THEMATIC REVIEW

HEREDITARY ENDOCRINE TUMOURS: CURRENT STATE-OF-THE-ART
AND RESEARCH OPPORTUNITIES**Challenges and opportunities in genetic
counseling for hereditary endocrine neoplasia
syndromes**

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Abstract

The Genetic Counseling Working Group from the 16th International Workshop on Multiple Endocrine Neoplasia (MEN 2019) convened to discuss contemporary challenges and opportunities in the area of genetic counseling for individuals and families affected by hereditary endocrine neoplasia syndromes. As healthcare professionals with multidisciplinary training in human genetics, risk assessment, patient education, psychosocial counseling, and research methodology, genetic counselors bring a unique perspective to working toward addressing these challenges and identifying their subsequent opportunities. This Working Group focused on the following broad areas: (1) genetic counseling resources for endocrine neoplasias, (2) candidate gene discovery, (3) implications of increasingly sensitive and expansive genetic testing technologies for both the germline and the tumors, and (4) situating clinical diagnoses for hereditary endocrine neoplasia syndromes in the context of present-day knowledge.

Key Words

- ▶ multiple endocrine neoplasias
- ▶ genetic counseling
- ▶ hereditary endocrine disease
- ▶ clinical genetics

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Introduction

The goals of achieving a genetic diagnosis in the setting of hereditary endocrine neoplasia (HEN) syndromes include: to understand the basis for disease, provide anticipatory guidance for early detection (or prevention) of manifestations, predict likelihood of tumor progression toward malignancy, uncover targeted treatment options, and offer inherited risk information for family members. Genetic counseling has long been an integral component of the care of individuals and families with these syndromes.

Familial endocrine diseases such as von Hippel Lindau syndrome (VHL) and multiple endocrine neoplasia (MEN) are among the first described hereditary syndromes in medical genetics. The early identification of some of these diseases is owed, in part, to the high hereditary burden associated with certain endocrine diagnoses such as medullary thyroid carcinoma (MTC) and pheochromocytoma/paraganglioma (PCC/PGL). Although the recognition of inherited endocrine disease dates back to the turn of the twentieth century, the underlying molecular changes behind these classically described syndromes were not mapped until the late 1980s (*MEN1*) and 1990s (*VHL*, *RET*, *SDHB*, *SDHC*, and *SDHD*) (Larsson *et al.* 1988, Donis-Keller *et al.* 1993, Leckschat *et al.* 1993, Mulligan *et al.* 1993, Richards *et al.* 1993, Hirawake *et al.* 1997).

The progression of gene discovery paralleled advances in DNA analysis (Fig. 1). In the 1990s and early 2000s,

single nucleotide variant detection methods relied heavily on Sanger sequencing, while copy number variant analysis was done via Southern blot. Subsequent technologies enhanced the ability to detect deletions and insertions, which were previously indiscernible by traditional karyotype analysis. The advent of massively parallel sequencing (MPS) resulted in high-throughput data analysis that was more rapid and economical than the traditional methods. Broad phenotype-based multi-gene panels replaced the single gene testing approach which historically required the provider to prioritize genetic analysis using personal and/or family history presentation as a prediction tool.

The increasing availability and affordability of genetic testing allowed genome sequencing to enter the translational science arena of gene discovery and enhanced phenotyping. In this new era, novel genetic conditions are emerging (for instance, *AIP*-associated familial isolated pituitary adenoma) along with a new appreciation for previously uncharacterized phenotypes (Vierimaa *et al.* 2006). Furthermore, the spectrum of disease is evolving, blurring the lines between once separate and well-defined genetic syndromes. For instance, fumarate hydratase deficiency and increased risk of PCC/PGL in the case of *FH* gene pathogenic variants (Clark *et al.* 2014).

