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Pheochromocytoma and Paraganglioma: Diagnosis, Genetics, Management, and Treatment

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Introduction

Pheochromocytomas (PHEOs) are rare neuroendocrine tumors that arise from the chromaffin cells of the adrenal glands. Paragangliomas (PGLs), the extra-adrenal counterparts of PHEOs, arise from ganglia along the sympathetic and parasympathetic chain. Although these tumors have been recognized since the early 20th century, many recent advances in the field of PHEO/PGL have fundamentally changed our understanding of these tumors, leading to better diagnostic evaluation, more appropriate patient-specific treatment strategies, and improved patient outcomes. However, there is still no cure for these tumors or successful long-term treatment for patients with metastatic disease; therefore a great deal of research still needs to be done. This extensive review will focus on the most updated information about the diagnosis, genetics, and management of patients with PHEO/PGL and conclude with some perspectives on future treatment strategies and continuing research.

Incidence of PHEO/PGL

PHEO/PGL are rare tumors, affecting about 1 in 2500-6500 individuals, with 500-1600 cases diagnosed annually in the United States.¹ However, their true incidence may be higher due to lack of diagnosis until after death; a review of autopsy cases in Australia found that 0.05% had undiagnosed PHEO/PGL.² They are a rare cause of secondary hypertension, with an incidence in hypertensive patients of only about 0.3-0.5%.^{3,4} Although adrenal PHEOs, the more common of the two, account for about 80-85% of these tumors,⁵ only

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approximately 5-7% of adrenal incidentalomas are PHEOs.^{6,7} The mean age at diagnosis is approximately 43 years of age, but 10-20% of PHEO/PGL are identified in children, commonly associated with underlying genetic conditions.⁸⁻¹⁰

Genetics of PHEO/PGL

Underlying germline mutations in one of 17 susceptibility genes have been associated with approximately 35% of PHEO/PGL. An additional 15% of tumors are associated with somatic mutations in these same genes.¹¹⁻¹⁴ In children, this rate is even higher, with 69% of pediatric PHEO/PGL cases in a Spanish study⁸ and 87.5% of metastatic PHEO/PGL patients who developed their first tumor in childhood⁹ linked to underlying germline mutations. This high percentage of genetically linked tumors underlines the need for appropriate genetic testing as part of the work-up for most patients with PHEO/PGL. A summary of the clinical characteristics of patients with each genetic mutation is presented in Table 1.

Multiple endocrine neoplasia type 2

Multiple endocrine neoplasia type 2 (MEN2) is associated with underlying mutations in the rearranged during transfection (*RET*) protooncogene. The RET protein is a receptor tyrosine kinase that regulates cellular proliferation and apoptosis. Patients with MEN2 are usually first diagnosed with medullary thyroid cancer (MTC), which is the most common condition in these patients. MEN2 is divided into three subclassifications: MEN2A, MEN2B, and familial MTC. Patients with MEN2A have a 95% chance of developing MTC, a 50% chance of PHEO, and a 15-30% chance of hyperparathyroidism; this form of MEN2 is the most common, accounting for approximately 90% of cases. Patients with MEN2B have a 100% chance of developing MTC and a 50% chance of PHEO, but also typically present with a marfanoid body habitus and mucosal ganglioneuromas. Patients with familial MTC do not have a risk of developing PHEO.^{15,16}

Patients who do develop PHEOs usually present with epinephrine/metanephrine-secreting tumors in the adrenal gland, with approximately half presenting with bilateral tumors. However, malignancy is rare, though higher in patients with the more aggressive MEN2B. The age of onset for PHEO is typically between 30 and 40. Although approximately 5% of MEN2A and 50% of MEN2B patients present with *de novo* mutations, the majority have a strong family history, so carriers are typically identified early in life. Thus, early and regular screening usually catches tumors while they are still small, keeping the rate of metastasis low for patients with MEN2.^{15,16}

Von Hippel-Lindau

Mutations in the von Hippel-Lindau (*VHL*) gene cause VHL syndrome.¹⁷ The VHL protein regulates the activity of hypoxia-inducible factor alpha (HIF α) and regulates cellular processes, including angiogenesis. As with MEN2, VHL is characterized by a predisposition to multiple tumor types and can be divided into subclassifications based on the risk of PHEO/PGL. Patients with VHL type 1, the more common form, develop retinal angiomas, central nervous system hemangioblastomas, renal carcinomas, islet cell tumors of the

pancreas, endolymphatic sac tumors, or cysts and cystadenomas of the kidney, pancreas, epididymis, or broad ligament, but do not develop PHEO/PGL. Patients with VHL type 2 are at risk of PHEO/PGL and are further divided into type 2A (without renal carcinomas and infrequent type 1 tumors), type 2B (with renal cell carcinoma or any type 1 tumors), and type 2C (only PHEO/PGL, without any type 1 tumors).^{15,16}

VHL patients usually develop norepinephrine/normetanephrine-secreting adrenal PHEOs, with a high rate of bilateral tumors. The age of onset of PHEO/PGL with VHL is approximately 30 years, though patients as young as 5 have been reported. In addition, there is a relatively high rate of *de novo* mutations (approximately 20%). Metastases are infrequent in patients with VHL, though recurrent and multiple primary tumors can occur.^{15,16}

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) has multiple manifestations that can include PHEO/PGL, in addition to MTC, carcinoid tumors, parathyroid tumors, peripheral nerve sheath tumors, and chronic myeloid leukemia. However, the rate of PHEO/PGL development in NF1 is significantly lower than in VHL or MEN2. Although NF1 is caused by germline mutations in the *NF1* gene,¹⁸ which encodes a GTPase activating protein involved in multiple signaling cascades important to cellular growth and differentiation, genetic testing is rarely performed due to the large size of the gene. Instead, diagnosis is usually based on clinical criteria, often at a young age due to the frequent presence of characteristic café au lait spots from birth. Family history, while a factor in diagnosis, is not necessary, as 50% of cases result from *de novo* mutations. PHEO/PGL are relatively infrequent in NF1 patients, and therefore screening is not usually performed as regularly as with other symptoms. PHEO/PGL tumors usually appear at the same age as sporadic tumors, with a mean age at diagnosis of 42. Epinephrine/metanephrine-secreting adrenal PHEOs are more common than PGLs, and bilaterality is infrequent. However, the metastatic rate for NF1 tumors, approximately 12%, is higher than MEN2 or VHL.^{15,16}

Recently, somatic *NF1* mutations have been linked to the pathogenesis of apparently sporadic PHEO/PGL. In a study of 53 sporadic tumors, 41% were found to have inactivating somatic *NF1* mutations, suggesting that these events are a relatively common cause of PHEO.¹⁹

Succinate dehydrogenase mutations

For many years, additional familial syndromes associated with PHEO/PGL development were recognized clinically, but the mechanism of inheritance was unexplained. It was only with the identification of succinate dehydrogenase subunit D (*SDHD*) mutations in families with familial PGL in 2000 that these syndromes began to be explained molecularly.²⁰ Further study in the following years identified two other subunits, *SDHB*²¹ and *SDHC*,²² as heritability genes for PHEO/PGL. The final subunit in the complex, *SDHA*, was initially only linked to a rare early onset encephalopathy, Leigh syndrome, found in homozygous carriers; however, very recently, heterozygous *SDHA* mutation carriers with PHEO/PGL have been identified.²³ Mutations in a complex assembly factor, SDH assembly factor 2

(*SDHAF2*, also known as *SDH5* in yeast), were also linked to familial PHEO/PGL.²⁴ Because of its role as mitochondrial complex II in both the Krebs cycle and the electron transport chain, *SDH* mutations severely disrupt cellular metabolism. Studies have shown that mutated *SDH* proteins are recognized by cellular protein degradation machinery and have shorter half-lives than wild-type *SDHB*.²⁵ This results in insufficient levels of the *SDH* complex within cells, increasing the accumulation of succinate and causing a state of pseudohypoxia.

Although mutations in the *SDH* genes all affect the same complex, their clinical presentations can vary greatly. *SDH*-related tumors are typically extra-adrenal, although some cases of adrenal PHEOs have also been reported. Tumors related to these mutations usually have noradrenergic or dopaminergic phenotypes, though biochemically silent tumors have also been more frequently associated with *SDH*-related PGLs.^{15,16,26,27} PGLs in the mediastinum and organ of Zuckerkandl are frequently related to underlying *SDHB* or *SDHD* mutations.^{28,29} *SDHD* mutations are also common in head and neck PGLs, the majority of which are biochemically silent.³⁰ However, approximately 20% secrete dopamine and/or its metabolite methoxytyramine, which can be useful for monitoring these patients.³¹ Of note, *SDHD* undergoes maternal imprinting, and therefore PHEO/PGL only arise in patients with affected fathers.^{15,16,32} Multiple tumors are common with *SDHD*, but metastases are rare.^{15,16,30,33}

SDHB mutations, which are the most common gene mutations in PHEO/PGL, tend to be linked more frequently to abdominal or thoracic extra-adrenal PGLs.³⁰ Multiple tumors are identified in many *SDHB* carriers. *SDHB* mutations are also associated with more aggressive tumors, with younger ages at presentation and higher rates of metastases.^{15,16,30,33,34} The explanation for this is unclear, but may be due to lower catecholamine activity in *SDHB*-related tumors, leading to later presentations. In addition, the penetrance of these mutations is lower than with other clinical syndromes, so mutation carriers are often not identified until after they present with a tumor.

