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REVIEW

10 rare tumors that warrant a genetics referral

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Abstract The number of described cancer susceptibility syndromes continues to grow, as does our knowledge on how to manage these syndromes with the aim of early detection and cancer prevention. Oncologists now have greater responsibility to recognize patterns of cancer that warrant referral for a genetics consultation. While some patterns of common cancers are easy to recognize as related to hereditary cancer syndromes, there are a number of rare tumors that are highly associated with cancer syndromes yet are often overlooked given their infrequency. We present a review of ten rare tumors that are strongly associated with hereditary cancer predisposition syndromes: adrenocortical carcinoma, carcinoid tumors, diffuse gastric cancer, fallopian tube/primary peritoneal cancer, leiomyosarcoma, medullary thyroid cancer, paraganglioma/pheochromocytoma, renal cell carcinoma of chromophobe, hybrid oncocytoic, or oncocytoma histology, sebaceous carcinoma, and sex cord tumors with annular tubules. This review will serve as a guide for oncologists to assist in the recognition of rare tumors that warrant referral for a genetic consultation.

Keywords Genetic predisposition to disease · Neoplasms · Genetic counseling · Medical genetics · Rare tumor

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Introduction

In general, 5–10 % of cancer is due to a hereditary cancer syndrome. Well known examples include hereditary breast and ovarian cancer syndrome and Lynch syndrome. Certain rare tumors are *more* likely to be due to inherited causes. Although rare, these tumors should trigger a cancer genetics work-up in any patient diagnosed with one of these tumors, often regardless of additional personal or family history.

Identification of a hereditary cancer syndrome provides information about future cancer risks for the patient as well as important information for the patient's family members. Knowledge of future cancer risks allows for early detection through targeted high-risk surveillance and in some instances, risk-reducing measures to prevent additional cancers in the patient and family members.

This paper reviews ten rare tumors that have a high likelihood of being due to a hereditary predisposition: adrenocortical carcinoma, carcinoid tumors, diffuse gastric cancer, fallopian tube/primary peritoneal cancer, leiomyosarcoma, medullary thyroid cancer, paraganglioma/pheochromocytoma, renal cell carcinoma of chromophobe, hybrid oncocytotic, or oncocytoma histology, sebaceous carcinoma, and sex cord tumors with annual tubules (Table 1).

Table 1 Summary of the 10 rare tumors

Associated hereditary cancer syndrome/s	Associated gene/s	Clinical manifestations of hereditary cancer syndrome	% associated with inherited predisposition	Single case indication for referral to genetics (regardless of family history)[a]
Adrenocortical carcinoma				
Li Fraumeni syndrome (LFS)	*p53*	Adrenocortical carcinoma	Up to 80 % of pediatric cases	All individuals with adrenocortical carcinoma
		Sarcomas		
		Breast cancer		
		Leukemia		
		Brain tumors, and others		
Carcinoid tumors				
Multiple	*MEN1*	Parathyroid tumors	Thymic gland carcinoid tumors: 25 %	All individuals with thymic gland carcinoid tumors
		Pituitary tumors		
		Pancreatic tumors		
Endocrine		Carcinoid tumors of the thymus gland, lung, and stomach	Bronchial and stomach carcinoids: unknown	
Neoplasia type 1 (MEN1)		Other non-endocrine tumors		
Diffuse gastric cancer				
Hereditary diffuse gastric cancer	*CDH1*	Diffuse gastric cancer	Unknown	All individuals with:
		Lobular breast cancer		Diffuse gastric cancer diagnosed under age 40
				Diffuse gastric cancer and lobular breast cancer
Fallopian tube and primary peritoneal cancer				
Hereditary breast and ovarian cancer syndrome	*BRCA1*	Breast cancer (female and male)	Fallopian Tube: 16–43 %	All individuals with fallopian tube or primary peritoneal cancer
	BRCA2	Ovarian, fallopian tube, and primary peritoneal cancer		
		Prostate cancer	Primary Peritoneal: 28–41 % in Ashkenazi population	
		Pancreatic cancer		
Leiomyosarcoma				
HLRCC	*FH*	Leiomyomas of the skin and uterus	Unknown	Individuals with:
		Papillary type 2 and collecting duct renal carcinomas		Leiomyosarcoma ND a personal or family history suggestive of HLRCC or Lynch syndrome
		Uterine leiomyosarcoma		Multiple cutaneous leiomyomas with at least one histopathologically confirmed leiomyoma
Lynch syndrome (HNPCC)	*MSH2 MLH1 MSH6 PMS2*	Colorectal cancer		
	EPCAM	Endometrial cancer		
		Gastric cancer		
		Ovarian cancer		
		Hepatobiliary cancer		
		Urinary tract cancer		
		Small bowel cancer		
		Glioblastoma		
		Sebaceous carcinomas		