Despite these advances, incorporating multi-gene panel testing via MPS into patient care has also obscured the distinction between clinical and research testing. It has become a common practice to include genes on

Figure 1

Advancements in genetic testing technology have led to the discovery of genes associated with hereditary endocrine neoplasia syndromes. This includes well-established syndromes as well as many newly described genes (*italicized*) with emerging associations to inherited disease.

multi-gene panels that are lacking robust data, such as disease association or management guidelines. On the other hand, increased clinical sensitivity of testing and rapid gene discovery has taken place at unprecedented rates. Newer gene associations have demonstrated genetic heterogeneity by explaining small numbers of previously unsolved cases (e.g. *CDKN1B*-associated multiple endocrine neoplasia type 4) (Clark *et al.* 2014). In addition to the advances in DNA sequencing technology, there is an emerging role of epigenetics, RNA sequencing, polygenic risk (SNPs), and mobile insertion elements on disease causation.

With the influx of candidate genes, critical review of the published literature is necessary to discern variant association with disease from variant observation with disease. Standards in variant classification were not routinely used until the seminal joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) was issued in 2015, rendering published literature prior to that date subject to scrutiny (Richards *et al.* 2015). In addition, the understanding of normal human variation in non-Caucasian and Latinx populations is severely lacking, leading to challenges when interpreting genetic test results in under-represented minority populations. That said, while there has been great progress in the field of genetic counseling as it relates to HEN syndromes and, as shown below, there continue to be opportunities for immense growth.

HEN resources for genetic counselors and other healthcare professionals

Despite the mounting literature in the sub-specialty of HEN syndromes, the publication of comprehensive and consolidated genetic counseling resources for endocrine neoplasia has lagged behind other hereditary cancer/tumor indications. The varied resources are spread across different journals, consortia, and professional societies (Table 1). For providers caring for individuals with personal and/or family histories of breast, ovarian, and colorectal cancers, the National Comprehensive Cancer Network (NCCN) 'Genetic/Familial High-Risk Assessment' guidelines clearly articulate indications for offering genetic testing (NCCN 2019a,b). In addition, these evidence-based recommendations establish surveillance and management recommendations for individuals who have an identified pathogenic or likely pathogenic variant in certain genes.

Since breast, ovarian, and colorectal cancers represent the most common cancer genetics referral indications, many genetic counselors are accustomed to consulting NCCN for testing and management recommendations. These 'Genetic/Familial High-Risk Assessment' guidelines address some diseases, such as Cowden and familial adenomatous polyposis (FAP) syndromes, that have endocrine manifestations. However, there is no dedicated 'Genetic/Familial High-Risk Assessment' NCCN document for all endocrine tumors and even existing recommendations for HEN syndromes are not as easily identifiable within the NCCN guidelines. Specifically, recommendations for multiple endocrine neoplasia syndrome types 1 and 2 (MEN1 and MEN2) are contained within the NCCN 'Neuroendocrine and Adrenal Tumors' treatment guideline and fall short of addressing some of the more complex genetic counseling aspects of these diseases (NCCN 2019c). Furthermore, some diseases regularly assessed in the endocrine clinic, such as hyperparathyroidism-jaw tumor (HPT-JT) syndrome and familial isolated pituitary adenoma (FIPA) syndrome, are not addressed in the NCCN guidelines at all. Anecdotally, cancer genetic counselors who do not specialize in HEN syndromes do not regularly review NCCN treatment guidelines and, therefore, may not be aware that these guidelines from NCCN exist.

Apart from NCCN, many HEN syndrome specialists rely on practice guidelines published by professional organizations, including the Endocrine Society and American Thyroid Association, and by self-assembled expert groups (Thakker *et al.* 2012, Lenders *et al.* 2014, Wells *et al.* 2015). Genetic counseling resources are published by disease-specific consortia or as part of larger hereditary cancer syndrome reviews (Krueger & Northrup 2013, Achatz *et al.* 2017, Evans *et al.* 2017, Rednam *et al.* 2017, Wasserman *et al.* 2017). Genetic counselors and other medical providers who do not routinely see patients with endocrine tumors may not be as familiar with these resources and therefore may not be referencing the most up-to-date guidelines or statements.