SDHC, *SDHAF2*, and *SDHA* mutations are rare, so clinical information is limited. *SDHC* mutations are most frequently associated with multiple head and neck tumors, with a mean age of onset similar to that of sporadic patients. Some extra-adrenal abdominal/thoracic PGLs and adrenal PHEOs have also been found in *SDHC* carriers.^{15,16} *SDHAF2* also appears to be associated with the development of multiple head and neck tumors, often in young patients. Like *SDHD*, *SDHAF2* also appears to undergo maternal imprinting.^{15,16,32} The rate of penetrance of *SDHAF2* mutations appears to be high.^{15,16} *SDHA* mutations have been found in patients with PHEOs and PGLs, but these cases have been isolated, so no larger conclusions can be drawn regarding the importance of *SDHA* testing or the clinical presentation of these carriers.^{15,16}

Although the *SDH* genes were initially thought to be linked exclusively to PHEO/PGL, additional tumor types linked to these mutations have been discovered. Renal cell carcinoma has been found in a fraction of *SDH* carriers, particularly those with *SDHB*, *SDHC*, and *SDHD* mutations, with an estimated 14% of *SDHB* carriers developing this tumor type.³⁵⁻³⁷ Some cases of rare tumor syndromes, Carney-Stratakis dyad and Carney triad have also

been linked to mutations in *SDH* genes.^{38,39} Carney-Stratakis dyad consists of gastrointestinal stromal tumors (GIST) and PHEO/PGL, while Carney triad also includes pulmonary chondromas in addition to GIST and PHEO/PGL. A recent link between *SDH* gene mutations and pituitary adenomas has also been identified, with *SDHA*, *SDHB*, *SDHC*, and *SDHD* mutations all linked to these tumors.^{35,40,41} *SDH* mutations have also been identified in patients with neuroblastoma.⁴²⁻⁴⁴ Finally, there is also an unclear association between *SDH* mutations and breast cancer development^{45,46}; papillary thyroid carcinomas have also been reported in *SDH* mutation carriers.^{45,47} Taken together, these data suggest that *SDH* mutations may represent a metabolic tumor syndrome.

SDH mutations are often found in the absence of family history. However, this is not due to a high rate of *de novo* mutations, but rather a low rate of penetrance. Maternal imprinting in patients with *SDHD* and *SDHAF2* mutations can mask familial inheritance. However, *SDH* carriers who lack a family history of PHEO/PGL may have a family history of other conditions, such as renal cell carcinoma or pituitary adenomas, which could be related to the *SDH* mutation. Studies of the penetrance of *SDH* mutations have established various penetrances. A report by Benn et al. determined a 29% and 45% penetrance of *SDHB* mutations by ages 30 and 40, respectively, and a 48% and 73% penetrance of *SDHD* mutations by ages 30 and 40, respectively (in patients who inherited the mutation from their fathers).³⁰ Similar penetrance values have been determined by Ricketts et al., who calculated a 52% penetrance in *SDHB* carriers by age 60 and a 71% penetrance for *SDHD* carriers.³⁷ However, Schiavi et al. estimated a much lower penetrance of only 30% by age 80 for *SDHB* carriers.⁴⁸ Further study on large patient cohorts will need to be performed to resolve this debate, but the rarity of these mutations makes these studies difficult.

There is a great deal of interest in understanding the mechanism by which *SDH* mutations lead to tumor formation. Loss of heterozygosity resulting in the loss of the wild-type allele has been observed in tumor tissue from affected patients, consistent with Knudsen's two-hit hypothesis.^{13,49} The tumorigenic properties of *SDH* mutations are not believed to be due to dysfunction of the *SDH* protein, but rather to increased mutant protein degradation. In fact, studies of mutant *SDHB* proteins have found a markedly reduced protein half-life, but intact protein localization and *SDH* complex formation.²⁵ However, this increased degradation, and the loss of heterozygosity in tumors, results in decreased activity of complex II (*SDH*), which also results in decreased ATP production and an increase in succinate accumulation.⁵⁰ A recent study has also suggested that increased succinate may lead to increased methylation that affects gene expression, leading to tumorigenesis.⁵¹

Although mutation analysis is the recommended procedure for diagnosing *SDH* mutations, immunohistochemistry can be used on resected tumors to indicate patients with these mutations. Previous reports have shown that *SDHB* immunostaining accurately detects the presence or absence of the *SDHB* protein.⁵²⁻⁵⁴ In cases in which *SDHB* immunostaining is weak, a somatic or germline *SDH* mutation is highly probable. This procedure has a sensitivity of 100% and a specificity ranging from 84-94%.^{52,54} It has also been suggested that the intensity of staining can prioritize certain testing; absent staining is more suggestive of an *SDHB* mutation, while weak staining may be indicative of an *SDHD* mutation.⁵³ Furthermore, patients with *SDHA* mutations, which can sometimes be hard to identify by

traditional sequencing due to gene structure, can be identified by performing a second immunostain for the SDHA protein. While all tumors with *SDHA*, *B*, *C*, and *D* mutations will show negative staining for SDHB, only tumors with *SDHA* mutations will have negative SDHA immunostaining.^{23,55}

MAX

In recent years, the rate of gene discovery in PHEO/PGL has accelerated rapidly, due in large part to advances in genetic research techniques and the broader availability and lower costs of performing genetic analysis. Such studies have identified several genes that are minor contributors to the spectrum of heritable PHEO/PGL through whole-genome analyses. One such gene is myc-associated factor X (*MAX*), which encodes a transcription factor that acts as part of the MYC/MAX/MXD1 network in regulating the myc oncoprotein and interacting with the mTOR pathway to control cellular differentiation, growth, and apoptosis.^{15,16,56} This rare gene mutation, reported in 1.12% of presumed sporadic PHEO/PGL, is predominantly associated with adrenal PHEOs, though some extra-adrenal tumors have been identified.^{15,16,57,58} Bilateral adrenal PHEOs are common.^{15,16,57} Higher rates of metastases have also been reported in patients with *MAX* mutations.^{15,16,56,57} Data has suggested that these mutations may, like *SDHD* and *SDHAF2*, be paternally transmitted.^{15,16,56}

TMEM127

Another gene associated with PHEO/PGL development is transmembrane protein 127 (*TMEM127*).⁵⁹ This gene is linked to the mTOR pathway, though its exact function is unknown. A suggested role in protein trafficking within the endomembrane system has been proposed.⁶⁰ *TMEM127* mutations are a rare cause of PHEO/PGL.^{15,16,58–60} Patients typically present at a mean age of 43, usually with benign, unilateral or bilateral adrenal PHEOs that secrete both norepinephrine/normetanephrine and epinephrine/metanephrine.^{15,16,60} Very rare extra-adrenal tumors have been associated with *TMEM127* carriers. In addition, carriers with breast cancer and papillary thyroid cancer have been identified, but whether these cancers are linked to *TMEM127* mutations is unclear at the present time.^{15,16}

Hypoxia-inducible factor 2-alpha

One of the most recently discovered genes in PHEO/PGL pathogenesis is hypoxia-inducible factor 2-alpha (*HIF2A*). It was first identified as somatic mutations in tumor tissue from patients who presented with multiple PGLs and polycythemia, one of whom also had multiple somatostatinomas.⁶¹ After two additional patients with multiple PGLs, somatostatinomas, and polycythemia were described, a new syndrome, Pacak-Zhuang syndrome, was proposed.⁶² Additional studies confirmed these findings⁶³ and extended this syndrome to adrenal PHEOs.⁶⁴ The mutations in *HIF2A* affected the hydroxylation site, preventing recognition by VHL and decreasing the degradation rate.^{61,65} Interestingly, all patients identified with this syndrome have been female. Germline mutations of *HIF2A* have also been identified, including in one male patient with PGL and polycythemia.⁶⁶

After the initial discovery of *HIF2A* mutations in PHEO/PGL, additional studies were performed to determine whether these mutations underlie other cases of PHEO/PGL previously identified as sporadic. A study of 41 PHEO/PGL with no known mutations identified 7 patients with somatic *HIF2A* mutations, 3 of whom had multiple PHEO/PGLs and polycythemia. The other 4, however, had no known polycythemia, suggesting that *HIF2A* mutations can be factors in the development of PHEO/PGL even in the absence of polycythemia, most likely due to differences in the timing of the occurrence of the mutation.⁶⁷

