the *CDKN2A/ARF* gene, which encodes *p16* and *p14ARF*, and the *CDK4* gene. Hereditary melanoma is characterized by multiple melanocytic nevi (usually >50) and a family history of melanoma. Individuals with hereditary melanoma have a 17% risk for pancreatic cancer by age 75 (ref. 82). The penetrance for melanoma in families with *CDKN2A* mutations is at least 28%, although it is perhaps as high as 91% in families with multiple cases.[83–85] A review of 466 families with at least three cases of melanoma revealed 38% had *CDKN2A* mutations.[86] Penetrance and detection rate vary by geography.[84] In addition, 2–3% of these families have mutations in *CDK4* ($n = 5$) and *p14ARF* ($n = 7$). *CDKN2A* gene mutations seem to be rare in families with pancreatic cancer without any cases of melanoma[44] but occur in up to 11% (2/18) of families with both pancreatic cancer and melanoma.[87]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) three or more melanomas in the same person or (ii) three or more cases of melanoma and/or pancreatic cancer.

**Hereditary mixed polyposis syndrome (OMIM 201228 and 610069)**

Hereditary mixed polyposis syndrome is characterized by multiple polyps of mixed histology (hyperplastic, adenomatous, and juvenile polyps), leading to an increased risk for colorectal cancer. The major gene(s) responsible for hereditary mixed polyposis syndrome have not been identified; however, some cases are caused by mutations in the *BMPR1A* gene.[88–90] Also, a founder mutation involving the *GREM1* gene was identified in Ashkenazi Jewish patients with hereditary mixed polyposis syndrome.[91]

Referral should be considered for any individual with a personal history of or first-degree relative with ≥10 colorectal polyps with mixed histology.

**Hereditary papillary RCC (OMIM 605074)**

Hereditary papillary RCC is caused by mutations in the *MET* gene and is characterized by an increased risk of developing papillary type 1 RCC. In a series of 129 patients with papillary RCC, 6% (8/129) had a germline *MET* mutation.[92] Because this tumor type is rare, our referral criteria are for anyone with a papillary type 1 RCC. Note that patients with a papillary type 2 RCC should be referred as well because of the possibility of hereditary leiomyomatosis and renal cell cancer.

Referral should be considered for any individual with a personal history of or first-degree relative with a papillary type 1 RCC.

**Hereditary paraganglioma–pheochromocytoma syndrome (OMIM 115310, 168000, 605373, 601650, 154950, and 613403)**

Hereditary paraganglioma–pheochromocytoma syndrome is caused by mutations in the *SDHB*, *SDHD*, *SDHC*, *SDHAF2*,

*MAX*, and *TMEM127* genes and is characterized by an increased risk for paragangliomas and pheochromocytomas. In multiple series of individuals with paragangliomas and pheochromocytomas, 8–25% had hereditary paraganglioma–pheochromocytoma syndrome due to a germline mutation in the *SDHB*, *SDHC*, or *SDHD* genes.[93–98] Rates of hereditary paraganglioma–pheochromocytoma syndrome in individuals with a positive family history or other clinical factors (e.g., multiple tumors, head and neck location) are considerably higher.[93–97]

Referral should be considered for any individual who has a personal history of or a first-degree relative with a paraganglioma or pheochromocytoma.

### Hereditary retinoblastoma (OMIM 180200)

Hereditary retinoblastoma is caused by mutations in the *RB1* gene and is characterized by a malignant tumor of the retina, usually occurring before age 5. It is estimated that about 40% of all retinoblastomas are hereditary.[99] Individuals with a positive family history of retinoblastoma, bilateral tumors, and multifocal tumors have the highest chance to have hereditary retinoblastoma.[99] Individuals with hereditary retinoblastoma can also have an increased risk for pinealoblastoma,[100] osteosarcomas, sarcoma (especially radiogenic), and melanoma.[101,102]

Referral should be considered for any individual who has a personal history of or first-degree relative with a retinoblastoma.

