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Endocrine

Genetic testing in endocrine surgery: Opportunities for precision surgery

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ABSTRACT

Recent innovations in molecular and genetic diagnostic techniques have led to rapid advances in genomic medicine and their application to the clinic. The identification and classification of various genetic associations, syndromes, and susceptibility genes in endocrine surgical disorders are increasingly relevant to patient care. Hereditary endocrine disorders represent a significant proportion of disease encountered by endocrine surgeons. Hence, genetic testing has emerged as an important adjunct for the diagnosis and management of patients with endocrine surgical disorders. This article summarizes commonly encountered inherited endocrine disorders and their tumor susceptibility genes, with a focus on the clinical utility of genetic testing and its impact on the surgical management of endocrine disorders.

Introduction

Advances in genetics over the last decade have played a significant role in our understanding of the pathogenesis, diagnosis, and management of various medical conditions. The entire human genome was first sequenced in 2003, an endeavor that cost approximately $3 billion and took about 13 years to complete.[1] Since this milestone, there have been extraordinary technological advances that have reduced the cost and time of sequencing. Currently, clinical evaluation of the entire coding genome can be performed for as little as $1,500 and for even less for targeted, disease-specific gene panels. This reduced cost and accessibility of DNA sequencing has transformed medicine to enable "precision medicine." Precision medicine is the management of disease that is informed by the individual patient's variability in genes, environment, and lifestyle.

The advances in genomic medicine, particularly in endocrine surgery, have led to the clinical use of genetic testing for the identification of new inherited conditions (germline mutations) and tumor-specific genetic drivers (somatic mutations). The importance of genetic changes in human tumors is well documented in publicly available resources such as The Cancer Genome Atlas database,[2] where numerous genetic alterations, both germline and somatic, have been linked to prognosis, treatment response, and/or survival. These advances have made personalized diagnosis and management based upon specific underlying gene mutations identified through genetic testing possible.

In this review, we focus on genetic testing for germline mutations in patients with endocrine surgical disorders. Importantly, germline mutation testing has the potential to benefit (1) affected individuals by providing prognostic, risk of malignancy, and additional disease risk information and (2) at-risk family members through identification and exoneration of affected and unaffected individuals, respectively. Importantly, genetic testing allows for early diagnosis through screening and surveillance and gene-based treatments that are likely to reduce patient morbidity and mortality. Historically, genetic testing has been highly utilized in the diagnosis of endocrine disorders owing to the high heritability and syndromic nature of many of these conditions. Here, we provide an up-to-date overview of genetic testing in endocrine diseases encountered by the endocrine surgeon and its impact on surgical management.

Primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a common endocrine disorder resulting from the autonomous and inappropriate production of parathyroid hormone from 1 or more abnormal parathyroid glands. The diagnosis of PHPT is established by biochemical testing that reveals hypercalcemia with increased, inappropriately high, or non-suppressed parathyroid hormone

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Table I
Hereditary primary hyperparathyroidism*