Other rare genes

Because of the frequency of isocitrate dehydrogenase (*IDH*) mutations in glioblastoma multiforme, a screening of 365 PHEO/PGL tumors was performed to determine if these mutations also contribute to PHEO/PGL. Only one somatic mutation was discovered in a patient with no underlying germline mutation.⁶⁸ Four additional genes, *KIF1Bβ*, *PHD2* (also known as *EGLN1*), fumarate hydratase (*FH*), and BRCA-1 associated protein-1 (*BAP1*), have been identified in isolated cases of familial PHEO/PGL.^{15,16} *KIF1Bβ* is a gene involved in the regulation of apoptosis. Rare cases of patients with PHEOs and neuroblastomas have been reported in association with *KIF1Bβ* mutations.⁶⁹ *PHD2* is a member of the prolyl hydroxylase family and is involved in interactions with HIFα. A *PHD2* mutation has been identified in one family with multiple PGLs and congenital erythrocytosis.⁷⁰ A germline *FH* mutation was identified in one patient with an adrenal PHEO.⁵¹ *FH* mutations have previously been identified in patients with leiomyomatosis and renal cell carcinoma,⁷¹ but so far no widespread evidence has been found for their involvement in PHEO/PGL.⁵¹ After previous reports identifying *BAP1* mutations in melanoma, meningioma, and mesothelioma, one family with a *BAP1* mutation was found, with one carrier in the family manifesting with a PGL with confirmed loss of the wild-type allele in the PGL tumor; the significance of this finding is currently unclear.⁷²

Somatic mutations in *H-RAS* have also been identified in limited cases of PHEO/PGL. Although mutations in *RAS* have been previously identified in other types of cancer, no definitive evidence of these mutations had ever been found in PHEO/PGL until recently. In a screening of 58 tumors with no previously identified mutations, 6.9% had somatic *H-RAS* mutations. These mutations led to the constitutive activation of the GTPase domain of *RAS*, increasing cell proliferation through activated RAS/RAF/ERK and PI3K/AKT/mTOR pathways.⁷³

Algorithm and procedures for genetic testing

Although genetic testing is a critical component of the clinical evaluation of patients with PHEO/PGL, testing can be costly. Therefore, determining an algorithm for prioritizing gene testing can help reduce costs while maintaining high accuracy.^{1,15} Family history can eliminate the need for such an algorithm, as only the known mutation needs to be analyzed. In patients lacking family history, the biochemical and clinical profile can be combined to determine a cost-effective strategy.^{15,74} The current recommended algorithm is detailed in Figure 1.

As more genes become identified in the pathogenesis of PHEO/PGL, the need for more effective and less expensive genetic testing strategies is becoming evident. Although algorithmic testing based on clinical presentation can reduce costs and remain effective, it is a timely process, as each gene must be ruled out individually before testing can proceed. The use of next-generation sequencing techniques has been proposed as a method for more rapidly analyzing multiple genes in at-risk patients at a reduced cost. This method was preliminarily tested in a study of 205 patients, 85 of whom had known mutations detected by traditional sequencing. Nine of the most common genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *MAX*, *RET*, *TMEM127*, and *VHL*) were sequenced simultaneously, with a 98.7% sensitivity for detecting mutations.⁷⁵ Whole exome sequencing has also recently been introduced as a possible technique for both rapidly sequencing known PHEO/PGL susceptibility genes and also potentially identifying new genes. In a study of whole exome sequencing in PHEO/PGL, the authors were able to effectively identify mutations in *SDHB*, *SDHC*, *SDHD*, *RET*, and *VHL* in a small sample of patients when appropriate techniques were used, at a much lower cost than traditional sequencing.⁷⁶

Beyond genetic testing

A great deal of interest has been given to determining underlying similarities in various forms of hereditary PHEO/PGL, in the hopes of determining broader mechanisms and pathways for pathogenesis. Microarray studies determining the expression profiles of hereditary PHEO/PGL have broadly classified these tumors into two clusters. Cluster 1 tumors, which include *VHL*, *PHD2*, and *SDH* tumors, as well as presumably *FH* and *IDH* mutations, have increased hypoxia and angiogenesis signatures.⁷⁷⁻⁷⁹ Changes in oxidation and reduction enzyme levels have also been described in these tumors.⁷⁷ Overexpressed genes include the glucose transporter, vascular endothelial growth factor (*VEGF*), and genes known to be involved in angiogenesis.⁷⁸ Tumors in this cluster also appear to have reduced *SDHB* protein levels, regardless of the underlying genetic mutation, representing a broader oxidoreductase signature caused by mitochondrial dysfunction.⁷⁷ Although both HIF-1 α and HIF-2 α overexpression have been linked to Cluster 1 tumors, their exact roles remain unclear.^{77,78,80,81} One study reported that HIF-1 α was particularly overexpressed in *VHL* tumors compared to *SDH* tumors⁸¹; however, other reports have described overexpression of HIF-2 α in *VHL* tumors and increased HIF-1 α in *SDH* tumors.⁸² Cluster 2 tumors, including *MEN2*, *NF1*, *KIF1B β* , *MAX*, *TMEM127*, and presumably *H-RAS* tumors, are associated with disruptions in kinase signaling.^{59,60,77} Sporadic tumors are almost equally distributed between the two clusters.⁶⁰

In addition to the well-established clustering of PHEO/PGL, other microarray analysis studies have proposed other clustering methods. Recent microarray data comparing *SDHB*, *SDHD* head and neck, *SDHD* abdominal and thoracic, and *VHL* tumors revealed two distinct clusters based on expression profiles: *SDHB* and *SDHD* abdominal and thoracic tumors in one cluster and *SDHD* head and neck and *VHL* tumors in the other. This suggests that *SDHD* tumors of the parasympathetic and sympathetic nervous system, though related to the same underlying pathogenic mutation, develop by different mechanisms. Whether this is true for all PHEO/PGL of the parasympathetic and sympathetic nervous system remains to be seen.⁸³

MicroRNAs (miRNAs) have become an area of interest in many cancers, due to their ability to regulate mRNA expression through degradation. miRNA profiling has been done in several series of PHEO/PGL. These expression profiles appear to vary based on genetic background, with unique signatures that broadly cluster similar to the previously described mRNA profile clusters. Certain miRNAs have been suggested to contribute to the development of PHEO/PGL tumors by interfering with cellular differentiation, but further studies are needed.⁸⁴ In addition, increased expression of specific miRNAs, particularly those associated with IGF2, was found to be more frequently associated with malignant PHEO/PGLs and could represent a novel marker.^{85,86} Differences in miRNA expression between different hereditary forms of PHEO and between recurrent, metastatic, and primary tumors have also been described.⁸⁷

Unifying pathways and mechanisms linking multiple underlying germline mutations across clusters are also being explored. One pathway linking these is the egl nine homolog 3 (EGLN3)/c-Jun/JunB apoptotic pathway. Mutant VHL proteins demonstrated a failure to downregulate JunB; higher quantities of JunB lead to increased antagonization of c-Jun and therefore inhibition of apoptosis. The accumulation of succinate due to dysfunctional SDH protein blocks EGLN3 activity, which is necessary for Jun-induced apoptosis. NF1 and RET mutations have been found to work upstream of JunB, affecting a neuronal growth factor receptor and thereby preventing apoptosis.⁸⁸

Another unifying paradigm is the link between hereditary forms of PHEO/PGL and HIFs. A link between hypoxia and PHEO/PGL is well-established, demonstrated for example by the high rates of PGL in Peruvian patients living at high altitudes in the Andes.⁸⁹ As previously mentioned, Cluster 1 tumors have a hypoxic signature. The VHL protein directly binds to HIFs and targets them for hydroxylation and subsequent degradation in oxygen-rich conditions; this degradation cannot occur in the absence of a functional VHL protein. This hydroxylation is carried out by PHDs, such as PHD2; therefore mutations in PHD2 also prevent HIF degradation. The accumulation of succinate due to dysfunction of the SDH protein inhibit PHD activity, also leading to overexpression of HIFs. As additional enzymes involved in the Krebs cycle, *IDH* and *FH* mutations also result in the accumulation of metabolic intermediates that prevent HIF hydroxylation by PHDs.^{80,90} In tumors with *RET*, *NF1*, and *H-RAS* mutations, activation of the Ras/MAPK pathway leads to upregulation of HIF. The NF1 protein directly activates Ras, which in turn activates the MAPK, PI3K, and mTOR pathways, all of which may increase HIF levels. RET mutations lead to increased activation of the Ras/MAPK pathways and PI3K/AKT pathways, also leading to HIF upregulation. H-RAS mutations also affect the Ras/MAPK pathway and lead to increased HIF signaling. TMEM127 and MAX appear to upregulate HIF through the mTOR pathway; TMEM127 is directly involved in negatively regulating the mTOR signaling pathway, so mutations prevent this inactivation and lead to increased mTOR signaling. The MAX protein is involved in c-Myc signaling, which affects both the PI3K/mTOR pathway and directly regulates HIF-1alpha. KIF1B β is a downstream target of PHD3 and therefore may be involved in HIF signaling as well, though current evidence is lacking.⁹⁰