### Juvenile polyposis syndrome (OMIM 174900)

Juvenile polyposis syndrome is caused by mutations in the *SMAD4* (20%) and *BMPR1A* (20%) genes[103] and is characterized by juvenile-type hamartomatous polyps throughout the gastrointestinal (GI) tract. The term *juvenile polyp* refers to a specific histologic type of polyp, not the age at diagnosis. The risk for GI cancers (mainly colorectal cancer, although cancers of the stomach, upper GI tract, and pancreas have been reported) in families with juvenile polyposis syndrome ranges from 9 to 50%.[104] Extraintestinal features such as valvular heart disease (11%), telangiectasia or vascular anomalies (9%, all in *SMAD4* carriers), and macrocephaly (11%) can occur.[105] Some individuals with juvenile polyposis syndrome due to mutations in the *SMAD4* gene may also have symptoms of hereditary hemorrhagic telangiectasia.[106,107]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) three to five cumulative histologically proven juvenile GI polyps[108–110]; (ii) any number of juvenile GI polyps with a positive family history of juvenile polyposis syndrome; or (iii) multiple juvenile polyps located throughout the GI tract.[38,103]

### Li–Fraumeni syndrome (OMIM 151623)

Li–Fraumeni syndrome (LFS) is caused by mutations in the *TP53* gene and is characterized by the core cancers of breast, brain, adrenocortex, and non-Ewing sarcoma,[111] with onset often before age 50 and multiple primary tumors.[112] Young age at diagnosis (before age 30) and the type of malignancy are good indicators of a *TP53* mutation.[113] In individuals diagnosed with an adrenocortical tumor or choroid plexus tumor at or before age 18, the likelihood of identifying a *TP53* mutation approaches 80 and 100%, respectively.[112,114,115] Individuals with a childhood sarcoma have a higher likelihood of LFS; 6.6% had a *TP53* mutation in one series (although the majority of these cases would meet the classic LFS criteria).[116] For these guidelines, we are adopting a combination of the Eeles and revised Chompret criteria.[117] In two large studies, 29%[118] and 35%[112] of individuals who met the original, slightly more restrictive, Chompret criteria[119] had a *TP53* mutation. However, 14% of individuals who met the looser Eeles criteria also had a *TP53* mutation.[112]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) two or more close relatives with a tumor in the LFS spectrum (**Table 5**), one diagnosed at or before age 45; (ii) breast cancer diagnosed before age 30; (iii) two or more LFS tumors in the same person, one diagnosed at or before age 45; (iv) adrenocortical tumor; (v) choroid plexus tumor; or (vi) childhood sarcoma.[117]

### Lynch syndrome (OMIM 120435 and 120436)

Lynch syndrome (LS) is caused by mutations in the following mismatch repair genes: *MLH1*, *MSH2* (including methylation due to an *EPCAM* deletion), *MSH6*, or *PMS2*; LS is characterized by increased lifetime risks for colorectal (40–80%), endometrial (25–60%), ovarian (4–24%), and gastric (1–13%) cancers.[120,121] Individuals with LS can also have an increased risk for urothelial carcinoma, glioblastoma, and sebaceous, biliary, small bowel, and pancreatic adenocarcinomas[122–125] (**Table 6**). The lifetime risks for cancer are lower in individuals with *MSH6* and *PMS2* mutations.[121,125] Most tumors (77–89%) from individuals with LS are characterized by microsatellite instability, which is an expansion or contraction of repetitive areas in the DNA, called microsatellites, due to defective mismatch repair.[126] In addition, there are immunohistochemical antibodies available for the four mismatch repair proteins, and one or two of the proteins is absent in 83% of tumors from individuals with LS.[126] One or both of these tumor screening tests are sometimes performed at the time of diagnosis for colorectal and endometrial cancer and can serve as an indication for referral for a LS evaluation. The most well-known criteria developed for LS include the Amsterdam criteria and the Bethesda guidelines, both of which have undergone revision.[127–130] Yet neither of these criteria sufficiently considers the breadth of cancers associated with LS. Furthermore, they are complex and difficult to apply. Thus, the criteria selected for this referral guideline are

**Table 5** Tumors associated with Li–Fraumeni syndrome

| |
|---|
| • Soft-tissue sarcoma |
| • Osteosarcoma |
| • Brain tumor |
| • Breast cancer (often early onset) |
| • Adrenocortical tumor |
| • Leukemia |
| • Bronchoalveolar cancer |
| • Colorectal cancer |