Table 1 continued

Associated hereditary cancer syndrome/s	Associated gene/s	Clinical manifestations of hereditary cancer syndrome	% associated with inherited predisposition	Single case indication for referral to genetics (regardless of family history)[a]
Medullary thyroid carcinoma (MTC)				
MEN2A	*RET*	MTC	25 % overall in MTC	All individuals with medullary thyroid cancer
		Adrenal PC		
		Hyperparathyroidism		
MEN2B	*RET*	MTC		
		Adrenal PC		
		Mucosal neuroma		
FMTC	*RET*	MTC		
Paraganglioma/pheochromocytoma (PGL/PC)				
MEN2	*RET*	MTC	>30 % overall in PGL/PC	All individuals with
		Adrenal PC		Paraganglioma or
		Hyperparathyroidism		Pheochromocytoma
VHL	*VHL*	Retinal and CNS hemangioblastoma		
		Renal and pancreatic cysts		
		Renal cell carcinoma		
		Adrenal and extra-adrenal PC		
NF1	*NF1*	Café au lait macules		
		Neurofibromas,		
		Axillary/inguinal freckling,		
		Lisch nodules		
		Adrenal PC		
Hereditary PGL/PC	*SDHA*	PGL		
	SDHB	PC		
	SDHC SDHD	Thyroid cancer		
	SDHAF2	Kidney cancer		
		GIST		
Familial PC	*TMEM127*	PC		
		PGL		
	MAX	PC		
		PGL		
Renal cell carcinoma—chromophobe, hybrid oncocytotic, oncocytoma histologies				
Birt Hogg Dube	*FLCN*	Renal carcinoma	Unknown	All individuals with multiple or bilateral chromophobe, oncocytotic, and/or hybrid renal tumors
		Follicular hamartomas		
		Lung cysts		
		Spontaneous pneumothorax		
Sebaceous Carcinomas				
Lynch Syndrome (HNPCC)	See above	See above	50 %	All individuals with a sebaceous carcinoma
Sex cord tumors with annular tubules				

Table 1 continued

Associated hereditary cancer syndrome/s	Associated gene/s	Clinical manifestations of hereditary cancer syndrome	% associated with inherited predisposition	Single case indication for referral to genetics (regardless of family history)[a]
Peutz-Jeghers Syndrome	*STK11*	Colorectal cancer Gastric cancer Breast cancer Pancreatic cancer Lung cancer Gynecologic cancers	Up to 37 %	All individuals with sex cord tumors with annular tubules

[a] The criteria listed in this table are targeted for simplex cases when appropriate. Patients with any of these tumors *and* suggestive family history also meet criteria for referral to genetics

Adrenocortical carcinoma (ACC)

In contrast to benign adrenal cortical tumors (prevalence of 3–5 %), adrenocortical carcinomas (ACCs) are exceedingly rare tumors with an estimated incidence of 0.72 per million in the United States [1]. In the pediatric setting, and to a lesser extent in the adult setting, ACCs are a well known component of at least two genetic conditions: Li-Fraumeni syndrome (LFS) and Beckwith-Wiedemann syndrome (BWS). There have also been reports of an association between ACC and neurofibromatosis type I, multiple endocrine neoplasia type 1, and familial adenomatous polyposis [2–9] but these associations are less established than the two afore-mentioned syndromes.

Li-Fraumeni syndrome

Li-Fraumeni syndrome is a highly penetrant cancer predisposition syndrome associated with pediatric and adult malignancies. It is caused by inherited mutations in the *p53* gene. Individuals with LFS are at risk for a wide range of malignancies, with lifetime cancer risks approaching 100 % for females and 73 % for males [10–12]. Individuals are at risk for multiple primary tumors as well as radiation-induced tumors [13]. The "core" cancers associated with LFS include ACC, sarcomas, breast cancer, leukemia, and brain tumors, however there are many other tumors individuals with LFS are at risk to develop [14, 15]. In families with LFS, the median age at diagnosis of ACC is 3 years, but it can also occur in early adulthood [16].

Diagnostic criteria for classic LFS require a proband with a sarcoma before the age of 45, a first degree relative with cancer before the age of 45, and another first or second degree relative with cancer before the age of 45 or a sarcoma at any age [17]. Studies have found that 50–70 % of families meeting these classic criteria for LFS have an identifiable *p53* mutation [18–22]. In addition to the diagnostic criteria, criteria also exist for consideration of *p53* genetic testing, with lower testing sensitivity [20, 23].

A significant proportion (at least 7 %) of probands with *p53* mutations appear to carry *de novo* mutations [24]. In such cases, family history is often negative. A recent study found that children with ACC may have one of the highest probabilities, up to 80 %, of carrying a *p53* mutation [25]. Per the 2009 Chompret criteria for *p53* testing, all individuals diagnosed with adrenocortical carcinoma at any age, regardless of family history, are candidates for germline *p53* genetic testing [26], preferably in the setting of pre-test genetic counseling.

Management of individuals with LFS must consider the dramatically increased risk for cancer, the early age of onset of these cancers, and the wide spectrum of cancers that can occur. Management is generally impacted by

patient age, personal cancer history and prognosis, and the spectrum of cancers occurring within the family. Historically, there has been limited data to show a particular surveillance protocol can decrease morbidity or mortality in individuals with LFS. However, there is emerging data on a small LFS population that shows frequent biochemical and imaging surveillance may improve survival [27]. In addition, management recommendations for individuals with LFS can also be found in the National Comprehensive Cancer Network (NCCN) Practice Guidelines.

Beckwith-Wiedemann syndrome

Pediatric ACCs are also associated with Beckwith-Wiedemann syndrome (BWS) [28]. A clinical diagnosis of BWS is typically made based on the combination of macroglossia, pre and postnatal overgrowth, and abdominal wall defects (omphalocele, umbilical hernia, or diastasis recti) [29]. Other features of BWS may include hemihypertrophy, kidney anomalies, distinctive ear pits and creases, and an increased risk for a number of malignancies, including ACCs [30]. In contrast to ACC within LFS families, ACC is *not* typically the initial symptom leading to a diagnosis of BWS but rather is a complication to be aware of within patients with BWS.