Syndrome	Susceptibility genes	Clinical features	Surgical management
FHH	*CaSR, GNA11, AP2S1*	Mild to moderate hypercalcemia with relative hypocalciuria. Frequently benign clinical course.	Surgery is not indicated.
FIHP†	*GCM2*	Significant hypercalcemia, nephrolithiasis, and severe osteoporosis.	The optimal surgical approach is still unclear. Given the severity of the disease and high risk of persistence/recurrence, bilateral neck exploration to identify and inspect all parathyroid glands should be performed.
HPT-JT	*CDC73*	Higher risk (>15%) of parathyroid cancer of 1 or more parathyroid glands. High risk of multigland disease. In addition to PHPT, may have uterine cancer, renal cysts, ossifying fibromas of the mandible and/or maxilla, and adult Wilm's tumor.	Bilateral neck exploration. En bloc resection of tumor with surrounding muscles and thyroid lobectomy if carcinoma is suspected. Subtotal parathyroidectomy if no cancer is suspected. Avoid seeding of parathyroid tissue (because of the risk of parathyromatosis). No autotransplantation recommended given increased risk of parathyroid cancer.
MEN1	*MEN1*	Multiple enlarged parathyroid glands. Higher risk of multigland disease, recurrence, thymic carcinoid tumor, and ectopic and supernumerary parathyroid tissue.	Subtotal parathyroidectomy and bilateral cervical thymectomy for index operation. Subtotal or total parathyroidectomy with cryopreservation/autotransplantation (forearm) for recurrent disease.
MEN2A	*RET*	Higher risk of multiple enlarged (25%) parathyroid glands. Typically, asymptomatic versus mild symptoms. Must rule out pheochromocytoma and treat it first before parathyroid surgery. Mutation of codon 634 in exon 11 associated with ~20% risk of PHPT. Mutations in codons 609, 611, 618, 620, 804, and 891 in exons 10 and 13–15 associated with ~5% risk of PHPT.	Directed parathyroidectomy with resection of affected glands. Concurrent total thyroidectomy for prophylactic treatment of medullary thyroid cancer, if thyroid gland is in situ at the time of parathyroid surgery.
MEN4	*CDKN1B, (CDKN1A, CDKN2B, CDKN2C)*‡	Multiple enlarged parathyroid glands. Similar presentation as MEN1. Suspected in patients with MEN1 phenotype but negative *MEN1* gene testing.	Subtotal versus total parathyroidectomy with autologous reimplantation (forearm) and bilateral cervical thymectomy
NSHPT	*CaSR*	Parathyroid hyperplasia. Severe hypercalcemia with relative hypocalciuria in neonates. Hypotonia, osteopenia, and respiratory distress are common.	Most respond appropriately to medical management with cinacalcet. However, subtotal or total parathyroidectomy with auto-transplantation within the neonatal period may rarely be necessary for recalcitrant disease

FHH, familial hypocalciuric hypercalcemia; *FIHP,* familial isolated primary hyperparathyroidism; *NSHPT,* neonatal severe hyperparathyroidism.

* Commercially available testing for these genes is available through companies such as Invitae, BluePrint Genetics, Ambry Genetics, ARUP, and GeneDx. In rare cases when testing is unavailable for individual genes, Exome sequencing or Prevention Genetics offers opportunities for testing of almost any gene. Cost and range of genes tested is subject to change and may vary between companies. In most instances, a custom genetic testing panel is available for specific disease sites.

† FIHP may be inherited in an autosomal recessive fashion.

‡ *CDKN1A*, *CDKN2B*, and *CDKN2C* have been identified but occur with a very low frequency.

levels. PHPT is frequently sporadic, but up to 15% of PHPT cases are inherited.[3] Inherited PHPT has an autosomal dominant pattern of inheritance. Multiple endocrine neoplasia (MEN) types 1, 2A, and 4; hyperparathyroidism jaw-tumor syndrome (HPT-JT); and nonsyndromic familial isolated primary hyperparathyroidism account for inherited PHPT. Inherited PHPT are typically characterized by younger age at presentation, the presence of multigland parathyroid disease, lower rates of biochemical cure, and higher risks of disease recurrence and parathyroid cancer.[4] Although familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism are inherited, they are not surgical disorders.

Although the diagnosis of PHPT is established by biochemical testing, specific genetic mutations influence the clinical manifestation of the disease and the risk of disease recurrence. As such, genetic testing is an important adjunct for the management of these patients. Because of its autosomal dominant pattern of inheritance and the association with various syndromes, genetic testing in all at-risk family members is imperative to institute presymptomatic disease screening, surveillance, and treatment. Additionally, negative genetic testing in a family with a known gene mutation reassures at-risk family members and reduces unnecessary resource utilization for lifelong surveillance.