Diagnosis of PHEO/PGL

Symptoms

One of the most challenging aspects of diagnosing PHEO/PGL can be identifying the signs and symptoms of a tumor. In fact, many tumors are missed and are not discovered until autopsy.^{2,5,7} Patients can present with a variety of non-specific symptoms that can mimic many other conditions. These can vary greatly from one patient to another, even within the same family. The frequency of various symptoms is summarized in Table 2. The classic triad of PHEO/PGL symptoms is headaches, sweating, and palpitations.⁵ Many patients also present with hypertension, which may be sustained or paroxysmal.^{5,91} Other symptoms may include pallor, feelings of anxiety or panic, fever, or nausea and vomiting.^{5,91} Nausea and vomiting may specifically be exercise-induced, which is particularly common in children.⁹² Another rare sign is the onset of diabetes, particularly in younger patients without typical risk factors for diabetes.⁹³ Hypertensive crises caused by catecholamine surges after accidental tumor manipulation or anesthesia administration may also indicate the presence of a PHEO/PGL.⁵ In addition, patients with resistant hypertension should be considered for evaluation of PHEO/PGL.⁵ Patients with a family history of PHEO/PGL who begin exhibiting suspicious symptoms or patients with incidentally discovered adrenal masses, even in the absence of symptoms, should also undergo evaluation to rule out PHEO/PGL.⁵⁻⁷ Recognizing the signs and symptoms of PHEO/PGL and making the appropriate diagnosis is critical, as patients who are undiagnosed or misdiagnosed can suffer severe consequences of hypertensive crises, including heart attacks, strokes, and even death. A recent review of published cases in the literature found 106 cases of patients who experienced hypertensive emergencies as a result of PHEO/PGL, with 15% resulting in death.⁹⁴

Biochemistry

PHEO/PGL tumors produce, store, synthesize, and metabolize catecholamines. Although previous methods of diagnosis relied on the measurement of catecholamines in the plasma or urine, these are not always the most effective measurements. Many tumors have fluctuating levels of catecholamine release,⁵ which can lead to false-negatives during periods of low catecholamine release. Instead, the measurement of plasma or urine metanephrines, the metabolites of catecholamines, are the most accurate test currently available.^{1,5,95} Although catecholamine release fluctuates, their metabolism remains fairly constant, leading to a steady release of metanephrines.^{1,5} Therefore, these are consistently elevated in patients with biochemically active PHEO/PGL. At the present time, there is no clear evidence favoring plasma or urine metanephrines.

In addition to the measurement of metanephrines, recent studies have demonstrated the utility of plasma methoxytyramine in diagnosing PHEO/PGL. Measurements of this biomarker can be valuable for detecting exclusively dopamine-secreting tumors, which are rare but easily overlooked by traditional measurements of metanephrines.^{96,97} Methoxytyramine, a metabolite of dopamine, also appears to serve as a predictor of malignancy.⁹⁸

Chromogranin A (CgA) is often commonly measured in patients with PHEO/PGL. CgA is a polypeptide that is commonly secreted by chromaffin cells, typically with catecholamines.⁹⁹ Elevated CgA is found in 91% of PHEO/PGL patients.¹⁰⁰ Although it is a nonspecific marker of neuroendocrine tumors, in some patients CgA can be a valuable marker for monitoring disease.¹⁰¹ When combined with catecholamine measurements, the sensitivity for diagnosing PHEO/PGL can be close to 100%.¹⁰⁰ CgA has been found to be significantly higher in patients with certain hereditary syndromes than in other patients, suggesting possible differences in vesicle formation and catecholamine secretion rates between different hereditary forms of PHEO/PGL.¹⁰²

In most patients, especially those presenting with signs and symptoms of PHEO/PGL, catecholamines and metanephrines will be elevated to diagnostic levels, defined as levels greater than four times the upper reference limit. In these patients, diagnostic workup can immediately move forward to anatomical and functional imaging. However, some patients will have equivocal test results, with elevations between the upper reference limit and the diagnostic level. In these patients, several steps should be initiated. First, medication interferences should be ruled out. Anti-depressants, some anti-hypertensives, and other common medications can cause false-positive elevations. Patients on these medications should, if possible, be taken off them or switched to other medications before testing is repeated; a list of contraindicated medications for patients with known or suspected PHEO/PGL is listed in Table 3.^{5,103–106} In addition, several foods, such as caffeine, can cause elevations in catecholamines and metanephrines and should be avoided before repeat testing.^{5,103,104} Caution should also be exercised when evaluating patients with chronic kidney disease, particularly those on dialysis, as elevated plasma metanephrines are common in this population, even in the absence of PHEO/PGL.¹⁰⁷

If interfering drugs cannot be discontinued or if medication interferences have been ruled out, a clonidine suppression test should be performed. This can only be done for patients with elevated norepinephrine or normetanephrine. The clonidine test is most sensitive when performed with plasma normetanephrine as the biomarker.^{5,103} If levels of plasma normetanephrine fail to suppress below the upper reference limit or by 40% of the initial value even after the addition of clonidine, further workup for suspected PHEO/PGL should be performed.⁵ Previously, clinicians used a similar strategy with the glucagon stimulation test, but this test is no longer recommended due to its low sensitivity and high risk of complications such as hypertensive crises.¹⁰⁸

While most PHEO/PGL are biochemically active, a small percentage have no abnormal hormonal activity. These tumors are deemed biochemically silent and are often associated with underlying *SDH* mutations.^{26,27} In other rare cases, PHEO/PGL can co-secrete other hormones, such as cortisol or ACTH. These patients often present with Cushing's disease in addition to PHEO/PGL.^{109–111}

Appropriate biochemical testing is critical both for the diagnosis and management of PHEO/PGL. Determining a patient's biochemical phenotype (adrenergic for patients with predominantly epinephrine/metanephrine secretion, noradrenergic for patients with predominantly norepinephrine/normetanephrine secretion, and dopaminergic for patients

with predominantly dopamine/methoxytyramine secretion) can help guide genetic testing in the absence of family history. Biochemical levels can also serve as important markers for monitoring the efficacy and response to treatment. Therefore, obtaining accurate measurements is critical. Plasma catecholamine and metanephrine levels should be drawn through an in-dwelling catheter after the patient has rested supine for at least 20 minutes in a dark, quiet room, to remove any environmental impacts on stress levels; failure to obtain blood tests under these conditions can result in false-positive elevations relative to supine reference ranges.¹¹² Patients should have fasted overnight before the blood draw.¹¹² The use of appropriate age-adjusted reference ranges is critical; a recent study showed an increase in the sensitivity of plasma metanephrine and normetanephrine from 88.3% to 96.0% when reference intervals based on patient age were used.¹¹³ Urine measurements should be done over a 24-hour period. Interfering medications should be discontinued or avoided, if possible, and foods that can elevate catecholamines or metanephrines should be avoided from at least 24 hours prior to testing until testing is complete.

Imaging

In addition to biochemical testing, imaging plays an important role in the diagnosis of PHEO/PGL. If the biochemical testing has been completed and is positive for elevated metanephrine/epinephrine, imaging can be focused on the adrenal gland, since the majority of tumors that secrete epinephrine are found in the adrenal gland. Computed tomography (CT) or magnetic resonance imaging (MRI) should be sufficient to detect such a tumor.⁵ If the PHEO is less than 3 cm and the patient is under 40 years of age and has no family history of PHEO, no further imaging workup needs to be performed.¹¹⁴ If adrenal imaging is negative, imaging of additional areas of the body should be performed. Imaging should be completed of the abdomen, followed by the pelvis, chest, and neck.

With regards to sensitivity, CT and MRI have similar success in detecting PHEO/PGL.⁵ However, MRI may be slightly favored in patients with extra-adrenal tumors. MRI is also preferred in patients with CT-contrast allergies, in pregnant or pediatric patients, and in patients in whom radiation exposure should be limited.⁵ On CT, PHEO/PGL typically have a heterogeneous appearance, often with some cystic areas.^{115–118} They typically have attenuation values greater than 10 Hounsfield units, though some PHEOs with fatty components may have appearances more consistent with adenomas.¹¹⁷ Calcifications or hemorrhage may also be present.¹¹⁷ On dual-phase contrast-enhanced CT, PHEOs can also be distinguished from other adrenal masses due to higher intensity during the arterial phase, with enhancement levels greater than 110 Hounsfield units.¹¹⁸ On MRI, PHEO/PGL typically appear as T2-bright lesions, although cystic or necrotic components may affect this classic appearance.^{115–117} On T1 imaging, PHEO/PGL enhance about equally to muscle and are less intense than the liver.¹¹⁷ PHEO/PGL also typically enhance with gadolinium contrast agents, though cystic or necrotic areas can reduce this enhancement.¹¹⁷

Ultrasound has also been used in PHEO/PGL, but its utility is limited. However, it can be valuable in evaluating metastatic liver lesions as well as tumors in the urinary bladder. On ultrasound, PHEO/PGL can have varied appearances; some appear cystic, while others may

be solid, and still others may be somewhere between the two extremes. Necrotic areas or hemorrhages can be present and may appear echogenic.¹¹⁷