**Table 6** Tumors associated with Lynch syndrome

| |
|---|
| • Colorectal adenocarcinoma |
| • Endometrial adenocarcinoma |
| • Urothelial carcinoma (ureter and renal collecting ducts) |
| • Gastric cancer |
| • Ovarian cancer |
| • Small bowel cancer |
| • Glioblastoma |
| • Sebaceous adenocarcinoma |
| • Biliary tract cancer |
| • Pancreatic cancer |

modified from the "Finnish criteria," which are simple, easy to apply, based on two large population-based studies, and identify the majority of patients found to have LS.[124,131–133]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) colorectal or endometrial cancer diagnosed before age 50; (ii) colorectal or endometrial cancer diagnosed at or after age 50 if there is a first-degree relative with colorectal or endometrial cancer at any age; (iii) synchronous or metachronous colorectal or endometrial cancer; (iv) sebaceous adenoma or carcinoma and one or more additional case of any LS-associated cancer (**Table 6**) in the same person or in relatives; or (v) a tumor exhibiting mismatch repair deficiency (high microsatellite instability or loss of a mismatch repair protein based on immunohistochemical staining). Individuals with a family history of three or more LS-associated cancers (**Table 6**) should also be referred.

### Melanoma–astrocytoma syndrome (OMIM 155755)

Melanoma–astrocytoma syndrome is caused by mutations involving both *CDKN2A* and *p14ARF*, *p14ARF* alone, and possibly the *ANRIL* antisense noncoding RNA; it is a rare condition that leads to an increased risk for melanoma and astrocytoma tumors.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) melanoma and astrocytoma in the same person or (ii) one case of melanoma and one case of astrocytoma in two first-degree relatives.

### Multiple endocrine neoplasia type I (OMIM 131100)

Multiple endocrine neoplasia type I (MEN1) is caused by mutations in the *MEN1* gene and is characterized by increased risk of endocrine and nonendocrine tumors.[134] Of individuals with two MEN1 manifestations, 26% had a *MEN1* mutation.[135] Because of the relatively low mutation detection rates in sporadic cases,[134,136–139] no single MEN1-associated tumor is sufficient to warrant genetic counseling referral, with the exception of gastrinoma, of which 20% are due to *MEN1* mutations.[140] For this guideline, we are adopting the recommendation of the MEN1 International Consensus[134] and the MEN1 Clinical Practice Guidelines.[140] Note that this guideline is less stringent than the clinical diagnostic criteria for MEN1.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) two or more different MEN1-associated tumors (adrenal, parathyroid, pituitary, pancreas, or thymic tumor or bronchial carcinoid tumor) in the same person[134,141]; (ii) gastrinoma[134,140]; (iii) multiple different pancreatic neuroendocrine tumors in the same person[134,140]; (iv) parathyroid adenoma diagnosed before age 30 (refs. 140,142); (v) parathyroid adenomas involving multiple glands[140,142]; or (vi) parathyroid adenoma with family history of hyperparathyroidism or MEN1-associated tumors.[142]

### Multiple endocrine neoplasia type II (OMIM 171400, 155240, and 162300)

Multiple endocrine neoplasia type II (MEN2) is caused by mutations in the *RET* gene and is characterized by increased risks for medullary thyroid cancer (MTC) (≤100%), pheochromocytomas (≤50%), and parathyroid disease (≤30%).[143–145] As many as 25% of unselected individuals with MTC have a *RET* mutation.[146] Individual series found that 4–11% of individuals with isolated MTC have a *RET* mutation.[147–149] Genetic testing of individuals with nonsyndromic pheochromocytomas detected a *RET* mutation in 5% of these individuals in one study,[150] but lower rates were found in other studies.[93,95] *RET* testing is not indicated in apparently sporadic hyperparathyroidism in the absence of other clinical suspicion for MEN2 (ref. 134). MEN2A accounts for 80% of hereditary MTC syndromes.[151] Families with MTC and no other MEN2-associated tumors are referred to as having familial medullary thyroid cancer.[143,152] Familial medullary thyroid cancer accounts for 15% of hereditary MTC syndromes.[151] MEN2B accounts for 5% of hereditary MTC syndromes and is a more severe type of MEN2, differentiated by the presence of benign oral and submucosal neuromas and a distinct appearance (tall and lanky with an elongated face and large lips).[151] Of individuals with MEN2B, 40% have diffuse ganglioneuromatosis of the GI tract. The large majority of patients with MEN2B have mutations in exon 16 (M918T) and, less often, in exon 15 (A883F). There are genotype–phenotype correlations between the specific mutation in *RET* and the various clinical features.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) MTC; (ii) pheochromocytoma; (iii) oral or ocular neuromas (lips, tongue, sclera, or eyelids); or (iv) diffuse ganglioneuromatosis of the GI tract.