In addition to a family history of PHPT (including a history of hypercalcemia and/or kidney stone) in 2 or more first-degree relatives, an age of <45 years at diagnosis, recurrent PHPT, and the presence of multigland disease should prompt genetic testing.[3,4] Patients with a positive genetic test should then undergo screening and surveillance biochemical testing and imaging, as dictated by the specific mutated gene and their susceptibility for other diseases (Table I). The most commonly encountered inherited PHPT syndromes, susceptibility gene, and recommended surgical management based on the specific gene mutation are summarized in Table I.

Parathyroidectomy is the only curative treatment for PHPT. The goal of parathyroidectomy is to restore eucalcemia for as long as possible, while avoiding iatrogenic hypoparathyroidism. As described in Table I, the type of genetic mutation identified on a preoperative genetic test influences the surgical approach and the extent of parathyroidectomy. For example, patients with HPT-JT syndrome owing to a germline *CDC73* gene mutation have a high-risk of parathyroid cancer and multigland disease causing their PHPT. Therefore, a bilateral neck exploration, en bloc resection of the tumor with surrounding muscles, and thyroid lobectomy are warranted if cancer is suspected. Furthermore, autografting of parathyroid tissue in patients with HPT-JT syndrome should be avoided because of the risk of parathyroid cancer. In patients with

Table II
Syndromic familial non-medullary thyroid cancer*

Syndrome	Susceptibility gene(s)†	Associated thyroid cancer	Clinical features
Ataxia-telangiectasia	*ATM*	PTC	Impaired coordination of voluntary movements (cerebral ataxia); apraxia of eye movements; oculocutaneous telangiectasia; the absence or rudimentary appearance of a thymus; immunodeficiency; lymphoid tumors; insulin resistant diabetes; radiosensitivity.
Bannayan-Riley-Ruvalcaba syndrome	*PTEN*	PTC, FTC	Macrocephaly; intestinal hamartomatous polyps; lipomas; pigmented maculae of the glans penis; developmental delay and mental retardation.
Cowden syndrome	*PTEN*	PTC, FTC	Hamartomas and epithelial tumors of the breast, kidney, colon, endometrium, and brain; mucocutaneous lesions; macrocephaly.
Carney complex	*PRKAR1*	PTC, FTC	Myxomas of soft tissues; skin and mucosal pigmentation (blue nevi); schwannomas; tumors of the adrenals, pituitary gland, and testicles.
DICER1 syndrome	*DICER1*	DTC	Familial pleuropulmonary blastoma; cystic nephroma; ovarian Sertoli-Leydig cell tumors, Cushing's Syndrome.
Familial adenomatous polyposis	*APC*	PTC	Multiple adenomatous polyps with malignant potential lining mucosa of GI tract, particularly colon.
Pendred syndrome	*SLC26A4, FOXI1, KCNJ10*	PTC, FTC, ATC	Hearing impairment and benign multinodular goiter.
Peutz-Jeghers syndrome	*STK11*	PTC, DTC	Hamartomatous polyps in the gastrointestinal tract; epithelial malignancies, such as pancreas, breast, uterus, ovaries, and testes.
PTEN hamartoma tumor syndrome	*PTEN, PIK3CA, C160RF72, PTPN2, SEC23B, KLLN*	FTC	Cowden syndrome; Bannayan-Riley-Ruvalcaba syndrome; Proteus syndrome; and Proteus-like syndrome.
Werner syndrome	*WRN*	PTC, FTC, ATC	Premature aging; scleroderma-like skin changes; cataracts; premature greying and/or thinning of scalp hair; short stature.

ATC, anaplastic thyroid cancer; *DTC*, differentiated thyroid cancer; *FTC*, follicular thyroid cancer; *PTC*, papillary thyroid cancer.
* Surgical management for syndromic FNMTC is the same as for patients with sporadic thyroid cancer.
† Commercially available testing for these genes is available through companies such as Invitae, BluePrint Genetics, Ambry Genetics, ARUP, and GeneDx. In rare cases when testing is unavailable for individual genes, Exome sequencing or Prevention Genetics offers opportunities for testing of almost any gene. Cost and range of genes tested is subject to change and may vary between companies. In most instances, a custom genetic testing panel is available for specific disease sites.