Carcinoid tumors

Carcinoid tumors represent a heterogeneous group of tumors that arise from diffuse components of the endocrine system. Carcinoids are typically indolent but have malignant potential and comprise less than 1 % of all malignancies. Their overall incidence is estimated at 1–2 per 100,000 individuals. The age distribution of carcinoid tumors ranges from the second to the ninth decade, with the peak incidence occurring between 50 and 70 years of age [31, 32]. More than 60 % of carcinoids originate in the gastrointestinal tract (with half of these in the small intestine) and the remaining in the lungs/bronchi [31].

Carcinoid tumors have been associated several hereditary cancer syndromes, specifically multiple endocrine neoplasia type 1 (MEN1) and neurofibromatosis type 1 (increased risk for periampullary tumors, particularly somatostatin-rich Carcinoids) [33–35]. The most frequent association has been with multiple endocrine neoplasia type 1 (MEN1), specifically carcinoid tumors of the thymus gland, lung and stomach [36–38].

MEN1 is an autosomal dominant syndrome characterized by development of tumors in the parathyroid glands, pituitary and pancreas. It is caused by inactivating mutations of a putative tumor suppressor gene, *MEN1*. MEN1 onset commonly occurs between 15 and 40 years of age [39]. Hyperparathyroidism is often the first sign of MEN1 and typically occurs between the ages of 20 and 25 years [40]. By age 70, nearly 100 % of MEN1 patients will develop parathyroid tumors, 30–75 % will develop pancreatic endocrine tumors and between 10 and 60 % will develop a pituitary tumor [41]. Non-endocrine tumors are also common in patients with MEN1 and can include lipomas, facial angiofibromas, cutaneous collagenomas, leiomyomas or benign thyroid adenomas and are useful adjunct features in establishing a clinical diagnosis.

Individuals with MEN1 can also develop tumors of the adrenal cortex and carcinoid tumors of the thymus gland, lung or stomach. Thymic, bronchial, and type II gastric enterochromaffin-like (ECL) carcinoids occur in approximately 10 % of individuals with MEN1 syndrome [42, 43]. Typically carcinoid tumors in MEN1 do not cause symptoms until they reach an advanced stage. As these tumors are capable of infiltrating surrounding tissues and metastasizing, early detection is important. Of all the MEN1-related tumors, thymic carcinoids are the most aggressive and management recommendations for patients with MEN1 incorporate surveillance for these tumors.

MEN1 is diagnosed clinically when two of the three major endocrine tumors (parathyroid glands, pituitary and pancreas) are present, or when an individual has one of the major tumors and has a first degree relative with two of the three endocrine tumors, or when an individual harbors an MEN1 disease-causing germline mutation. Germline *MEN1* mutations have been found in 75–90 % of patients with a clinical diagnosis of MEN1, regardless of family history, and approximately 10 % of these are *de novo* mutations. Amongst individuals with thymic carcinoids, approximately 25 % are due to a germline *MEN1* mutation. Given this high prevalence of causative gene mutations, a genetic evaluation for *MEN1* is warranted and recommended for all patients with thymic carcinoid.

Experts have generally suggested initiating MEN1 management in adolescence, but the optimal surveillance initiation age, tests, and frequencies are still undefined. Best clinical judgment guidelines proposed by the International Workshop on MEN1 [41] recommend to start annual biochemical screenings and periodic imaging studies at age 5 years for known or suspected carriers of *MEN1* mutations. Detailed management recommendations for patients with MEN1 can be found in this reference and in the applicable NCCN Practice Guidelines.

Diffuse gastric cancer

Although gastric cancer is one of the most common cancers worldwide, only 1–3 % is due to an inherited syndrome [44, 45]. Hereditary gastric cancers are typically of the

diffuse or linitis plastic histologic type, as opposed to the more common intestinal histologic type [45–47]. Hereditary Diffuse Gastric Cancer (HDGC) is clinically diagnosed in families with either two or more cases of diffuse gastric cancer among first/second degree relatives when one is diagnosed under the age of 50, or families with three cases of diffuse gastric cancer among first/second degree relatives diagnosed at any age [48–50]. In populations with low rates of gastric cancer, 30–50 % of families meeting these criteria have been shown to carry germline *CDH1* mutations [51–53]. *CDH1* (E-cadherin) codes for a highly conserved cell adhesion molecule which is highly expressed in epithelial tissues [54].

Lifetime risk for gastric cancer in patients with HDGC is greater than 80 % and women also have up to a 60 % risk for breast cancer, specifically lobular histology [45, 51, 55]. Emerging data indicates that there may also be an increased risk for colon cancer in families with HDGC [45]. The average age at gastric cancer diagnosis is 38 years but reported ages range from 16 to 68 [53]. Surveillance recommendations for gastric cancer in HDGC have been controversial given limited efficacy of endoscopy for detection of diffuse (intermucosal) gastric cancer [56, 57]. Prophylactic gastrectomy is an option with relatively high uptake per case series of HDGC families; in 2010, the International Gastric Cancer Linkage Consortium recommended that patients with *CDH1* mutations be advised to consider prophylactic gastrectomy [45, 51, 52]. High-risk breast surveillance with inclusion of breast MRI has been recommended for women with HDGC given the elevated risk for lobular breast cancer [45].