### *MUTYH*-associated polyposis (OMIM 608456)

*MUTYH*-associated polyposis is a recessive condition caused by biallelic mutations in the *MUTYH* gene and is characterized by an increased risk for adenomatous colon polyps and colorectal cancer (80%).[153] Individuals with *MUTYH*-associated polyposis can develop only a few adenomatous colon polyps or they can have >100 adenomatous colon polyps.[38,154] As a result, this condition can overlap with FAP, attenuated FAP, and LS. Testing is often ordered for both *APC* and *MUTYH* at the same time for patients with ≥10 adenomatous colon polyps. *MUTYH* testing might also be appropriate for patients with colorectal cancer diagnosed before

age 50 after LS has been ruled out (the tumor exhibits mismatch repair proficiency), as 0.8–6% have biallelic *MUTYH* mutations.[155–158] Biallelic *MUTYH* mutations are found in 2% of patients with ≥1,000 adenomas, 7% of patients with 100–999 adenomas, 7% of patients with 20–99 adenomas, and 4% of patients with 10–19 adenomas.[37]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) ≥10 cumulative adenomatous colon polyps with or without colorectal cancer or (ii) mismatch repair proficient (microsatellite stable and/or normal mismatch repair protein based on immunohistochemical staining) colorectal cancer diagnosed before age 50.

### Nevoid basal cell carcinoma syndrome (OMIM 109400)

Nevoid basal cell carcinoma syndrome is caused by mutations in the *PTCH* gene and is characterized by the presence of multiple jaw keratocysts beginning in the teens and multiple basal-cell carcinomas beginning in the 20s. Physical features such as macrocephaly, bossing of the forehead, coarse facial features, facial milia, and skeletal anomalies are present in most individuals with nevoid basal cell carcinoma syndrome (**Table 7**). Less common features include cardiac fibromas (2%), ovarian fibromas (20%), medulloblastoma (primitive neuroectodermal tumor; 5%). The diagnosis is made clinically when an individual has two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria[159–161] (**Table 7**).

Referral should be considered for any individual with a personal history of or first-degree relative with any two criteria from the major or minor diagnostic criteria lists (**Table 7**).

### Peutz–Jeghers syndrome (OMIM 175200)

Peutz–Jeghers syndrome (PJS) is caused by mutations in the *STK11* gene and is characterized by mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; multiple hamartomatous polyps in the GI tract; and increased risks for colorectal (39% between ages 15 and 64), pancreatic (36%), gastric (29%), and small intestinal (13%) cancers. In addition, there are increased risks for breast cancer (54%), ovarian sex cord tumors with annular tubules (21%), and adenoma malignum of the cervix (10%) and the testes, especially Sertoli cell tumors (9%).[162] PJ polyps are hamartomatous with glandular epithelium supported by smooth muscle cells contiguous with the muscularis mucosa.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) two or more histologically confirmed PJ GI polyps; (ii) one or more PJ GI polyp and mucocutanous hyperpigmentation; (iii) ovarian sex cord tumor with annular tubules; (iv) adenoma malignum of the cervix; (v) Sertoli cell tumor; (vi) pancreatic cancer and one or more PJ GI polyp; (vii) breast cancer and one or more PJ GI polyp; or (viii) one or more PJ polyp and a positive family history of PJS.