MEN1 mutation, a bilateral neck exploration with subtotal versus total parathyroidectomy (with autograft) and cervical thymectomy should be performed, because these patients may have parathyroid rests in the thymus that can cause recurrence, and they are at risk of thymic carcinoid. Patients with familial isolated PHPT owing to *GCM2* mutations should also have a bilateral neck exploration and removal of all enlarged parathyroid glands, and, if all 4 parathyroid glands are involved, a subtotal parathyroidectomy should be performed.[5,6]

Familial thyroid cancer

Familial nonmedullary thyroid cancer

Familial nonmedullary thyroid cancer (FNMTC) accounts for 3% to 9% of all thyroid cancer cases and is defined as syndromic (thyroid cancer occurs with other tumors) or nonsyndromic (thyroid cancer is the predominant cancer). Nonsyndromic FNMTC is more common (90% of FNMCT cases), and most studies suggest it is associated with more aggressive disease compared with sporadic thyroid cancer.[7] Patients with nonsyndromic FNMTC present at an earlier age and have a higher rate of persistent and/or recurrent disease, with increased mortality and relatively shorter disease-free survival.[7] Previously, nonsyndromic FNMTC was defined as 2 or more first-degree relatives being affected in the kindred in the absence of other risk factors for thyroid cancer. However, given the high prevalence of thyroid cancer in the general population, a family with only 2 first-degree relatives diagnosed with thyroid cancer (in the absence of other associated diseases) is likely to represent sporadic thyroid cancer. Screening studies[8,9] suggest that nonsyndromic FNMTC should instead be defined as the presence of nonmedullary thyroid cancer (NMTC) in 3 or more first-degree relatives. This definition significantly reduces the likelihood of erroneously diagnosing sporadic thyroid cancer as FNMTC.

In nonsyndromic FNMTC, NMTC occurs in an autosomal dominant pattern with variable penetrance. Compared with syndromic FNMTC, nonsyndromic FNMTC is more common (90%), but the susceptibility gene(s) are not established.[8] Thus, genetic testing is not recommended in affected patients and may not be helpful for at-risk family members. However, all at-risk family members should be screened with thyroid ultrasound, because timely screening leads to earlier detection of FNMTC and has been associated with requiring less aggressive initial treatment in these patients.[9] Screening should begin either 10 years before the earliest age of diagnosis in an affected family member or at 18 years old. Screening ultrasound should be performed every 2 to 3 years.[9]

In syndromic FNMTC, patients are at risk of NMTC in combination with other associated tumors. The syndromes, susceptibility genes, clinical features, and predominant thyroid cancer types found in patients with syndromic FNMTC are summarized in Table II. Owing to the high-risk of thyroid cancer in these patients, screening ultrasound for thyroid cancer should be performed in all at-risk individuals with a germline mutation. Genetic testing therefore allows for the identification of patients at risk of syndromic disease, which is beneficial for early intervention. Surgical management of patients with syndromic FNMTC is the same as that for the management of sporadic thyroid cancer, but these patients are at risk of having tumors at other sites which should be investigated based on the specific gene mutation present.

Medullary thyroid cancer

Medullary thyroid cancer (MTC) represents approximately 5% to 10% of all thyroid cancers, with up to 25% to 40% of these cases being inherited. The penetrance of MTC is almost 100% in inherited

Table III
Genotype-phenotype associations of *RET* mutations and MTC risk*

Risk category based on mutation		Timing for prophylactic thyroidectomy
Highest risk of MTC		
RET Mutation	*Exon*	Prophylactic total thyroidectomy in first few mon or before the first year of life
M918T	16	
High risk of MTC		
RET Mutation	*Exon*	Prophylactic total thyroidectomy by 5 y of age, based on monitoring of calcitonin levels
C634F/G/R/S/W/Y	11	
A883F	15	
Moderate risk of MTC		
RET Mutation	*Exon*	Prophylactic total thyroidectomy anytime in childhood if surveillance and monitoring is not ideal. Otherwise, can monitor calcinonin levels and perform total thyroidectomy when calcitonin levels become elevated.
G533C	8	
C609F/G/R/S/Y	10	
C611F/G/S/Y/W	10	
C618F/R/S	10	
C620F/R/S	10	
C630R/Y	11	
D631Y	11	
K666E	11	
E768D	13	
L790F	13	
V804L	14	
V804M	14	
S891A	15	
R912P	16	