While the criteria described above are used to make a clinical diagnosis of HDGC, *CDH1* genetic testing can aid in the evaluation of families suspicious and/or diagnostic of HDGC. A clinical genetic evaluation is available and recommended for any patient meeting the above diagnostic criteria *or* any one of the following criteria: (1) single case of diffuse gastric cancer diagnosed before the age of 40; (2) both diffuse gastric cancer and lobular breast cancer in the same woman; (3) a family member with diffuse gastric cancer and a family member with lobular breast cancer [45, 58]. Identification of the genetic cause in these families allows for high-risk management in the proband, identifies the elevated risk for breast cancer in women, and allows for identification of family members who are, and are not, at significantly heightened risk for gastric and breast cancer.

Fallopian tube and primary peritoneal cancers

Primary peritoneal carcinomas and fallopian tube carcinomas are rare gynecologic malignancies, often difficult to distinguish pathologically from primary ovarian cancers [59]. Over the past 10 years, it has become evident that these tumors can be associated with the well-recognized hereditary breast and ovarian cancer (HBOC) syndrome [60–62].

HBOC is caused by inherited mutations in the *BRCA1* and *BRCA2* (*BRCA*) genes. In women, *BRCA* mutations confer a 45–87 % lifetime risk of breast cancer and an 11–54 % risk of ovarian cancer [63–67], compared to general population risks of 12 and 1.4 %, respectively [68]. For women with *BRCA* mutations, the risk ratio to develop a fallopian tube cancer has been calculated to be 11.3 [60] and following prophylactic bilateral salpingo-oophorectomy, the remaining risk of primary peritoneal cancer is estimated to be as high as 4.3 % at 20 years post-BSO [69]. In men, *BRCA2* mutations confer up to a 7 % lifetime risk of breast cancer; the risk is felt to be considerably lower in *BRCA1* mutation carriers [70, 71]. Other cancers in which there has been shown to be an increased risk include prostate cancer, pancreatic cancer, and malignant melanoma [70, 72].

Several small studies, often in isolated ethnic populations, have looked to determine the incidence of *BRCA* mutations in individuals with primary peritoneal carcinomas or fallopian tube carcinomas, unselected for age and family history. In two studies of Ashkenazi Jewish populations in which the carrier frequency of *BRCA* mutations is increased, 28–41 % of women with primary peritoneal carcinoma were found to harbor a founder *BRCA* mutation [60, 73]. In a Canadian sample of 51 women with fallopian tube cancers, 16 % were found to carry *BRCA* mutations [74]. In an American sample of 28 patients with primary fallopian tube cancers, 43 % were found to carry *BRCA* mutations [75]. In a study of 29 Ashkenazi Jewish women with primary fallopian tube cancers, 17 % were found to carry a *BRCA* founder mutation [60]. For both types of cancer, the diagnosis has been shown to occur on average 8–10 years younger in *BRCA* mutation carriers in comparison to those with sporadic cancers [60, 75].

A variety of risk management options exist for mutation carriers, including increased surveillance, chemoprevention, and prophylactic surgical options. Detailed management recommendations for individuals with HBOC can be found in the NCCN Practice Guidelines. Given the risk for fallopian tube cancer, it has been recommended that female *BRCA* mutation carriers who undergo risk-reducing oophorectomy have their fallopian tubes removed as well [61, 62, 76]. Given the risk of an occult cancer at the time of prophylactic bilateral salpingo-oophorectomy (PBSO), serial-sectioning of the ovaries and fallopian tubes is recommended following a high-risk protocol [76–78]. Studies have shown that 2–17 % of *BRCA* mutation carriers who undergoing PBSO are found to have an occult ovarian or fallopian tube carcinoma at the time of surgery, many of

which are shown to arise in the fimbriae of the fallopian tube [69, 77, 78].

Primary peritoneal carcinoma and fallopian tube carcinomas are recognized as part of the HBOC tumor spectrum and genetic risk assessment is recommended for any woman with a diagnosis of one of these tumors, regardless of age at diagnosis or family history [79].

Leiomyosarcoma

Leiomyosarcomas (LMS) are malignant mesenchymal tumors with features of smooth muscle differentiation. They account for 23.7 % of all soft tissue sarcomas (STS) and are the most common STS subtype [80]. LMS develop principally in adults between 50 and 60 years of age, are more common in women than men, and can occur in a variety of anatomical sites including the uterus, retroperitoneum, skin, superficial soft tissues, and deep compartments of the extremities [81].

While most LMS are sporadic in origin, LMS have been reported in families with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome, Lynch Syndrome, and Hereditary Retinoblastoma. There have also been a few case reports in patients with *p53* and *BRCA* gene mutations [82–84].

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome

This rare syndrome is characterized by leiomyomas of the skin and uterus and renal cell carcinomas (papillary type II and collecting duct) [85]. HLRCC is caused by germline mutations in fumarate hydratase (*FH*), a tumor suppressor gene that encodes for a Krebs cycle enzyme. Mutations are found in approximately 90 % of individuals with cutaneous leiomyomas [86, 87].

In females, the risk for uterine leiomyomas by age 45 years is greater than 75 %, and the risk for cutaneous leiomyomas is greater than 70 % [88]. Nearly all males with HLRCC have cutaneous leiomyomas by age 35 years [85]. The estimated frequency of renal cell carcinoma (papillary type 2 and collecting duct) is approximately 15–30 % [86]. Individuals with HLRCC are also at risk for developing leiomyosarcomas at various sites, most often the uterus [89]. To date, six cases of "uterine leiomyosarcoma" have been reported in HLRCC families; however the exact risk in HLRCC remains unclear [90].