In most cases, functional imaging also plays an important part in the work-up of PHEO/PGL. Functional imaging may help detect primary or metastatic tumors that could be missed on CT/MRI. It can also help characterize tumors in terms of their metabolic activity *in vivo*. Historically, functional imaging has been performed with ¹²³I- or ¹³¹I-metiodobenzylguanidine (MIBG) scintigraphy. MIBG has a structure that resembles norepinephrine and enters cells through norepinephrine transporters. While both ¹²³I- and ¹³¹I-MIBG have been used in imaging, ¹²³I-MIBG has been found to be more sensitive and clinically useful, due to its better detection rate, higher possible doses, and shorter intervals between injection and image acquisition.^{114,117,119,120} Both CT and MRI have been used in combination with single-photon emission computed tomography (SPECT) imaging for added colocalization. A recent comparison study of these techniques within the same patients have found that ¹²³I-MIBG SPECT/MRI has the highest sensitivity for adrenal PHEOs. Both adrenal MRI and SPECT/CT were found to be equally sensitive in diagnosing adrenal lesions and inferior to SPECT/MRI, but they had the advantage of offering better diagnostic imaging in patients in whom PHEO was ruled out.¹²¹ However, it is important to note that this study did not evaluate the use of these techniques on extra-adrenal or metastatic tumors, for which MIBG scintigraphy has been found to be less sensitive.¹²² A less common form of MIBG, ¹²⁴I-MIBG, has been infrequently used in positron emission tomography (PET) imaging for neuroendocrine tumors. This technique offers the advantage of PET scanning, which provides higher quality images than traditional scintigraphy. Available studies are limited, but a recent case report using ¹²⁴I-MIBG PET/MRI in a patient with metastatic PHEO found that this technique allowed for more accurate tumor volume determination and therefore better dose-planning for ¹³¹I-MIBG therapy.¹²³ It has also been suggested that the intensity of MIBG scintigraphy uptake could be used to distinguish benign from malignant disease, as a study of 9 patients with benign PHEO and 9 patients with malignant disease found more intense MIBG uptake in the metastatic patients.¹²⁴ However, further validation of these findings must be done in a larger series.

In addition to improvements in diagnostic accuracy, important limitations of MIBG scintigraphy have also been discovered in recent years. False-negative results occur more commonly with extra-adrenal tumors or tumors associated with succinate dehydrogenase subunit B (SDHB) mutations.^{114,125} MIBG scintigraphy may also miss metastatic disease.¹¹⁴ Certain medications, such as opioids, tricyclic antidepressants, and antihypertensives like labetalol, can also affect MIBG uptake, leading to less intense or false-negative scans.^{114,126} MIBG scintigraphy is also suboptimal for head and neck PGLs.¹¹⁴ Therefore, additional functional imaging techniques may be warranted or preferred.

PET has become more widely available and more widely used in the field of PHEO/PGL in recent years, due to its increased sensitivity, shorter acquisition times, and higher image resolution compared to SPECT.^{114,123} PET also offers the advantage of standard uptake values (SUV), which can quantify tracer uptake and therefore some aspect of tumor metabolism.¹¹⁴ Often, PET scans are performed with a corresponding CT for attenuation

purposes to increase their sensitivity. Multiple tracers have been studied in patients with PHEO/PGL. The most widely available is ^{18}F -fluorodeoxyglucose (FDG), an analog of glucose that is taken up by the glucose transporter.^{117,119} FDG PET scanning can be a valuable technique, particularly for patients with SDHB mutations or metastatic disease.^{127–129} Higher standard uptake values on FDG PET have also been suggested as possible indications of malignant disease, though further validation is needed.¹²⁷ However, FDG is not specific to PHEO/PGL, so caution should be exercised when interpreting scan results, as other tumor types may also be identified by this technique.¹¹⁴

More specific tracers have been developed, but these are less widely available. The first is ^{18}F -fluorodopa (FDOPA), an amino acid analog and catecholamine precursor that is taken up by the amino acid transporter.^{117,119} FDOPA is specific to neuroendocrine tumors, increasing the likelihood that findings represent true PHEO/PGL, though other neuroendocrine tumors may also be identified by this modality.¹¹⁴ However, false-positives are rare.¹³⁰ Pretreatment with carbidopa, which inhibits DOPA decarboxylase, enhances tumor uptake and improves its sensitivity.¹³¹ FDOPA PET is extremely sensitive for patients with head/neck PGLs, sometimes identifying small tumors missed by all other imaging techniques.^{132,133} This technique also appears to be particularly effective for patients with *SDH* mutations and/or biochemically silent PHEO/PGL and may be valuable as a screening technique, particularly for patients with *SDHD* mutations.^{133,134} In a recent large study focusing on tumors missed by FDOPA PET, a high rate of *SDH* mutations were found, suggesting that patients with false-negative FDOPA PET scans should be tested for these mutations.¹³⁵

The second PHEO/PGL-specific tracer is ^{18}F -fluorodopamine, which is similar to dopamine and taken up by norepinephrine transporters, though with higher affinity than MIBG.^{117,119} Unfortunately, this technique is only available at limited institutions worldwide, but studies have shown its value in identifying PHEO/PGL, particularly for primary tumors in the abdomen.^{136–139} It has been found to be more sensitive than MIBG or Octreoscan.^{136,138,139} FDA PET also appears to be a valuable modality for patients with metastatic tumors.^{129,138,139} Increased availability of FDOPA and FDA PET in the future will significantly improve diagnosis; at the present time, patients with more challenging cases of PHEO/PGL who would benefit from these imaging modalities should be referred to tertiary care centers that can offer these techniques.

Newer PET scanning tracers are also being explored in PHEO/PGL, though clinical experience remains limited. One such tracer is ^{18}F -fluorothymidine (FLT), which has been used previously in multiple cancers to detect rapidly proliferating tumor cells. Studies on this imaging modality in PHEO/PGL are currently being performed. However, one published report on a patient with metastatic PGL imaged with FLT PET showed no uptake in any tumors; the only uptake was a bright rim around metastatic bone lesions, where proliferating bone cells took up the tracer.¹⁴⁰ While this provides interesting insights into the *in vivo* activity of PHEO/PGL tumors, this imaging modality does not appear to have any utility for patient diagnosis.

More promising results have been found with radiolabeled DOTA peptides (DOTATATE, DOTATOC, and DOTANOC), which target somatostatin receptors on the cell membrane. Recent studies of ^{68}Ga -labeled DOTA peptides on patients with neuroendocrine tumors, including PHEO/PGL, have found high sensitivities of these modalities, even for small tumors and head and neck tumors.^{141–150} These DOTA peptides may also help distinguish adrenocortical adenomas from PHEOs; in a recent series, 10 patients with adrenal lesions were identified with FDG PET, but only the 2 patients with PHEO had positive uptake on DOTA imaging.¹⁴⁸ Their superiority to MIBG scintigraphy for metastatic tumors and possibly for primary tumors as well has also been demonstrated.^{142,145–147,150} ^{68}Ga -DOTATOC PET/CT was also found to be superior to FDOPA PET/CT in the diagnosis of metastatic tumors.¹⁴⁴ However, these results have been limited, and ongoing research at limited centers is being performed to try to expand these findings to larger cohorts of PHEO/PGL patients.

Other functional imaging techniques have also been used in PHEO/PGL. One such technique is Octreoscan, or ^{111}In -pentetreotide scintigraphy. This modality exploits the somatostatin receptors often expressed on the cell membranes of PHEO/PGL by introducing radioactively labeled octreotide to bind to these receptors.¹¹⁴ However, the expression of these receptors can vary between PHEO/PGL patients, with certain subtypes less expressed or even absent in certain tumor specimens, affecting the sensitivity of this technique.¹⁵¹ Several efforts have been made to incorporate this technique more broadly into the algorithm for PHEO/PGL diagnosis, but suboptimal sensitivities have precluded more widespread use. Small or metastatic tumors, as well as PGLs in the head and neck or abdomen, are more frequently missed on Octreoscan.¹¹⁴ False-positives have also been reported in patients with renal cysts, abdominal hernias, accessory spleens, inflammatory diseases, and other neuroendocrine tumors.¹¹⁴ However, Octreoscan can be of value in patients with metastatic disease.¹³⁶ In addition, a recent study of *SDHB* mutation carriers found that adding Octreoscan to the routine screening of carriers increased diagnostic sensitivity.¹⁵² As Octreoscan is more widely available than FDOPA/FDA PET, these findings may benefit a great deal of patients. In addition to Octreoscan, bone scans are sometimes performed in patients with bony metastases. These scans are not commonly used, but can be of value for patients with osseous metastases.¹²⁹ Figure 2 shows the current recommended functional imaging algorithm for patients with PHEO/PGL, and Table 4 summarizes sensitivities of imaging modalities in different PHEO/PGL types.