* Modified from Wells et al (2015).[11]

cases and is, in fact, the main cause of morbidity and mortality seen in patients with MEN2. Compared with patients with sporadic MTC, patients with inherited MTC have higher rates of multifocal tumors, have an earlier age of onset, and often have C-cell hyperplasia. The MEN2 syndrome has an autosomal dominant pattern of inheritance and is owing to germline mutations in the *RET* proto-oncogene. An activating mutation in this susceptibility gene is seen in patients with both MEN2A and MEN2B. The specific codon involved confers a particular genotype-phenotype association (Table III), which guides the surgical management (Table IV). The age of onset as well as aggressiveness of the tumor also depend on the type of mutation present. Genetic testing enables early detection of the disease and also allows for the identification of other possible associated syndromes. In fact, earlier detection of MTC has been associated with overall better survival in patients with MTC.[10] Genetic testing should therefore be offered to all patients with a suspected diagnosis of MTC.

The genotype-phenotype associations and options for surgical management in inherited MTC are summarized in Table III and Table IV. Prophylactic and/or early thyroidectomy is the only curative option for patients with MTC who test positive for a *RET* mutation, but who have no clinical evidence of disease (normal calcitonin and thyroid ultrasound). Due to the high risk of developing MTC over their lifetime (>90%), prophylactic thyroidectomy is recommended for all patients who are carriers of the *RET* mutation.[11] Surgical resection also provides the best chance of cure for patients who present with locoregional disease. In patients with MEN2 diagnosed by genetic testing with no prior clinical evidence of MTC, the timing of surgery is critical and is based on a genotype-phenotype association that is used to stratify risk (Table III) and determines an age-appropriate surgical intervention (Table III).[11] For example, patients with the highest risk gene (codon M918T) mutation should undergo total thyroidectomy in early infancy.[11] Furthermore, because of the high risk of tumor multifocality in patients harboring the *RET* mutation, total thyroidectomy is recommended. Genetic testing, therefore, determines the timing, as well as extent of thyroidectomy in patients with MTC. Furthermore, work up for other tumors such as pheochromocytoma have a genotype-phenotype association and should be treated before thyroidectomy for MTC.

Pheochromocytoma/paraganglioma

Pheochromocytoma and paraganglioma (PPGL) are rare neural crest cell-derived tumors of the adrenal medulla and extra-adrenal sympathetic and parasympathetic ganglia, respectively. PPGL represents the most heritable tumor in humans, with up to 50% of PPGL occurring as a result of germline mutation in a susceptibility gene. Furthermore, prior studies have shown that up to 27% of patients with apparently sporadic disease harbor a PPGL-related germline mutation.[12] As a result, it is recommended that all patients with PPGL should undergo genetic testing.[13]

A growing number of susceptibility genes and syndromes associated with PPGL have been identified with some genotype-phenotype associations (Table V). Most PPGL are benign, but the specific gene mutation present may be associated with high rates of metastatic PPGL, particularly in patients with *SDHB* germline mutations.[14] Management of PPGL is increasingly influenced by emerging genotype-phenotype associations, making genetic testing central to disease management. The preoperative identification of these genes by genetic testing has been shown to impact the surgical approach and the extent of adrenalectomy.[15,16] For example, patients with PPGL and a mutation in *NF1*, *RET,* or *VHL* have a low risk of metastatic disease, and as such may be good candidates for laparoscopic and/or partial adrenalectomy, especially if the tumor is small (<2–3 cm), and there is no family history of metastatic disease. Conversely, patients with a mutation in *SDHB*, *FH,* or *MAX* and a large primary tumor have a higher risk of metastatic disease and may require open and total adrenalectomy. Additionally, knowledge of genetic mutation status has been associated with increased overall disease-free survival[17] and leads to optimal treatment, follow-up, and surveillance.[18]