There are currently no consensus criteria for a clinical diagnosis of HLRCC. The diagnosis is generally based on testing the enzymatic levels of fumarate hydratase and/or germline genetic testing. The following features warrant referral for genetic risk assessment: multiple cutaneous leiomyomas of which at least one has been histopathologically confirmed; an individual who has a single leiomyoma in the presence of a family history of HLRCC; or, an individual who has one or more tubulopapillary, collecting duct, or papillary type II renal tumors, with or without a family history of HLRCC [91].

Identification of HLRCC identifies the increased risk for renal cancer and allows for high-risk management in the proband and family members. At present there is no consensus on clinical surveillance of individuals with HLRCC. Published management recommendations [92, 93] include: baseline renal ultrasound examination and abdominal CT scan with contrast or MRI at age 20 to screen for renal tumors followed by annual MRI and semi-annual ultrasound examinations, annual gynecological ultrasound examination of females starting at age 20, in addition to detailed dermatologic examination for evaluation of lesions suspicious for cutaneous leiomyosarcoma.

Lynch syndrome (also known as hereditary non-polyposis colorectal cancer syndrome, HNPCC)

Lynch syndrome is an autosomal dominant syndrome characterized by an increased risk of colorectal cancer as well as cancers of the endometrium, biliary tract, ovary, ureter and renal pelvis, stomach, pancreas, brain, and sebaceous neoplasias [94]. The lifetime risk of cancer is as high as 80 % by age 70 with colon and uterine being the most common tumors [95, 96]. Lynch Syndrome is caused by an inherited mutation in the DNA mismatch repair genes *MLH1* and *MSH2* and, to a lesser extent, *MSH6, PMS2,* and *EPCAM* (*TACSTD1*) [97, 98].

In 2002, Medina et al. [99] reported the occurrence of a pleiomorphic paravertebral leiomyosarcoma in a young female whose family history was diagnostic of Lynch syndrome. Tumor analysis revealed microsatellite instability, reinforcing the association of the leiomyosarcoma as a component Lynch tumor in this family. Additional cases of leiomyosarcomas in individuals with Lynch Syndrome have been reported [100, 101]. While not formally part of Lynch Syndrome, individuals with LMS should be worked up for Lynch Syndrome in the context of additional suggestive personal and/or family history. Identification of Lynch Syndrome allows for implementation of high risk surveillance and prevention options to reduce morbidity and mortality. Management recommendations for patients with Lynch Syndrome can be found in the NCCN Practice Guidelines.

Hereditary retinoblastoma

Long-term follow-up of a cohort of survivors of hereditary retinoblastoma revealed a statistically significant excess of

leiomyosarcoma and other soft tissue sarcomas that persists decades after the retinoblastoma (RB) diagnosis [102]. Osteosarcoma is the most common soft tissue secondary malignancy in individuals with hereditary retinoblastoma, although there have been at least 18 cases of leiomyosarcoma reported as a secondary neoplasm [103]. These often originate within the field of prior radiation with 78 % of leiomyosarcomas diagnosed 30 or more years after the retinoblastoma diagnosis. Bladder leiomyosarcoma has also been associated with hereditary RB with the longest reported interval between diagnosis and follow-up evaluation being 5 years [102, 104].

At this point in time, a single case of leiomyosarcoma does *not* warrant genetic testing for a particular gene/s but if a detailed personal and family history identified features suggestive of one of the aforementioned hereditary cancer syndromes, genetic testing would be indicated [92]. Genetic counseling for patients with leiomyosarcoma can help determine which cases warrant genetic testing and which do not.

Medullary thyroid carcinoma

Medullary thyroid carcinoma (MTC) accounts for 5–10 % of all thyroid cancers diagnosed in the U.S. [105]. Twenty-five percent of these cases are hereditary (due to germline *RET* mutations) [106]. Germline mutations in the *RET* proto-oncogene cause Multiple Endocrine Neoplasia Type 2 (MEN2). MEN2 can be further categorized into MEN2A, MEN2B, and Familial Medullary Thyroid Carcinoma (FMTC). All MEN2 subtypes confer a nearly 100 % lifetime risk of MTC. Individuals with MEN2A also have up to a 50 % risk of pheochromocytoma and up to a 20–30 % risk of hyperparathyroidism. Those with MEN2B have up to a 50 % risk of pheochromocytoma and exhibit characteristic physical features, including a Marfanoid habitus and mucosal neuromas [107]. FMTC has historically been used to describe families in which four or more individuals have MTC in the absence of pheochromocytoma or hyperparathyroidism [108]. Some individuals with MEN2A or FMTC may also have Hirschsprung's disease due to a specific mutation in exon 10 of the *RET* gene [108].

Genetic testing for the *RET* proto-oncogene is available through several clinical laboratories. Testing typically begins with select exons (10, 11, 13–16), and if no mutation is identified, more extensive testing may be considered. In patients with a clinical diagnosis of MEN2, over 98 % will have an identifiable *RET* mutation [108]. For those presenting with "sporadic MTC," that is MTC in the absence of family history or other signs of MEN2, approximately 7 % will be found to have a germline *RET* mutation [109].

Genetic testing is not only a highly sensitive method used to diagnose MEN2, it also helps to direct medical management as significant genotype-phenotype correlations exist [106]. Probands presenting with MTC should undergo standard surgical treatment and surveillance for residual or recurrent disease [106, 110]. Prophylactic thyroidectomy is recommended for at-risk family members who test positive for a familial mutation. The age at which to perform prophylactic thyroidectomy or biochemical screening for MTC, as well as the age to begin surveillance for pheochromocytoma and/or hyperparathyroidism is dependent on the specific *RET* mutation identified [106]. In contrast to many hereditary cancer syndromes, genetic testing for children *is* recommended because of the obvious benefits of prophylactic thyroidectomy and early surveillance [106].