In addition to the challenges of identifying resources, there are differences among recommendations put forth for genetic evaluation and/or testing in these conditions (Table 1). MEN1 genetic evaluation and testing guidelines, for example, differ in the age at diagnosis cut-off for individuals with a single parathyroid adenoma, with cut-off ages between 30 and 45 years (Thakker *et al.* 2012, Hampel *et al.* 2015, Wasserman *et al.* 2017). Genetic evaluation and testing guidelines also provide varying levels of detail regarding referral criteria. For example,

Table 1 Current professional society or expert group guidelines relevant to genetic counseling for HEN syndromes.^a

Hereditary syndromes	Genetic evaluation and/or genetic testing	Management and/or surveillance
Hereditary endocrine neoplasia syndromes		
Carney Complex	ACMG/NSGC (Hampel <i>et al.</i> 2015)	ATA (Haugen <i>et al.</i> 2016)
FIPA	None	None
Hereditary PCC-PGL	NCCN (NCCN 2019c)	
	ACMG/NSGC (Hampel <i>et al.</i> 2015)	
	Endocrine Society (Lenders <i>et al.</i> 2014)	
	CCR Pediatric Oncology Series (Rednam <i>et al.</i> 2017)	
HPT-JT	None	CCR Pediatric Oncology Series (Wasserman <i>et al.</i> 2017)
MEN1	NCCN (NCCN 2019c)	
	ACMG/NSGC (Hampel <i>et al.</i> 2015)	
	Expert Consortium Resource (Thakker <i>et al.</i> 2012)	
	CCR Pediatric Oncology Series (Wasserman <i>et al.</i> 2017)	
MEN2	NCCN (NCCN 2019c)	
	ACMG/NSGC (Hampel <i>et al.</i> 2015)	
	ATA (Wells <i>et al.</i> 2015, Haugen <i>et al.</i> 2016)	
	CCR Pediatric Oncology Series (Wasserman <i>et al.</i> 2017)	
MEN4	CCR Pediatric Oncology Series (Wasserman <i>et al.</i> 2017)	
VHL	ACMG/NSGC (Hampel <i>et al.</i> 2015)	Syndrome Specific Resource
	Syndrome Specific Resource	CCR Pediatric Oncology Series (Rednam <i>et al.</i> 2017)
Other CPS with increased risk for endocrine tumors		
Cowden syndrome	NCCN (NCCN 2019a,b)	
	ACMG/NSGC (Hampel <i>et al.</i> 2015)	
	ATA (Haugen <i>et al.</i> 2016)	
	CCR Pediatric Oncology Series (Schultz <i>et al.</i> 2017)	
DICER1 syndrome	CCR Pediatric Oncology Series (Schultz <i>et al.</i> 2017)	
FAP	NCCN (NCCN 2019b)	
	ACMG/NSGC (Hampel <i>et al.</i> 2015)	
	ATA (Haugen <i>et al.</i> 2016)	
	CCR Pediatric Oncology Series (Achatz <i>et al.</i> 2017)	
LFS	NCCN (NCCN 2019a)	
	ACMG/NSGC (Hampel <i>et al.</i> 2015)	
	CCR Pediatric Oncology Series (Kratz <i>et al.</i> 2017)	
MAP	NCCN (NCCN 2019b)	
	ACMG/NSGC ^b (Hampel <i>et al.</i> 2015)	
	CCR Pediatric Oncology Series (Achatz <i>et al.</i> 2017)	
NF1	Syndrome Specific Resource (Hersh 2008)	
	CCR Pediatric Oncology Series (Evans <i>et al.</i> 2017)	
TSC	ACMG/NSGC ^b (Hampel <i>et al.</i> 2015)	
	Syndrome Specific Resource (Krueger & Northrup 2013)	

Entries with ^b denote genetic evaluation and/or genetic testing guidelines that do not include endocrine tumors as an indication.