### Rhabdoid tumor predisposition syndrome types I and II (OMIM 609322 and 613325)

Rhabdoid tumor predisposition syndrome is characterized by an increased risk for rhabdoid tumors (rare and aggressive tumors of children). Rhabdoid tumor predisposition syndrome type I is caused by mutations in the *SMARCB1* gene. Germline mutations in the SMARCB1 gene occurred in 35% (26/115 and 35/100) of patients with apparently sporadic childhood rhabdoid tumors.[163,164] Only 10 of 61 parents harbored the germline mutation in both series combined, indicating a high proportion of germ cell mosaicism or de novo mutations in rhabdoid tumor predisposition syndrome type I.[163,164] Rhabdoid tumor predisposition syndrome type II is caused by mutations in the *SMARCA4* gene. In two small series of apparently nonfamilial small cell carcinoma of the ovary, hypercalcemic type (which is a rare, aggressive rhabdoid tumor affecting children and young women), germline mutations in *SMARCA4* were found in 29% (2/7)[165] and 50% (6/12)[166] of cases.

Referral should be considered for any individual with a personal history of or first-degree relative with a rhabdoid tumor, including small cell carcinoma of the ovary, hypercalcemic type.

**Table 7** Nevoid basal cell carcinoma syndrome criteria

| **Major criteria** |
|---|
| • Lamellar calcification of the falx in an individual younger than age 20 |
| • Jaw keratocyst |
| • Palmar or plantar pits |
| • Multiple basal cell carcinomas (>5 in a lifetime) or a basal cell carcinoma diagnosed before age 30 (excluding basal cell carcinomas that develop after radiotherapy) |
| • First-degree relative with nevoid basal cell carcinoma syndrome |
| **Minor criteria** |
| • Childhood medulloblastoma (primitive neuroectodermal tumor) |
| • Lymphomesenteric or pleural cysts |
| • Macrocephaly (occipital frontal circumference >97th percentile) |
| • Cleft lip or cleft palate |
| • Vertebral or rib anomalies observed on x-ray |
| • Preaxial or postaxial polydactyly |
| • Ovarian or cardiac fibromas |
| • Ocular anomalies (cataract, developmental defects, and pigmentary changes of the retinal epithelium) |

### Serrated polyposis syndrome (not in OMIM)

Serrated polyposis syndrome is a syndrome characterized by serrated polyps (SPs) and an increased risk for colorectal cancer. SPs can be difficult to diagnose and include hyperplastic polyps, sessile SPs, or adenomas, as well as traditional serrated adenomas. For these guidelines we adopt the 2012 National Comprehensive Cancer Network modification (http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf) of the 2000 World Health Organization criteria[167] for the diagnosis of serrated polyposis syndrome. No causative mutations in *BMPR1A*, *SMAD4*, *PTEN*, *MUTYH*, or *GREM1* were found in a series of 65 individuals with serrated polyposis syndrome; it is likely that this condition is caused by novel genes that have yet to be discovered.[168] Although genetic testing may not be useful at present, a genetics referral is indicated because the diagnosis will affect future management, and other polyposis syndromes should be ruled out.

Referral should be considered for any individual with a personal history of or first-degree relative with (i) at least 5 SPs proximal to the sigmoid colon, 2 of which are >1 cm in diameter, (ii) >20 SPs throughout the large bowel,[38,169] or (iii) any number of SPs proximal to the sigmoid colon and a positive family history of serrated polyposis syndrome.

### Tuberous sclerosis complex (OMIM 191100)

Tuberous sclerosis complex (TSC) is caused by mutations in the *TSC1* and *TSC2* genes and is characterized by brain, kidney, and heart tumors, as well as skin and neurological abnormalities, among others[170,171] (**Table 8**). Brain lesions in TSC are complex and include subependymal nodules, cortical hamartomas, areas of focal cortical hypoplasia, and heterotopic gray matter.[171,172] When cerebral cortical dysplasia and cerebral white matter migration lines occur together, they should be counted as one rather than two features of TSC.[170,171] Renal lesions (angiomyolipomas and/or cysts) are usually present during childhood, and prevalence increases with age.[171] About two-thirds of newborns with TSC have one or more cardiac rhabdomyomas; they are largest during the neonatal period and regress with time.[173] Skin lesions occur in nearly 100% of individuals, although none are pathognomonic.[170] Retinal lesions are present in 87% of individuals with TSC but may be difficult to detect without dilating the pupils and using indirect ophthalmoscopy.[171,174] Interestingly, two-thirds to three-fourths of individuals with TSC have de novo mutations.[171] Clinical diagnostic criteria involve combinations of major and minor criteria[170,171] (**Table 8**). We recommend referral for anyone meeting any two criteria from the major or minor diagnostic criteria lists.