Given that 25 % of MTC cases are hereditary, all individuals with a history of MTC should be offered genetic testing in the setting of genetic counseling [106].

Paraganglioma and pheochromocytoma

Paragangliomas and pheochromocytomas are rare tumors derived from the parasympathetic and sympathetic nervous systems [111]. Parasympathetic head and neck paragangliomas are typically non-functioning. The sympathetic paragangliomas arise from the adrenal medulla or extra-adrenal ganglia and are typically functionally active as indicated by excess catecholamines [112]. The term pheochromocytoma is used to describe adrenal, intraabdominal, and thoracic catecholamine-producing paragangliomas.

Paragangliomas/pheochromocytomas are a key component of the hereditary cancer syndromes described below. Approximately 30 % of all individuals with a paraganglioma or pheochromocytoma harbor a germline mutation in *RET*, *VHL*, *SDHB*, *SDHC*, *SDHD*, or *NF1* [113]. Four additional susceptibility genes, *SDHAF2,TMEM127*, *SDHA*, and *MAX* have recently been identified which indicates an even higher prevalence of hereditary predisposition to these tumors [114, 115] [116, 117] .

Multiple endocrine neoplasia type 2 (MEN 2)

As described in the previous section, MEN2, caused by mutations in the *RET* proto-oncogene, is a hereditary condition which increases the risk for MTC and pheochromocytoma, as well as primary hyperparathyroidism in individuals with MEN2A. While most patients with MEN2 present with MTC, pheochromocytomas are the first sign in 13–27 % of individuals with MEN2A [118, 119]. Pheochromocytomas in patients with MEN2A are diagnosed at an earlier age, have subtler symptoms, and are more likely

to be bilateral than sporadic tumors [120, 121]. Identifying MEN2 in a patient with pheochromocytoma who has not yet been diagnosed with MTC allows for prophylactic, or in many cases, therapeutic, thyroidectomy.

Von Hippel-Lindau syndrome (VHL)

Germline mutations in the *VHL* tumor suppressor gene cause von Hippel-Lindau Syndrome (VHL). This hereditary cancer syndrome is characterized by hemagioblastomas of the retina, spine, and brain stem; renal cysts and clear cell renal cell cancer; pancreatic cysts and pancreatic islet cell tumors; endolymphatic sac tumors; epididymal cysts; and adrenal or extra-adrenal pheochromocytomas. Approximately 20–30 % of individuals with VHL are diagnosed with pheochromocytoma, typically at an early age (average 22 years) [122]. Genotype/phenotype correlations have been described, with missense mutations leading to higher risks of pheochromocytomas, and a lower incidence seen in families with large deletions or truncating mutations [123]. Identification of VHL in patients presenting with pheochromocytoma allows for appropriate medical management and surveillance including ophthalmologic screening and imaging of the abdomen, spine, and brain to identify benign and malignant lesions.

Hereditary paraganglioma-pheochromocytoma syndromes (PGL/PC)

Mutations of the *SDHB*, *SDHC*, and *SDHD* genes are associated with the three hereditary PGL/PC syndromes known as PGL 4, PGL 3, and PGL 1. Recently, two additional genes have been added to this syndrome. The gene associated with PGL 2 was identified as *SDHAF2* and mutations in the *SDHA* gene were proven to be associated with pheochromocytoma [116, 124]. Variation in the common locations and nature of tumors exists amongst the PGL/PC syndromes; *SDHB* mutation carriers are more likely to be diagnosed with extra-adrenal pheochromocytomas and have a higher risk of malignancy, while benign head and neck paragangliomas predominate in *SDHD,SDHC,* and *SDHAF2* mutation carriers [114, 125, 126]. There have been reports of gastrointestinal stromal tumors in individuals with hereditary PGL/PC, as well as renal cell carcinoma and papillary thyroid carcinoma in *SDHB* mutation carriers [127–129]. While no consensus for management of individuals with hereditary PGL/PC exists, yearly biochemical screening and imaging of the head, neck, thorax, abdomen, and pelvis to detect new tumors may be considered [130].

Neurofibromatosis type 1 (NF1)

Adrenal pheochromocytomas arise in less than 6 % of individuals with a diagnosis of NF1 [131]. Clinical diagnosis of NF1 in adults is based on meeting two of the following criteria: ≥6 café-au-lait macules, ≥2 neurofibromas or ≥1 plexiform neurofibroma, axillary or inguinal freckling, optic glioma, ≥2 Lisch nodules, osseous lesions, and positive family history [132]. Genetic testing for *NF1* is not indicated in simplex cases of pheochromocytoma as these individuals may be diagnosed based on clinical findings [133].

Familial pheochromocytoma (FP)

The first report of mutations in *TMEM127* found that one-third of patients with familial pheochromocytoma and 3 % of patients with sporadic pheochromocytoma without a mutation in the previously described pheochromocytoma genes carried a mutation in *TMEM127* [115]. Additional studies have confirmed the finding of *TMEM127* mutations in patients with adrenal pheochromocytoma as well as extra-adrenal and head/neck paraganglioma [134, 135]. Although knowledge of the pentrance of paraganglioma and pheochromocytoma in individuals with *TMEM127* mutations is in its infancy, studies suggest a surveillance approach similar to that in Hereditary Paraganglioma syndrome [134, 136].