^aACMG, American College of Medical Genetics and Genomics; ATA, American Thyroid Association; CPS, cancer predisposition syndrome; FIPA, familial isolated pituitary adenoma; NCCN, National Comprehensive Cancer Network; NSGC, National Society of Genetic Counselors; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.

many publications do not specify whether age at presentation should be considered for genetic evaluation referral criteria nor do they provide guidance regarding age at which genetic evaluation should be offered.

A similar degree of heterogeneity exists among existing surveillance and management recommendations, with recommendations for the same condition(s) published by multiple different organizations (Table 1). HEN syndrome surveillance and management recommendations have been generated using a variety of approaches including evidence-based literature review and expert consensus.

In many instances, the various recommendations are complementary. However, it can be challenging to reconcile differences between professional guidelines in regard to screening modalities, age at initiation, and frequency.

Given the issues outlined, an effort should be encouraged to consolidate the current knowledge regarding risk assessment, genetic testing, and syndrome management for HEN syndromes in the same way that NCCN has done for more common hereditary cancer syndromes (e.g. hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome). Collaboration

and coordination between specialists in oncology, endocrinology, and genetics would provide an opportunity to create comprehensive genetic counseling resources. While focusing this effort through NCCN would help to engage the oncology community, it may not adequately reach the greater endocrine community. Given the high hereditary burden of certain benign endocrine tumors, it is of utmost importance to engage and have the support of the providers who encounter these patients in their endocrine clinics. The input of genetic counselors with expertise in HEN syndromes in these efforts helps to bring the most current understanding of cancer genetic risk assessment, genetic testing technologies, and counseling resulting in elevated quality and increased visibility of these resources for the endocrine community as a whole.

Candidate gene discovery

The identification of new genes associated with HEN syndromes has accelerated with the use of exome and genome sequencing (ES and GS, respectively) studies, as well as with multi-gene panel testing. For example, the number of identified genes associated with hereditary primary hyperparathyroidism (PHPT) and PCC/PGL syndromes has increased in recent years (Cascon *et al.* 2015, Guan *et al.* 2016, Remacha *et al.* 2018, 2019). Efforts to identify candidate genes that may provide etiologies of currently unexplained phenotypes are critically important. Ideally, a candidate gene study will lead to an explanation for a hereditary disease. Several factors, though, impact whether or not a gene will make its way into the offers of a clinical genetic testing laboratory and subsequent incorporation into clinical genetics practice.

A genetic testing laboratory can provide analysis for nearly any isolated gene; however, gene analysis does not equate to potential clinical benefit for an individual patient and their family. It is critical that researchers working to identify new genes associated with HEN syndromes should be mindful of the important differences between an observation of gene and disease following ES/GS and a causal relationship. As genes possibly associated with HEN syndromes continue to be identified, it will be important for research groups to deliberate on what steps can be taken to help establish molecular and clinic relevance for a particular gene and/or a specific variant from the time of its discovery. Until evidence including, but not limited to, functional data, molecular pathways, and available population-level data

is uncovered, potential new genes should be considered genes of uncertain significance.

The classification of genetic variation should consider the joint ACMG/AMP variant classification guidelines, which clinical genetic testing laboratories use for diagnostic test reporting (Richards *et al.* 2015). Although these standards are not primarily intended for research use, they do provide important considerations which should be included when publishing research findings on new potential disease associated variants.

Once a candidate gene and/or specific variant has been associated with a HEN syndrome, it also becomes important for researchers to add their findings to publicly available databases of genetic variation. Both research labs and diagnostic genetic testing laboratories contribute variant data to ClinVar, which provides a compelling platform for data-sharing (Landrum *et al.* 2014, 2016, Rehman *et al.* 2015). Variant data in ClinVar can be used by diagnostic genetic testing laboratories to assist with variant classification. When a variant is submitted to ClinVar, another laboratory can reference that entry which could help more quickly establish or exclude a variant's role in hereditary disease. All of these considerations represent meaningful ways to help further the work being done to identify new genes associated with HEN syndromes, an effort that will ultimately benefit the patients and families for which we all care.