Neuroendocrine tumors

Neuroendocrine tumors (NETs) are a heterogenous group of neoplasms that arise from neuroendocrine cells of various endocrine organs. These include tumors of the gastroenteropancreatic system, catecholamine-secreting tumors (PPGL), medullary thyroid cancer, and pituitary tumors. Although a majority of NETs were previously thought to be sporadic, it has become increasingly evident that NETs are associated with various syndromes and arise from germline mutations in specific susceptibility genes.[19] The genetic background of pancreatic NETs (PNETs) has important implications in the natural history and optimal management of these tumors. Approximately 10% of PNETs are inherited, and the syndromes associated with PNETs are summarized in Table VI.

Indications for surgical management of PNETs include hyperfunctioning tumors (except for MEN1-associated localized gastrinomas) and nonfunctioning tumors causing locoregional symptoms or tumors that are metastatic or potentially malignant. In localized nonfunctioning PNETs, tumor size, in addition to biochemical profile, tumor grade, and imaging features, has been used as an indication for surgical resection based on a higher risk of

Table IV
Inherited medullary thyroid cancer*

Syndrome	Susceptibility genes	Clinical features	Surgical management
MEN 2A	*RET*	MTC, primary hyperparathyroidism, PPGL (usually bilateral).	Total thyroidectomy ± central /bilateral neck dissection based on location and size of the primary MTC, ultrasound findings, and results of biochemical screening (calcitonin, CEA).[11] In patients with both MTC and PPGL, PPGL should be resected first to prevent risk of fatal hypertension at the time of surgery for MTC. Prophylactic total thyroidectomy in children based on specific mutation identified (before age 5 in MEN2A with high-risk mutation, within first y of life in MEN2B —see Table III)
MEN2B	*RET*	MTC (typically more aggressive than in MEN2A, with increased risk of cervical lymph node metastasis and hematogenous spread), PPGL, marfanoid body habitus, mucosal neuromas.	

* Commercially available testing for these genes is available through companies such as Invitae, BluePrint Genetics, Ambry Genetics, ARUP, and GeneDx. In rare cases when testing is unavailable for individual genes, Exome sequencing or Prevention Genetics offers opportunities for testing of almost any gene. Cost and range of genes tested is subject to change and may vary between companies. In most instances, a custom genetic testing panel is available for specific disease sites.