Max

MAX is the most recently described hereditary pheochromocytoma and paraganglioma gene. In preliminary studies, it appears as though individuals with mutations in *MAX* have an increased likelihood of developing malignant pheochromocytomas and paragangliomas and tend to have a positive family history and/or multifocal tumors [117, 137] As with *TMEM127*, more research is necessary to determine the best surveillance approach for individuals with *MAX* mutations.

All of the above syndromes exhibit an autosomal dominant pattern of inheritance. *SDHD,SDHAF2,* and *MAX* are maternally imprinted; therefore, children of females with a mutation will not develop paragangliomas despite inheriting the mutation.

Given that at least 30 % of all individuals with a paraganglioma or pheochromocytoma harbor a germline mutation in one of these genes, all patients with this diagnosis should have a thorough genetics evaluation [113]. Factors that increase the likelihood of detecting a germline mutation include multifocal and bilateral tumors, early age of onset (<45 years), positive family history, and extra-adrenal location [133]. A genetics professional can help to prioritize the gene(s) to be tested by evaluating the patient for features of the associated hereditary conditions.

Renal cell carcinoma—chromophobe, hybrid oncocytotic, oncocytoma histologies

Chromophobe, hybrid oncocytotic, and oncocytoma renal cell carcinomas account for less than 10 % of all renal cell carcinomas [46]. These rare tumors are a key component of Birt-Hogg-Dube (BHD), a hereditary genodermatosis syndrome. Diagnosis of this syndrome amongst renal cell carcinoma patients with these histologies influences surgical management, identifies other symptoms to be screened for, and allows for targeted surveillance and intervention in family members.

BHD is an autosomal dominant syndrome caused by mutations in the tumor suppressor gene *BHD* (also known as *FLCN*) [138, 139] and is characterized by follicular hamartomas (fibrofolliculomas), lung cysts, spontaneous pneumothorax, and renal carcinoma [140, 141]. Germline *BHD* mutations have been identified in approximately 85–90 % of patients with histories highly suggestive of BHD [140, 141].

Confirmed fibrofolliculomas have been reported in 70–85 % of individuals with BHD [140–142]. Angiofibromas, trichodiscomas, and perifollicular fibromas have also been reported in BHD families [140]. Cutaneous manifestations are typically distributed over the face, neck, and/or upper trunk [140, 142, 143]. In regards to lung manifestations, approximately 75–90 % of patients develop lung cysts and 33–38 % have a history of spontaneous pneumothorax [140].

Kidney tumors have been reported in 7–34 % of patients with BHD [140]. The prevalence variability likely reflects ascertainment bias as some reports are based on families ascertained by dermatologic findings while others are based on families recruited because of renal tumor histories. Reported age at diagnosis ranges from age 20 to 74 [143]. Renal tumors in BHD patients are typically multifocal and bilateral and are often slow-growing and with mixed inter- and intra-tumor histology [142, 143]. Typical histologies include hybrid oncocytotic (67 %), chromophobe (23 %), and oncocytotic (3 %) although other renal cell carcinoma histologies, including clear cell, have been reported [142].

There are no consensus-based recommendations for management of patients with BHD however expert opinion recommendations have been put forth [142, 143]. Proposed recommendations include routine surveillance for renal tumors beginning between age 20 and 25 [143]. Given the typical nature of renal tumors in patients with BHD, observation of small tumors is recommended, reserving surgery for tumors over 3 cm or tumors demonstrating accelerated growth [142]. Additionally, nephron-sparing surgery is recommended as opposed to radical nephrectomy whenever possible for BHD patients to reduce morbidity [142, 143]. Identification of BHD in the patient with these rare tumor histologies influences surgical management and also alerts the medical team to the significantly elevated risk of spontaneous pneumothorax.

A genetics evaluation for BHD is recommended for patients with multiple and bilateral chromophobe, oncocytic, and/or hybrid renal tumors and for patients with a single oncocytic, chromophobe, or oncocytic hybrid renal tumor and a family history of renal cancer of these histologies [142–144].

Sebaceous carcinomas

Sebaceous carcinomas are rare adnexal tumors characterized by sebocytic differentiation [145]. These tumors may arise sporadically or in the setting of Lynch syndrome. As described above, Lynch syndrome is inherited in an autosomal dominant pattern due to germline mutations in any one of at least five genes involved in the mismatch repair pathway, *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*. Cancers arising due to defective mismatch repair, including sebaceous carcinomas, exhibit a "molecular fingerprint" known as microsatellite instability [101, 146–151].

Lynch syndrome is characterized by an increased risk for early onset colorectal and endometrial cancers, as well as ovarian, small intestine, stomach, upper urinary tract, and biliary tract cancers and sebaceous neoplasias [152]. When looked at collectively, sebaceous adenomas, epitheliomas, and carcinomas occur in approximately 1–9 % of individuals with Lynch syndrome [153, 154].

The subset of Lynch syndrome characterized by visceral malignancies and sebaceous gland neoplasms and/or keratoacanthomas is also referred to as Muir-Torre syndrome (MTS). Historically, a clinical diagnosis of MTS has been based on the presence of at least one sebaceous neoplasm (sebaceous adenoma or carcinoma) or keratocanthoma and a visceral malignancy [155]. Now, MTS can be diagnosed in patients with a sebaceous carcinoma *prior* to development of a visceral malignancy via germline genetic testing of the Lynch syndrome-associated genes.

The diagnosis of a sebaceous carcinoma provides an important diagnostic clue to a diagnosis of Lynch syndrome. The percentage of unselected sebaceous carcinomas that arise in the setting of Lynch syndrome is estimated to be at least 50 % [156, 157]. The location of sebaceous carcinomas may also be important when determining a risk of Lynch syndrome, with the highest association found in those occurring in non-head and neck locations [158, 159].