Tumor profiling and secondary germline findings

The marked accessibility of genetic analysis has also ushered in advances in tumor profiling; clinicians are able to mine tumor DNA for increasingly large number of somatic (acquired) variants for enhanced diagnostic and prognostication purposes. Testing of germline DNA may occur in parallel for the purpose of aiding the laboratory's bioinformatic ability to distinguish tumor specific variants from germline (inherited) variants. Paired tumor-normal sequencing is primarily used by oncologists to aid treatment decision-making; however, germline findings can incidentally diagnose patients with hereditary disease (Schraeder *et al.* 2016, Cheng *et al.* 2017, Mandelker *et al.* 2017). As the benefit of paired tumor-normal sequencing continues to expand, so too will the number of patients with endocrine tumors who undergo this testing. The oncologic endocrine community should be prepared for the implications this will have on patients and, possibly, their family members.

In some cases, a secondary germline finding is associated with the patient's diagnosis and in others it can be an unexpected, incidental finding. For patients with non-endocrine malignancies, paired tumor-normal sequencing could identify a germline variant associated with a previously unappreciated HEN syndrome (e.g. a woman with ovarian cancer is identified to have a pathogenic *RET* variant associated with MEN2A). Similarly, for patients with endocrine malignancies, an unanticipated hereditary cancer predisposition syndrome could be identified (e.g. a young patient with follicular thyroid cancer is identified to have a pathogenic *PTEN* variant associated with Cowden syndrome) or there could be incidental identification of a more common hereditary cancer syndrome associated with an increased risk for non-endocrine malignancies (e.g. a patient with malignant PGL is identified to have a pathogenic *BRCA1* variant associated with HBOC).

It is critically important that clinicians who incorporate paired tumor-normal sequencing into their practice recognize that this testing cannot be and is not a substitute for traditional germline genetic testing used to diagnose hereditary disease. Paired tumor-normal sequencing platforms may miss a germline alteration for various reasons. Firstly, the gene panel used for paired tumor-normal sequencing may not include all clinically relevant germline variants that have been associated with HEN syndromes. Additionally, understanding the limitations of a preferred paired tumor-normal sequencing platform is necessary, as there can be technical reasons that a germline variant is not reported. Lastly, in some cases, sequencing only investigates tumor DNA without germline analysis, and it would be incorrect to make an inference regarding data in these cases, as variants could be somatic or inherited. In addition to these issues of result interpretation, patients/families who would benefit from genetic counseling and traditional germline testing should still be referred for these services regardless of paired tumor-normal sequencing results. Recently, recommendations have been published to assist clinicians with when and how to incorporate germline analysis into tumor sequencing and how to best manage any subsequent germline implications (Mandelker *et al.* 2019, DeLeonardis *et al.* 2019). Collaborating with genetic counselors on paired tumor-normal sequencing efforts from the beginning can help clinicians interpret these results, make recommendations for the patient and their family members, and ultimately ease the burden of having to reconcile these results while making pivotal decisions about a patient's treatment.

The right approach for clinical diagnoses

Individuals suspected to have a specific HEN syndrome but without an identifiable pathogenic variant pose a tremendous opportunity for research and new discoveries. However, management of these patients and their families can pose a challenge for clinicians. This scenario can also be troubling for patients who may not have an explanation for their disease and who must cope with the uncertainty of whether additional manifestations may develop in themselves or in relatives. Before the identification of genes associated with HEN syndromes, clinicians relied on personal and family histories to determine whether a patient was affected by a given inherited disease. Specifically, if a patient and their family met certain diagnostic criteria, then a clinical diagnosis was assigned and appropriate medical management for affected and unaffected family members was pursued. Though the history and current status of clinical diagnoses for several HEN syndromes are worth discussing, the focus herein will be on MEN1.