Table V
Inherited pheochromocytoma/paraganglioma*

Syndrome	Susceptibility genes‡	Clinical features	Surgical management considerations†
Carney-Stratakis syndrome	*SDHB, SDHC, SDHD*	Dyad of PPGL and GISTs, with risk of RCC.	Patients with large tumors and SDHB mutation have a high risk of malignant tumors, so open resection and prophylactic lymphadenectomy should be considered.
Hereditary PPGL syndrome	*SDHA, SDHB, SDHC, SDHD, SDHAF2*	Most common germline mutations found in hereditary PPGL. *SDHB* related with higher morbidity and mortality and higher risk of malignancy. GISTs, renal cell carcinoma, pituitary adenomas.	Patients with large tumors and SDHB mutation have a high risk of malignant tumors, so open resection and prophylactic lymphadenectomy should be considered.
HIF-related PPGL	*HIF2α/EPAS1*	PPGL, polycythemia.	High risk for multiple tumors that should be localized preoperatively to avoid persistent disease.
MAX-related PPGL	*MAX*	PPGL, renal cell carcinoma, renal oncocytoma.	High risk of malignant tumors, should consider open resection for large tumors and include prophylactic lymphadenectomy.
MEN2A/B	*RET*	Recurrent and bilateral PPGL with a relatively low risk of malignancy. Pheochromocytoma much more likely than Paraganglioma. Mutation in codons 918, 833, and 634 on exons 16 and 11; associated with ~50% risk of pheochromocytoma. Mutation in codons 609, 611, 618, and 620 in exon 10; associated with ~20% risk of pheochromocytoma. Mutation in codons 804 and 891 in exons 13–15; associated with ~5% risk of pheochromocytoma.	Consider partial adrenalectomy to avoid need for steroid replacement because there is low risk of malignant tumors.
TMEM-related PPGL	*TMEM127*	Pheochromocytoma more likely than Paraganglioma. RCC.	
VHL	*VHL*	Pheochromocytoma more likely than Paraganglioma, low risk of malignancy. Clear-cell renal cell carcinoma, pancreatic islet cell tumors, lymphatic sac tumors, hemangioblastoma of the kidney, pancreas, cerebellum, and retina.	Consider partial adrenalectomy to avoid need for steroid replacement because there is low risk of malignant tumors.
Von Recklinghausen's disease	*NF1*	Relatively later age of presentation, pheochromocytoma more likely than paraganglioma. Neurofibromas, dermal café-au-lait spots, Lisch nodules, bone dysplasia, skinfold freckling, optic gliomas.	Consider partial adrenalectomy to avoid need for steroid replacement because there is low risk of malignant tumors.

GIST, gastrointestinal stromal tumor; *HIF*, hypoxia inducible factor; *RCC*, renal cell carcinoma.

* Mutations in the following genes have also been described but are either very rare, have not been well-studied, or have not been associated with any known genetic syndromes: *FH, SLC25A11, GOT2, MDH2, PHD2, KIF1β, MERTK, MET,* and *H3F3A*.

† Owing to the high risk of catecholamine secretion of PPGL, it is important that patients undergo preoperative alpha blockade before surgical intervention to reduce the risk of intraoperative and postoperative morbidity and mortality related to hemodynamic instability.

‡ Commercially available testing for these genes is available through companies such as Invitae, BluePrint Genetics, Ambry Genetics, ARUP, and GeneDx. In rare cases when testing is unavailable for individual genes, Exome sequencing or Prevention Genetics offers opportunities for testing of almost any gene. Cost and range of genes tested is subject to change and may vary between companies. In most instances, a custom genetic testing panel is available for specific disease sites.

metastasis/malignancy for tumors >2 cm in size. However, the risk of metastatic/malignant disease in inherited PNETs as compared with sporadic PNETs by tumor size is different. For example, the risk of metastatic/malignant disease is low in von Hippel Lindau (VHL)-associated PNETs that are less than 3 cm, and thus surgical intervention is only recommended for tumors >3 cm, or when there is tumor growth.[20] Recently, Tirosh et al demonstrated that patients with VHL-associated PNETs who had a missense mutation or any

Table VI
Genetic syndromes associated with pancreatic neuroendocrine tumors*

Syndrome	Susceptibility genes	Clinical features	Surgical management
MEN 1	*MEN1*	Pancreatic NETs. May be functioning or nonfunctioning. Functioning tumors typically secrete gastrin, but may also secrete insulin, glucagon, or VIPs. Primary hyperparathyroidism, adrenal adenoma, pituitary adenoma.	All functional tumors should be resected except for localized gastrinomas. Nonfunctional tumors <2 cm may be managed nonoperatively with close surveillance. Tumors >2 cm require surgical resection.
MEN4	*CDKN1B*	Similar to MEN1 with parathyroid, pancreas, and pituitary NETs.	All functional tumors should be resected except for localized gastrinomas. Nonfunctional tumors <2 cm may be managed nonoperatively with close surveillance. Tumors >2 cm require surgical resection.
Tuberous Sclerosis	*TSC1, TSC2*	Islet cell tumors in the pancreatic body or tail, leading to insulinomas (more common in *TSC2* mutations). Multiple hamartomatous lesions of the skin, brain, lungs, heart, and kidneys and neurologic symptoms.	Surgical management usually based on location of tumor, associated symptoms and risk of metastatic disease, and risks of planned intervention.
Von Hippel Lindau	*VHL*	Typically, nonfunctioning pancreatic NET. PPGL, clear-cell renal cell carcinoma, pancreatic islet cell tumors, lymphatic sac tumors, hemangioblastoma of the kidney, pancreas, cerebellum, and retina,	Surgical intervention indicated in patients with primary tumor >3 cm. Patients with missense mutations or any mutation in exon 3 are more likely to require surgical management.
Von Recklinghausen's disease	*NF1*	Gastroenteropancreatic NETs (GIST more common than pancreatic NETs). PPGL, multiple café-au-lait skin lesions, Lisch nodules, cutaneous fibromas, axillary and inguinal freckling.	No established guidelines on surgical management owing to limited data. Surgical management usually based on location of tumor, associated symptoms and risk of metastatic disease, and risks of planned intervention.