Imaging is also an important component of the screening process for patients with genetic predispositions to PHEO/PGL development and of follow-up for patients with a history of PHEO/PGL. For carrier screening, a CT or MRI is often recommended every few years, in conjunction with annual biochemical testing, to detect potential tumor growth. Adding whole-body imaging is particularly important for *SDH* mutation carriers, as these patients more frequently have normal biochemistry, so tumors can be missed by only biochemical evaluations.¹⁵³ In patients with specific genetic backgrounds, particularly those with *SDHB* mutations or a family history of biochemically silent tumors, occasional functional imaging may be a valuable addition to the regular screening evaluation. A similar strategy should be employed for patients after PHEO/PGL removal. Biochemical testing 6–8 weeks after the

procedure can be used to determine the success of the surgical resection, with additional biochemical testing and imaging studies on approximately 6-month intervals. Once the likelihood of recurrence has decreased based on patient risk factors such as age, genetic background, and tumor size and location, follow-up intervals can be extended to one to two years.

Metastatic PHEO/PGL

One of the largest challenges in PHEO/PGL management is the inability to predict which patients may develop metastatic disease. As previously mentioned, there are no clear features that distinguish benign from malignant primary PHEO/PGL. A scoring system, deemed the “pheochromocytoma of the adrenal gland scaled score” (PASS), was proposed,¹⁵⁴ but a large retrospective analysis found no significant correlation between PASS score and future malignancy.¹⁵⁵ While the Ki-67 index is often used as a marker of proliferation in other cancers, there is no clear value to this marker in PHEO/PGL. One study has suggested that the Ki-67 index, in addition to pS100 staining and the presence of tumor necrosis, may be a predictor of malignancy;¹⁵⁶ another study reported Ki-67 and c-erbB-2 staining was higher in malignant versus primary tumors.¹⁵⁷ However, studies of the Ki-67 index in relation to imaging findings, particularly standard uptake values on FDG PET or lesion intensity on MIBG, have found no correlation.¹⁵⁸ A large-scale microarray analysis of benign versus malignant tumors identified a large cohort of genes that were underexpressed in malignant tumors, suggesting that malignant tumors may develop due to dedifferentiated gene expression. Further analysis of this dataset may reveal genes that could be predictive markers for metastatic PHEO/PGL development.¹⁵⁹ Recently, expression of heat shock protein 90 (Hsp90) and activator of transcription 3 (STAT3) have been proposed as potential markers for distinguishing between benign and malignant tumors, as malignant tumors were more likely to stain positively for these proteins on immunohistochemistry. However, 22.37% and 26.32% of benign tumors also stained positively for Hsp90 and STAT3, respectively, showing that these technique may not be sufficient for distinguishing between these two types of tumors.¹⁶⁰ High telomerase activity has also been proposed as a marker of malignancy in PHEO/PGL, as this was more frequently associated with malignant PHEOs in one study, but its predictive value is unclear.¹⁶¹ Increased expression of angiogenesis genes has also been reported in malignant PHEO/PGL compared to benign tumors, but one study also found overexpression of these genes in 30% of benign tumors as well.^{162,163} A recent study has also found that high copy numbers of an N-terminal truncated splice isoform of carboxypeptidase E accurately predicted future recurrence or metastases in PHEO/PGL, but further study is needed to validate these findings in larger patient populations.¹⁶⁴ While these features may indicate a possibility for malignancy, more accurate and comprehensive predictive tools that can be used in routine diagnosis still need to be developed.

Several independent risk factors for metastases have been established. The first is the presence of an *SDHB* mutation.^{98,165,166} As previously discussed, *SDHB* tumors are more frequently associated with metastases. *SDHB* mutations have also been independently linked to higher rates of mortality in patients with PHEO/PGL.¹⁶⁵ One study found that approximately half of patients with metastatic PGL had *SDHB* mutations.³⁴ Extra-adrenal

location has also been independently associated with an increased risk of malignancy and a decreased rate of survival.^{98,166,167} Primary tumors in the mediastinum and organ of Zuckerkandl had particularly high metastatic rates in one study of 371 patients with metastatic PHEO/PGL.¹⁶⁷ The size of the primary tumor is a third risk factor for metastases.^{98,166–169} Tumor sizes over 5 cm have been associated with increased risk of metastatic disease development and shorter overall survival.^{98,166} The age at primary tumor diagnosis is also associated with increased risk of metastatic disease development, with patients who develop metastatic disease presenting at a statistically significantly younger age, a mean of 41 years vs. 50 years for patients without metastases.¹⁶⁹ Finally, increased levels of plasma methoxytyramine, even when not associated with extra-adrenal or *SDHB*-related tumors, have been established as an indication of metastatic disease risk.⁹⁸

With regards to the clinical characteristics of metastatic PHEO/PGL patients, a recent large retrospective analysis of adults with metastatic PHEO/PGL has been performed, which identified 287 patients with metastatic PHEO and 221 patients with metastatic PGL. Similar numbers of males and females were identified, suggesting there is no gender difference in the development of metastases. The mean age at diagnosis was in the sixth decade of life. Survival was significantly better for patients with metastatic PGL than for those with metastatic PHEO. The majority of patients underwent surgery, typically for primary tumors, though some patients were not identified until metastases were present, in which case debulking procedures were performed. Patients who did not undergo surgery for PHEO or who had metastases at presentation for PGL were at the highest risk of death from disease. As previously discovered, the metastatic patients included in the study typically had large primary tumor sizes (with mean sizes >5 cm). However, no improvement in survival rates were noted over the two decades encompassed by the patients in this study, highlighting the need for improved treatment strategies.¹⁷⁰

Typical sites of PHEO/PGL metastases include the lungs, liver, bones, and lymph nodes.^{166,171} Patients with PHEO/PGL, particularly metastatic disease, suffer diminished quality of life due to pain caused by tumor effects, side effects from treatments, and consequences of elevated catecholamines.^{166,172} Patients with bone metastases frequently report bone pain.¹⁷³ Other skeletal complications include spinal cord compression, bone fractures, and/or hypercalcemia.¹⁷³ In patients with bone metastases, skeletal events were reduced if patients responded to therapy.¹⁷³ Bone metastases appear to be less aggressive than other forms of metastatic tumors; in one study of patients with metastatic PHEO/PGL, patients with bone metastases only had an average survival of 12 years, compared to 7.5 years for patients without skeletal metastases and 5 years for patients with both skeletal and non-skeletal metastases.¹⁷³ However, the overall 5-year survival rate for patients with metastatic PHEO/PGL is less than 60%.^{171,174}

While treatment of patients with metastatic PHEO/PGL can have some benefit, the limited number of available therapeutic options warrants careful consideration of available options before treatment is initiated. Therapy should only be considered in patients with disease that is clearly progressing. Patients with metastatic PHEO/PGL may often have stable disease, even in the absence of therapy, and therefore should undergo close clinical monitoring without treatment.^{174,175} For instance, a recent retrospective study of 90 metastatic PHEO

patients who were monitored but never treated at several French institutions found that half of patients had stable disease after 1 year even in the absence of any therapeutic intervention.¹⁷⁵

Management of PHEO/PGL

Blockade

Patients with biochemically active PHEO/PGL should immediately be placed on anti-hypertensive medications to control symptoms and reduce the risk of hypertensive crises. A summary of the available drugs and suggested doses is listed in Table 5. Alpha blockade should always be initiated first, followed by beta blockade, if necessary. If beta blockade is initiated first, unopposed stimulation of alpha-adrenoceptors due to beta-adrenoceptor vasodilation can result in hypertensive crises.^{5,91,106} Several alpha-adrenoceptor blockers are available. Phenoxybenzamine is a long-lasting alpha blocker that is commonly used in patients with PHEO/PGL.^{91,106} However, phenoxybenzamine is not widely available, especially outside the United States.⁹¹ Short-acting alpha blockers can be used as alternatives to phenoxybenzamine, either when phenoxybenzamine is not available or when a patient's hypertension is not severe enough to warrant the use of a long-acting alpha blocker. These include prazosin, terazosin, and doxazosin. These medications should be started at bedtime, as they can cause orthostatic hypotension after the first dose.^{91,106} Doses should be adjusted until normotension or even mild hypotension is achieved.¹⁰⁶

After alpha blockade has been established, beta blockers may need to be introduced to address additional symptoms, such as tachyarrhythmia. Cardioselective beta blockers are frequently preferred in the management of patients with PHEO/PGL and include metoprolol and atenolol. However, the nonselective beta blocker propranolol may also be used.⁹¹

While combined alpha- and beta-adrenoceptor antagonists such as labetalol may seem ideally suited for patients with PHEO/PGL, these agents are not recommended. The beta-blocking activity of labetalol far outweighs its alpha-adrenoceptor activity, which could result in hypertensive crises.^{91,106} The lower alpha-blocking ability of labetalol also results in inadequate blood pressure control in most patients.^{91,106} Finally, labetalol can interfere with MIBG uptake, which can affect both scanning and treatment.^{106,114}

Calcium channel blockers can also be used for additional blood pressure and symptom control. Patients with persistent hypertension after alpha blockers may benefit from the addition of a calcium channel blocker rather than increased doses of alpha blocker. In addition, some patients may be unable to tolerate alpha blockers, in which case calcium channel blockers should be used.¹⁰⁶ Calcium channel blockers can also be valuable in the management of patients with very mild hypertension, in whom alpha blockade would cause hypotension.^{91,106} Amlodipine, nicardapine, nifedipine, and verapamil are all commonly used for pre-operative blockade.^{91,106}