MEN1 is a condition with longstanding criteria to both help establish a diagnosis and to provide an indication for genetic testing (Brandi *et al.* 2001). Prior to the identification of the *MEN1* gene, a diagnosis of MEN1 was made using these clinical diagnostic criteria. Still, today if an individual meets these criteria, many providers would continue to follow MEN1 surveillance guidelines even after negative germline genetic testing. Importantly, though, significant discordance has been recognized between index cases meeting clinical diagnostic criteria and their genetic test results wherein up to 10–30% of index MEN1 cases that meet clinical diagnostic criteria do not have an identifiable germline pathogenic variant in *MEN1* (Thakker *et al.* 2012, de Laat *et al.* 2016, Isailovic *et al.* 2019). Furthermore, there have now been several studies published by different groups comparing the phenotypes of gene-positive and gene-negative MEN1 cases, identifying significant differences between these groups (de Laat *et al.* 2016, Pardi *et al.* 2017, Kovesdi *et al.* 2019). Of additional importance, the gene-negative cases often have a weaker or nonexistent family history of MEN1, supporting the idea that these individuals may represent a different entity altogether from highly penetrant MEN1 due to a confirmed germline pathogenic *MEN1* variant (Isailovic *et al.* 2019).

In this era of relatively accurate genetic testing, it may be time to reconsider or redefine the criteria of a clinical diagnosis of MEN1. Additional longitudinal data are needed to confirm or refute the finding that

gene-negative cases tend not to develop a third MEN1-associated tumor, which could help bring into focus a renewed conversation around appropriate management for these apparent phenotype-positive genotype-negative patients (de Laat *et al.* 2016). The field would benefit from considering whether one set of criteria should be used to determine who should be offered gene testing and genetic counseling and then reserve the formal clinical diagnosis for the rare cases that remain highly suspicious for MEN1 even after negative comprehensive gene panel testing.

An alternative approach is to modify the MEN1 clinical diagnostic criteria in order to optimize its sensitivity and specificity. The 'two or more of the associated tumors' style of clinical diagnostic criteria work well for other multiple endocrine neoplasia syndromes, such as MEN2 and VHL, because they are composed of rarer, more specific lesions, but defining the clinical phenotype of MEN1 syndrome is a challenge because it is composed of more common tumors, notably those of the parathyroid and pituitary (Kloos *et al.* 2009, Maher *et al.* 2011). In fact, the combination of those two neoplasms, which currently meets clinical diagnostic criteria for MEN1, has long been identified as a weakness in the specificity of the MEN1 clinical diagnostic criteria, with this combination accounting for the majority of the 'false-positives' in some recently published studies (Agarwal *et al.* 2009, de Laat *et al.* 2016). The recent data discussed here illuminate the opportunity to re-convene an MEN1-experts group, similar to the consensus guidelines meeting of 2012, so that the different research teams can weigh in on the challenges of clinical diagnoses. Pooling experience and modern clinical data would establish a new consensus regarding the appropriate management for those patients and families who are clinically positive and gene-negative following comprehensive gene panel testing. Currently, management practices across and/or between institutions of these patients and their families may be discordant and/or inconsistent.

Efforts to reduce variant uncertainty

A major challenge for both endocrinologists and genetic counselors is managing variants of uncertain significance (VUS) in HEN syndrome-associated genes. For a rare genetic variant associated with a rare disease, particularly a missense or in-frame deletion, it can be difficult to escape the VUS classification even if there is clinical suspicion of pathogenicity. This is especially true for a gene like *MEN1*, when there is currently no well-established functional

study to support a variant's damaging effect on the protein product (Romanet *et al.* 2019b). In the ClinVar database for *MEN1*, approximately 80% of missense variants and 37% of all variants in the gene are classified as a VUS, demonstrating the difficulty of achieving a clinically beneficial variant classification in this gene (Romanet *et al.* 2019a). The VUS result also presents a challenge to the healthcare provider seeking to guide the patient and their family on appropriate next steps, as it is generally not appropriate to use a VUS for medical decision-making.