Recognition of Lynch syndrome has important clinical implications for the management of both the index patient and relatives. The benefit of identifying individuals with Lynch syndrome is realized through the initiation of a

heightened cancer surveillance for the index patient and at risk relatives. By enabling early detection, regular colonoscopies reduce the colorectal cancer risk by greater than 50 % in at-risk members of Lynch syndrome families [160]. Detailed management recommendations for individuals with Lynch syndrome can be found in the NCCN Practice Guidelines.

Due to the strong association between sebaceous carcinomas and Lynch syndrome, the uncommon occurrence of sebaceous carcinomas in the general population, and the proven clinical utility of the identification of families with Lynch syndrome, several experts recommend that the diagnosis of a sebaceous carcinoma alone should prompt an evaluation for Lynch syndrome regardless of family history, age of onset, or the presence of other malignancies [153, 161, 162].

Sex cord tumors with annular tubules

Sex cord tumors with annular tubues (SCTAT) are rare tumors that fall within the designation of ovarian sex cord-stromal tumors (OSCST), a heterogenous group of tumors that develop from the gonadal non-germ cell component of the ovary [163]. SCTATs were first described in 1970 by pathologist, Dr. Robert Scully [164]. In the initial report, he described 10 cases of distinctive-appearing ovarian tumors characterized by simple and complex ring-like tubules and a tendency for calcification. He also noted that three patients had clinical manifestations of Peutz-Jeghers syndrome (PJS), a hereditary polyposis and cancer predisposition syndrome described below [164].

PJS is an autosomal dominant syndrome characterized by hamartomatous polyps of the gastrointestinal tract and by distinctive mucocutaneous hyperpigmentation [165]. A clinical diagnosis of PJS is made when an individual has either: (1) two or more Peutz-Jeghers polyps in the gastrointestinal tract; or (2) one Peutz-Jeghers polyp in the gastrointenstinal tract, together with either classic PJS hyperpigmentation or a family history of PJS [166].

In addition to the findings of GI polyposis and mucocutaneous hyperpigmentation, individuals with PJS are predisposed to many cancers, including GI malignancies, breast cancer, pancreatic cancer, lung cancer, testicular cancer, and gynecologic malignancies [167–172]. The lifetime risk of cancer is as high as 67–93 % by ages 65–70 [168, 170–172]. Identification of PJS is imperative given the significant increases in cancer risk and the availability of targeted surveillance beginning in childhood. Detailed management recommendations for individuals with PJS can be found in the NCCN Practice Guidelines and in the literature [173, 174].

PJS is caused by inherited mutations in the *STK11* gene (alias of *LKB1*) [175, 176]. It has been shown that when both sequencing and deletion studies (via MLPA) of *STK11* are performed, 94 % of individuals who meet diagnostic criteria are found to have an *STK11* mutation [177]. The detection rate for those who meet these clinical criteria and have a positive family history approaches 100 %, whereas the detection rate is estimated to be 91 % when an individual meets clinical criteria but with absent family history [177]. Clinical genetic testing is available and can be used to help confirm a diagnosis of PJS as well as to provide predictive testing in asymptomatic individuals.

Amongst a series of 74 patients with SCTATs (the largest case series of this rare tumor), 27 (36.5 %) had a clinical diagnosis of Peutz Jeghers syndrome [178]. The mean age of diagnosis in the PJS subgroup was 27 years compared to 34 years in the non-PJS subgroup. Differences in pathologic findings were noted between the subgroups of patients with and without PJS; SCTATs in patients with PJS were more frequently bilateral, multifocal, and with calcifications. Given that approximately one-third of SCTAT patients are likely to have PJS, it is reasonable to consider referring all SCTAT patients for genetic risk assessment. Identification of PJS in these patients prior to development of additional malignancies allows for targeted surveillance and prevention, and ideally, reduced morbidity and mortality.

Conclusion

Although each is rare in occurrence, these ten tumors are commonly associated with inherited cancer susceptibility. As summarized in Table 1, any patient with an adrenocortical carcinoma, thymic gland carcinoid tumor, fallopian tube cancer, primary peritoneal cancer, medullary thyroid cancer, paranganglioma, pheochromocytoma, sebaceous carcinoma, or sex cord tumor with annular tubules has a significant likelihood of carrying a germline mutation and warrants a thorough genetics work-up. Patients with diffuse gastric cancer at a young age, patients with bilateral or multifocal chromophobe, hybrid oncocytotic, and oncocytoma renal carcinomas, and patients with leiomyosarcoma and personal/family history suggestive of HLRCC or Lynch Syndrome should also be referred for a thorough genetics evaluation.

For individuals who are found to have one of the above cancer susceptibility syndromes, both the patient and his/her family are alerted to potential future cancer risks and can take advantage of appropriate surveillance and/or risk reduction. In general, prior to undergoing genetic testing, genetic risk assessment by a cancer genetics specialist (i.e. medical geneticist, genetic counselor, genetic clinical nurse, or other healthcare provider with genetics expertise) is recommended [79, 179, 180]. This allows for

identification of the appropriate gene/s and approach to genetic testing and it allows the patient to receive pre-test counseling, including a discussion of the risks, benefits, and limitations of genetic testing. In addition, genetic test results must be interpreted in the context of the personal and family history given current limitations in genetic testing to ensure appropriate medical management for the patient and the patient's family members.

Conflict of interest The authors declare that they have no conflict of interest.

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