In patients who do not achieve adequate hypertensive or symptom control with alpha and beta blockers, metyrosine (Demser) can be added to prevent catecholamine synthesis. Metyrosine is a competitive inhibitor of tyrosine hydroxylase, a critical enzyme in

catecholamine synthesis. Metyrosine can significantly decrease levels of catecholamines and provide additional blood pressure control for patients with biochemically active PHEO/PGL. However, its availability is limited. In addition, its ability to cross the blood-brain barrier and deplete catecholamine levels in the brain can lead to side effects such as depression, anxiety and sleepiness, so patients should be carefully monitored.¹⁰⁶

Although blockade may not eliminate the possibility of intra-procedural hypertensive crises, it can dramatically reduce their severity and improve the ease of management.¹⁷⁶ In one study, intraoperative complications were present in only 3% of patients who received appropriate pre-surgical blockade, compared to 69% of patients without blockers.¹⁷⁷ Patients who are candidates for surgical resection or any treatment that could induce the release of catecholamines should be initiated on adequate alpha and beta blockade at least 2 weeks before the procedure or treatment. This includes patients who are normotensive, as unanticipated catecholamine release by the tumor during surgery or other procedures may lead to hypertensive crises. Mild alpha blockade or calcium channel inhibitors may be most appropriate for these patients. The only patients who may not require pre-procedural blockade are patients with non-secreting head and neck tumors.¹⁰⁶

Surgery

Currently, surgical resection remains the only curative treatment option for patients with PHEO/PGL. Laparoscopic surgery has been successfully performed in patients with both adrenal PHEO and extra-adrenal PGLs with outcomes similar to open surgery and is the preferred technique when feasible.^{5,176,178–185} For larger tumors over 6 cm, laparoscopy may still be used, though these are frequently converted to open procedures intraoperatively.^{176,184} Multiple, recurrent, or metastatic tumors can also be approached laparoscopically if performed by experienced surgeons, although open resection may be preferable to ensure complete removal of tumors suspected to be metastatic.^{171,185} Robotic assistance or robotic procedures can be used with similar success rates, with the added advantages of lower morbidity, less postoperative pain, and shorter postoperative hospital stays.¹⁸⁶ For patients with adrenal PHEOs, full adrenalectomies should be performed in the absence of a genetic background, in patients with a low risk of bilateral disease, or in patients with larger tumors. However, in patients with bilateral tumors or a high risk of bilateral tumors (such as in patients with VHL or MEN2), cortex-sparing surgery may be sufficient if the tumor is small enough, thereby eliminating the need for steroid replacement.^{5,187–193} The risk of recurrence with cortical-sparing adrenalectomies is small (approximately 7%) as long as the whole tumor is removed,¹⁸⁹ but repeat subtotal adrenalectomies in these patients may be successfully performed if tumors recur.^{187,188} The risks of operative mortality are extremely low if performed by an experienced surgical team, including a skilled anesthesiologist to monitor for intra-operative hypertensive crises.⁵ In the immediate post-operative period, patient should undergo fluid replacement to mitigate post-operative hypotension caused by the sudden drop in the amount of circulating catecholamines.⁵

For patients with small tumors, surgical resection can be curative, although hypertension may persist.^{5,194} In the absence of genetic background, with complete tumor removal, rates

of metastases and recurrence can be very low. In a large study of 114 patients who underwent successful removals of PHEO/PGL, only 16 (14%) later developed recurrent or metastatic disease.¹⁹⁴ Unfortunately, as there is no clear method for distinguishing benign from malignant tumors pathologically, patients should undergo close clinical follow-up after surgery, typically at least annually for ten years,^{5,194} regardless of pathological features of the tumor. Surgery can be used as a curative treatment for primary, recurrent, or limited metastatic tumors; it can also be used as a debulking technique for patients with extensive metastatic disease, to reduce symptoms and imminent complications from tumor size. However, the long-term benefits of debulking procedures for patients with metastatic disease may be limited.^{1,174,195} A recent study found that only 8.3% of patients who underwent a non-curative debulking procedure were able to cease antihypertensive medications for more than 6 months. In addition, only one patient out of 30 had a biochemical response to surgery that lasted for 12 months.¹⁹⁵ In this same study, though, patients who underwent aggressive surgical intervention with the goal of complete resection had very successful outcomes.¹⁹⁵ In addition, surgery may be the only option, though not curative, if tumors may pose an immediate risk to vital processes or are affecting critical organ structures.¹ The reduction of tumor burden through surgical debulking may also increase the efficacy of post-surgical therapies.^{1,174}

Radiofrequency ablation

In some patients for whom surgery may not be the best option, tumors in accessible locations can be addressed by radiofrequency ablation (RFA). RFA has been successfully used on osseous and liver metastases.^{196–199} One study of 10 patients who received RFA found that 56% had successful ablations without recurrence; in 2 of the patients, all identified metastatic lesions were ablated.¹⁹⁷ Another study of 6 patients with 7 metastatic lesions demonstrated complete ablation in 6 out of 7 lesions, with no serious adverse events reported.¹⁹⁹ Due to catecholamine release by the tumor during the procedure, experienced radiologists, in conjunction with experienced anesthesiologists, should perform the technique while monitoring blood pressure to reduce risks of intra-procedural catecholamine-induced hypertensive crises.¹⁹⁶

External radiation

In some cases, external beam radiation has been used for inoperable tumors or for symptom palliation. This is particularly popular for the treatment of bone lesions.^{171,174} The outcomes of radiation therapy on metastatic PHEO/PGL are unclear.¹⁷¹ One study of 17 patients who underwent external beam radiation for non-head and neck metastases reported local control and/or symptom relief in 76% of patients, all of which lasted at least 1 year or until death, suggesting an important palliative role for this therapy. Of note, 5 of these 17 patients also received systemic therapy with ¹³¹I-MIBG.²⁰⁰ It is important to exercise restraint when using external beam radiation on metastatic PHEO/PGL, as patients may have multiple bone lesions that require treatment and doses should be limited to avoid further radiation-related complications.¹⁷¹

External beam radiation is also a common treatment modality for non-resectable head and neck PGLs. In a retrospective analysis of 31 patients with head and neck PGLs, 14 of whom

had previously undergone partial resections, long-term local control was observed, with limited toxicity. Five-year, 10-year, and 15-year local control rates were 96%, 90%, and 90%, respectively.²⁰¹ Glomus jugulare PGLs are particularly popular candidates for external beam radiation, with high success rates and limited toxicities.²⁰² More recently, radiosurgery using gamma knife, LINAC, or CyberKnife have begun to replace traditional external beam radiation for glomus jugulare tumors, due to their more precise targeting of radiation and increased dose capability.²⁰² High success rates, determined by local control through stable or decreased tumor sizes, have been reported with all three techniques, up to 100%, with limited complications.²⁰²⁻²⁰⁵

Radiotherapy

For patients with positive MIBG scintigraphy, MIBG therapy can be a valuable treatment modality. When considering patients for treatment with radiolabeled MIBG, it is critical to obtain a recent MIBG scan to determine tumor uptake. Before the scan and for the duration of therapy, the patient should be taken off medications that can block MIBG uptake such as labetalol, tricyclic antidepressants, and certain calcium antagonists.^{5,114,126,206,207} The therapy is based on the emission of beta particles once the radioactive compound has been taken up into tumor cells, leading to their destruction.²⁰⁶ Broadly, two strategies are being evaluated with regards to MIBG therapy. In some trials and studies, ¹³¹I-MIBG therapy is given in small doses over a longer period. Doses usually range from 100-300 milliCuries (mCi) and are given once every 3-4 months for up to an approximately 1000 mCi dose total, although there are no strictly established guidelines on maximum cumulative dosage or repeated doses.²⁰⁶ A retrospective analysis of 116 patients who received mean single doses of 158 mCi for a range of 1-11 treatments, resulting in cumulative doses ranging from 96-2322 mCi, reported improved symptoms in 76% of patients, biochemical responses in 45%, and tumor responses in 30%; 5 patients reported complete tumor and biochemical responses for 16-58 months. Side effects were generally mild and reported in 41% of patients; only one patient suffered extreme toxicities and died from bone marrow aplasia.²⁰⁸ However, some centers have experimented with giving extremely large one-time doses of MIBG, followed by stem cell infusion to replace bone marrow.²⁰⁶ In one such study, 49 patients were treated with single doses of 492-1160 mCi, with 15 patients receiving multiple doses, for total doses of 492-3191 mCi. Fifty-seven percent of patients had a complete, partial, or minor response, and an additional 8% achieved stable disease for at least one year. However, severe toxicities were observed, including 2 patient deaths from myelodysplastic syndrome, acute respiratory distress in 3 patients, leading to an additional patient death, as well as high rates of grades 3-4 neutropenia (87%) and thrombocytopenia (83%).²⁰⁹ While there is no proven benefit to one method over the other, the significantly reduced toxicity of the first approach suggests that this may be a favorable treatment strategy, and this method is used far more frequently.²⁰⁶ Repeat staging is usually done 3-6 months after treatment to assess response and determine whether another dose is warranted.²⁰⁶