Referral should be considered for any individual with a personal history of or first-degree relative with any two criteria from the major or minor diagnostic criteria lists in the same person[170,171] (**Table 8**).

### Von Hippel–Lindau syndrome (OMIM 193300)

Von Hippel–Lindau syndrome is caused by mutations in the *VHL* gene and is characterized by RCC (clear cell histology), hemangioblastomas, pheochromocytomas, and endolymphatic sac tumors. Simplex cases of central nervous system hemangioblastoma, pheochromocytoma, and endolymphatic sac tumor are each sufficient to warrant genetic counseling referral. *VHL* mutations are detected in 10–40% of individuals with isolated central nervous system hemangioblastoma,[175] 46% of those with isolated retinal capillary hemangioma,[176] 3–11% of those with isolated pheochromocytoma,[93,95,96,150,175,177,178] and about 20% of those with an endolymphatic sac tumor.[179–183] Single cases of unilateral, unifocal RCC diagnosed at or after age 50 are insufficient to warrant referral to genetic counseling.[175,184]

Referral should be considered for any individual with a personal history of or first-degree relative with (i) clear cell RCC if he or she (a) has bilateral or multifocal tumors, (b) is diagnosed before age 50, or (c) has a close relative with clear cell RCC; (ii) central nervous system hemangioblastoma; (iii) pheochromocytoma; (iv) endolymphatic sac tumor, or (v) retinal capillary hemangioma.

## SUMMARY

This document suggests referral guidelines for 28 of the most common hereditary cancer susceptibility syndromes. The tables are meant to aid busy clinicians, enabling them to quickly search by cancer type (**Table 1** includes common cancers, **Table 2** includes rare benign and malignant tumors) to find appropriate referral criteria for the various syndromes detailed throughout this guideline. After locating the cancer of interest in the table, practitioners can learn more about the associated syndrome by looking it up in the text of this document. We recommend that patients (or their affected relatives) meeting

**Table 8** Tuberous sclerosis complex criteria

| Major criteria |
|---|
| • Facial angiofibromas or forehead plaque |
| • Nontraumatic ungual or periungual fibroma |
| • Hypomelanotic macules (≥3) |
| • Shagreen patch (connective tissue nevus) |
| • Cortical tuber in the brain |
| • Subependymal glial nodule |
| • Subependymal giant cell astrocytoma |
| • Multiple retinal nodular hamartomas |
| • Cardiac rhabdomyomas, single or multiple |
| • Lymphangiomyomatosis |
| • Renal angiomyolipoma |
| **Minor criteria** |
| • Multiple, randomly distributed pits in dental enamel |
| • Hamartomatous rectal polyps |
| • Bone cysts |
| • "Confetti" skin lesions |
| • Multiple renal cysts |
| • Nonrenal hamartoma |
| • Cerebral white matter radial migration lines |
| • Retinal achromic patch |
| • Gingival fibromas |

From refs. 170,171.

any of the cancer genetics referral criteria be referred to a cancer genetics specialist. To find a cancer genetics expert, visit the National Cancer Institute Cancer Genetics Services Directory (http://www.cancer.gov/cancertopics/genetics/directory), the National Society of Genetic Counselors website (http://www.nsgc.org; use the "Find a Genetic Counselor" feature), or the American College of Genetics and Genomics website (http://www.acmg.net; use the "Find Genetic Services" feature).

## ACKNOWLEDGMENTS

Document approved by the ACMG Board of Directors 31 July 2014. Document approved by the NSGC Board of Directors 25 August 2014.

## DISCLOSURE

H.H. has received grant support from Myriad Genetic Laboratories in the form of donated genetic testing she has received honoraria for speaking from Quest Diagnostics, InVitae Genetics, and Myriad Genetic Laboratories in the past 3 years. This has not impacted the referral guidelines. A.B. has received National Institutes of Health funding but reports that it does not conflict with the content of this practice guideline. R.P. has received grant support from Myriad Genetic Laboratories in the form of donated genetic testing G.W. was supported by institutional funds from the Vanderbilt University School of Medicine. A.B., G.W., and R.L.B. declare no conflict of interest.

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