One approach that has been taken for other genes, including *PTEN*, *TP53*, and *VHL*, is to assemble an expert panel on variant curation through the National Institutes of Health-funded Clinical Genome Resource (<https://search.clinicalgenome.org/kb/gene-validity>). These expert panels are composed of clinicians, researchers, and molecular diagnosticians with expertise in the gene of interest. The goal is to develop and implement gene-specific variant classification criteria, modifying the 2015 ACMG/AMP guidelines to improve the outcomes of variant classification for the gene, thus reducing the number of VUS. This ClinGen approach is similar to the 2019 paper published by the French TENGEn network in which they assembled an expert group to create *MEN1*-specific ACMG-adjusted variant classification criteria and successfully reclassified almost half (39/84) of their observed missense variants, classified as VUS, to pathogenic or likely pathogenic (Romanet *et al.* 2019b). Reducing the number of VUS in genes associated with HEN syndromes through gene-specific variant classification efforts could represent an important step toward clarifying disease status for many patients and their family members.

Emerging phenotype or incidental finding?

The previously described shift in clinical genetics practice from individual gene testing to broad panel-based assessment has led to several opportunities and challenges for the cancer genetics community as a whole and many of these extend to the area of HEN syndromes.

While genetic test ordering practices are still phenotype-driven to a certain extent, many patients will opt for more comprehensive testing since expanded panel testing is typically associated with a similar cost when compared to targeted testing (O'Leary *et al.* 2017). In addition, patients pursuing genetic testing related to an endocrine tumor may benefit from a comprehensive risk assessment due to a family history of other cancers. Beyond the obvious identification of additional risk

factors in a family, this opportunity may allow for further refinement of the risk phenotype associated with known tumor predisposition genes. For example, some studies have demonstrated an enrichment of pathogenic *MUTYH* variants in cohorts of patients with small bowel and pancreatic neuroendocrine tumors (Dumanski *et al.* 2017, Scarpa *et al.* 2017). While this may be coincidental and an artifact of small cohort sizes, it may indicate an emerging impact of this gene on the risk for neuroendocrine tumors and should be further studied.

A challenge that increasingly plagues the clinical cancer/tumor genetics community is the finding of a pathogenic variant in a gene that does not fit with the clinical presentation. Is this a truly incidental finding or is it an unappreciated aspect of an emerging phenotype? For example, when an older woman with metastatic breast cancer is identified to have a germline pathogenic variant in *SDHA*, it is unexpected and the clinician must navigate how to address this incidental finding. Should this woman receive comprehensive screening for PCC/PGL amidst her ongoing breast cancer treatment? If there is no personal or family history of PCC/PGL or other endocrine tumors, does this woman and do her family members face similar risks to families with *SDHA* variants identified as the result of a PCC/PGL diagnosis? Did this *SDHA* variant somehow contribute to her breast cancer diagnosis? In another example, a young man with anaplastic thyroid cancer undergoes paired tumor/germline testing and is identified to have a germline pathogenic variant in the *BRCA2* gene. Could this germline variant have contributed to his thyroid cancer? Are this man's family members who test positive for the same variant at an increased risk for anaplastic thyroid cancer?

It can be tempting to assume that a rare tumor is due to a pathogenic variant in a gene associated with a rare condition, especially in the setting of endocrine neoplasia. For examples, several tumors have been reported to occur in a patient with a diagnosis of Cowden syndrome, including a pancreatic neuroendocrine tumor, atypical lung carcinoid, malignant peripheral nerve sheath tumor, and Ewing sarcoma (Chandhanayingyong *et al.* 2015, Taylor *et al.* 2015, Neychev *et al.* 2016, Tsunezuka *et al.* 2016). Certainly, individuals with hereditary tumor predispositions can coincidentally develop sporadic tumors. So how do we weigh the likelihood of a sporadic co-occurrence vs an underlying association?