GIST, gastrointestinal stromal tumor; *VIP,* vasoactive intestinal peptide.
* Commercially available testing for these genes is available through companies such as Invitae, BluePrint Genetics, Ambry Genetics, ARUP, and GeneDx. In rare cases when testing is unavailable for individual genes, Exome sequencing or Prevention Genetics offers opportunities for testing of almost any gene. Cost and range of genes tested is subject to change and may vary between companies. In most instances, a custom genetic testing panel is available for specific disease sites.

mutation type of the *VHL* gene in exon 3 were more likely to undergo surgical intervention (had tumor growth or developed metastatic disease) at a higher rate compared with patients with other mutation types.[21] Furthermore, in silico computational analysis of the germline missense *VHL* mutations showed those that had >80% prediction for disease-causing mutations had aggressive tumors.[22] Similarly, in MEN1-associated nonfunctioning PNETs, genotype-phenotype associations have been reported. Christakis et al observed that patients with *MEN1* mutations in exon 2 had a higher rate of PNETs and distant metastasis as compared with patients with *MEN1* mutations in exons 3–10.[23] *MEN1* missense germline mutations have also been associated with PNET progression as compared with nonsense and frameshift mutations.[24] However, the genotype-phenotype associations in MEN1 have not been consistently observed in all studies.

Genetic testing in patients with PNETs provides an opportunity for early diagnosis even before the development of symptoms, thereby maximizing the potential for cure. In fact, genetic testing in patients with MEN1 has been shown to identify patients with the mutation on an average of 10 years earlier, before development of any clinical symptoms of the disease.[25] Moreover, the indication for treatment in patients with PNETs should consider whether it is sporadic or inherited because the natural history of these tumors may be different based on the susceptibility gene involved. As the number of genes implicated in NETs continue to increase, it is important that patients with NETs undergo genetic testing to allow comprehensive analysis of possible susceptibility genes and for early detection of at-risk patients. Although there are no well-established criteria for genetic testing in patients with PNETs, a family history of PNETs, presence of diseases involved in syndromic PNETs in the individual patient, and/or first-degree relative with any of the diseases associated with syndromic PNETs are suggestive of inherited PNETs. However, given the prevalence of 10% of PNETs being inherited, we believe all patients with PNETs should undergo genetic testing for the known susceptibility genes associated with PNETs.

In conclusion, many endocrine disorders encountered by endocrine surgeons are inherited with known susceptibility genes. Most of these diseases are also syndromic and may have known genotype-phenotype associations. Genetic testing therefore provides important information for the accurate diagnosis and surgical management of these patients, especially in patients with PHPT, MTC, PPGL, and PNETs. Advances in genomic medicine over the last decade with the introduction of next-generation sequencing and targeted disease-specific gene sequencing have allowed for more rapid, cost-effective, and accurate testing of susceptibility genes. It is imperative therefore that surgeons are aware of the various syndromes and genetic predisposition associated with frequently encountered endocrine diseases because this information provides opportunities for precision surgery and likely lead to better outcomes.

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