As mentioned earlier, ClinGen has assembled expert panels to create specifications by gene to the ACMG/AMP variant interpretation criteria in an effort to reduce variant uncertainty (Rivera-Munoz *et al.* 2018). Another of

ClinGen's ongoing efforts is to evaluate the clinical validity of gene-disease relationships, for which an evidence-based framework has been published and a hereditary cancer working group convened that has already curated many HEN genes, including the *SDHx* genes, *MAX*, *TMEM127*, *CDC73*, and *CDKN1B* (Strande *et al.* 2017; <https://search.clinicalgenome.org/kb/gene-validity>). The upfront application of this framework by researchers may become an important consideration as new HEN genes are discovered and new gene-disease associations suggested. Additional tools for delineating such possible relationships are growing more accessible and include tumor testing for second somatic hits or loss of heterozygosity, functional analyses, and immunohistochemistry. There is also a vital need for more robust national and international disease registries to collect co-diagnosis data in a systematic fashion, allowing the most rigorous and high quality data to be produced.

Toward a better understanding of penetrance and ascertainment

Over the years, much attention has been given to the challenge of estimating the cancer or tumor penetrance that results from the presence of a germline pathogenic variant in a given gene. Since most families are found to have pathogenic variants only after a tumor or cancer diagnosis prompts genetic testing, data gleaned from these families may not accurately reflect the true penetrance for individuals with similar variants and no personal or family history. While this remains a challenge for the field, the adoption of more comprehensive genetic testing patterns will provide the opportunity and data to better study clinical phenotypes and tumor penetrance. Long-term follow-up on individuals incidentally found to have pathogenic variants will provide useful data regarding the role of family history on tumor penetrance. Through cascade genetic testing in family members, additional individuals with pathogenic variants can be identified and followed prospectively, in an effort to more clearly define a disease's penetrance and phenotype. In addition, widespread availability of large-scale genome or exome datasets are proving to be useful tools in unraveling this mystery.

Several recent publications have attempted to leverage this data to address the challenge of penetrance estimates. In one such study, sequence data from 51,000 individuals from complex disease cohorts in the ExAC database (excluding those from The Cancer Genome Atlas, TCGA) were analyzed to determine the frequencies of pathogenic

Box 1: Summary of key points regarding genetic counseling for HEN syndromes

- Endocrine neoplasias have a high hereditary burden
- Multi-gene panels are replacing single gene testing approaches
- Tumor-normal sequencing is not a substitute for traditional germline genetic testing
- Guidelines addressing genetic testing indications, management, and/or surveillance for HEN syndromes originate from a variety of organizations and, in some cases, lack consistency
- Significant gene discovery for HENs is still ongoing, leading to challenges with discerning variant causation from variant association and opportunities for redefining clinical diagnoses, phenotypes, and penetrance

RET variants (Loveday *et al.* 2018). Their analysis found a higher than expected number of p.Val804Met variants which, based on MTC incidence, corresponded to a lifetime penetrance estimate of 4% (with conservative modeling estimating 46%). Both of these estimates are drastically lower than the previous lifetime risk estimate of approximately 74%, as estimated by more traditional methods (Rich *et al.* 2014). The identification of families with pathogenic variants and less tumor burden will also present opportunities for studies regarding genetic and/or environmental modifiers.

This is an area of considerable challenge but of even more significant opportunity. The number of incidental diagnoses made will inevitably increase as more individuals with advanced cancer undergo germline testing. This information has the potential to influence our understandings of HEN syndromes if researchers are prepared to conduct longitudinal studies collecting detailed phenotypic information over decades. Through insights gained regarding tumor penetrance and emerging phenotypes from these data, we have the opportunity to refine screening and surveillance recommendations for individuals found to have pathogenic variants in genes associated with hereditary endocrine neoplasia syndromes and optimize patient outcomes.

Seizing opportunities to better understand HEN syndromes and to provide the best care for the families affected by them is our collective ambition (Box 1). Genetic counselors, whether they be in patient- or non-patient facing roles, are well-positioned to help tackle the dynamic challenges described here and to identify new ones as they arise. This Working Group looks forward to continued, future collaborations in these efforts.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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