Complete response is rare from MIBG treatment, regardless of the technique, with the highest reported rates only around 15%.²⁰⁶ A systematic review of published studies on ¹³¹I-MIBG treatment found that of 243 patients treated with this modality, only 3% had a

complete response; 27% had a partial response and 52% had stable disease.²¹⁰ However, many patients benefit from partial responses, reduced symptoms, and/or lower biochemical levels.^{171,206} In addition to clinical benefits to the patient with regards to symptoms, the ease of this therapy, which can be performed as an outpatient treatment, and the relative lack of side effects compared to other available treatments makes MIBG the preferred first treatment for patients with moderately progressing MIBG-avid metastatic PHEO/PGL.^{174,206}

More recently, therapies targeting somatostatin receptors have been introduced for patients with PHEO/PGL. Using DOTA peptides (DOTATATE, DOTATOC, and DOTANOC) radiolabeled with lutetium (¹⁷⁷Lu), yttrium (⁹⁰Y), or indium (¹¹¹In), researchers have been able to give doses to patients with positive Octreoscan or Ga-DOTA-peptide imaging. Although data on this treatment technique are limited, preliminary reports have shown this to be a promising strategy. For example, a report on pediatric patients with neuroendocrine tumors, including 3 with PGL, used ⁹⁰Y-DOTATOC; 2 patients had stable disease and 1 had a minor response, with all 3 reporting symptomatic relief.²¹¹ Another study on 4 patients with non-resectable, non-metastatic *SDHD*-related PGL found stable disease or partial responses in all 4 patients.²¹² In a larger study by van Essen et al., 12 patients with PGL were treated with ¹⁷⁷Lu DOTATATE. Six patients had stable disease on follow-up, and two had a minor or partial response.²¹³ A retrospective analysis of 28 patients treated with ⁹⁰Y-DOTATOC found partial responses in 2 patients, minor responses in 5, mixed responses in 2, and stable disease in 13; responses were sustained from 6-44 months.²¹⁴

Chemotherapy

For patients with metastatic disease, chemotherapy may be valuable to palliate patient symptoms, reduce or stop the rate of tumor growth, and in some cases, shrink tumors. Although no chemotherapeutic treatment has been discovered with long-term efficacy, some chemotherapy regimens can maintain disease status for several years, prolonging patient survival and improving patient quality of life. Traditional chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has been used most extensively with PHEO/PGL and still remains one of the most effective treatments for widespread metastatic disease.^{171,174} An early study on 14 patients with metastatic PHEO/PGL found at least partial tumor responses in 57% of patients, with 79% showing complete or partial biochemical responses, with response durations from 5 to more than 35 months.²¹⁵ A single institution study of patients receiving CVD or similar chemotherapy regimens found a 33% rate of response (measured in terms of symptom relief) and prolonged overall survival.²¹⁶ In a more recent study of 17 metastatic PHEO/PGL patients from Japan who were followed between 12 and 192 months after initiating CVD, 47.1% showed partial responses in tumor size and/or biochemical levels; stable disease without significant response was observed in another 23.5%. Although no patients in the study showed a complete tumor response, progression-free survival ranged from 31 to 60 months (with a mean of 40 months) in patients with partial responses.²¹⁷ However, in a study that followed 18 patients with a 22-year follow-up, while a complete response was seen in 11% and a partial in 44% of patients, no significant difference was noted in overall survival between patients who responded to CVD and those who did not. The main benefit of CVD, therefore, is symptom

improvement.²¹⁸ CVD chemotherapy has been found to be particularly effective for patients with *SDHB* mutations (unpublished observations). CVD chemotherapy is usually well-tolerated for long periods, with side effects being relatively minor, such as nausea, vomiting, hair loss, thrombocytopenia, and paresthesia.^{171,174,215} Patients exhibiting toxicities can be offered reduced doses or prolonged intervals between cycles.¹⁷¹

There is limited experience with other chemotherapeutic agents in PHEO/PGL. Other chemotherapeutic combinations have been tried in limited cases. These include temozolomide; streptozotocin with other agents; ifosfamide; cyclophosphamide and methotrexate; etoposide, carboplatin, vincristine, cyclophosphamide, and doxorubicin; and cisplatin and 5-fluorouracil.^{166,171,174} The experience with most of these combinations is anecdotal. For example, a case report of a metastatic PHEO patient treated with streptozotocin reported tumor shrinkage, decreased biochemical levels, and reduced symptoms.²¹⁹ An isolated case report of cisplatin and 5-fluorouracil reported a minor tumor response and the loss of a need for antihypertensive medications followed by stable disease for 2 years after only 3 treatments with this regimen.²²⁰ Other therapies have been tried on small cohorts of neuroendocrine tumor patients. A retrospective analysis of patients with neuroendocrine tumors treated with temozolomide included 1 patient with PGL, who had stable disease after treatment.²²¹ Temozolomide has also been used in conjunction with thalidomide, which is thought to inhibit angiogenesis. One study of patients with neuroendocrine tumors, including 3 patients with PHEO/PGL, found a 33% partial response rate with limited mild toxicities.²²² Due to the isolated nature of these treatment options, no conclusions or recommendations about their use can be made for patients with PHEO/PGL.

Molecular targeted therapies

One drug that has begun to receive a great deal of attention is sunitinib (sutent), which was developed as a treatment for renal cell carcinoma. Sunitinib is a tyrosine kinase inhibitor that prevents angiogenesis through the targeting of vascular endothelial growth factor receptors (VEGFR) and other angiogenic processes. Conflicting reports have found varying effects of sunitinib on PHEO/PGL. *In vitro* studies have found that sunitinib appears to induce apoptosis in rat PHEO cells.²²³ Further studies have also suggested that sunitinib directly inhibits catecholamine synthesis by reducing the activity of tyrosine hydroxylase, a critical enzyme in catecholamine synthesis.²²⁴ While some studies have found partial or even complete responses in terms of tumor size, symptoms, catecholamine secretion, and metabolic activity as measured by PET scanning in small patient cohorts,^{225–227} other studies have not reported much success. For example, a case report of a patient with metastatic PGL reported a partial response to sunitinib initially, but disease progression was observed after 6 months of treatment.²²⁸ It has also been suggested that patients with *SDHB* mutations may respond less frequently, perhaps due to a lack of the necessary receptors for sunitinib targeting (unpublished observations).

Other more experimental regimens have been evaluated in limited cases of PHEO/PGL. Everolimus has been used in limited cases of PHEO/PGL to target the mTOR pathway, with disappointing results. In a study of 4 patients treated with everolimus, progressive disease was noted in all 4 after relatively short treatment periods of 3-6 months; one patient died of

metastatic disease while on the therapy.²²⁹ A phase II study of everolimus on patients with neuroendocrine tumors, including 7 patients with metastatic PHEO/PGL, reported stable disease in 5 and progressive disease in 2, with only a mean 3.8 month progression-free survival time.²³⁰

Future directions

The field of PHEO/PGL is rapidly expanding. As diagnostic techniques improve and the understanding and access to genetic testing in these tumors identifies more carriers, more patients are identified, leading to increased sample sizes for clinical trials and expanding the available knowledge database. However, there are still many aspects of PHEO/PGL that remain to be understood. The underlying pathogenetic mechanisms, particularly those that govern the transformation to malignancy, are not well understood. This is partially due to the lack of a human cell line. While several established mouse and rat cell lines have been used extensively in research, the development of a human cell line would improve *in vitro* experimentation and accelerate research to an unprecedented degree.

In addition, therapeutic options are still relatively limited for patients with metastatic PHEO/PGL. While some strategies can provide symptom relief and extend progression-free survival for some time, only surgery can cure patients long-term. Discovering new treatment targets is essential for providing additional treatment options. In addition, developing drugs to target potentially relevant targets needs to be accelerated. A link between PHEO/PGL development and the HIF genes has been explored in a recent review article, suggesting this as a potential treatment target.⁹⁰ However, there is no clinically approved drug to directly target the HIF protein.²³¹ Although HIF1-targeting drugs have been tested, compensatory mechanisms in PHEO/PGL tumors make these drugs ineffective *in vitro*. Therefore, a broader HIF1/2-targeting drug, or a HIF2-targeting drug that can be used in combination, is necessary and could prove extremely valuable in the treatment of PHEO/PGL, regardless of genetic background.

Another potential target is the mTOR pathway. The mTOR protein, a serine/threonine protein kinase, is regulated by two major mTOR complexes (mTORCs), mTORC1 and mTORC2. Cell proliferation and migration were reduced *in vitro* through the use of an ATP-competitive inhibitors that target both major mTORCs, cell proliferation and migration was reduced *in vitro*.²³² Furthermore, the introduction of a dual mTORC inhibitor to metastatic PHEO/PGL mouse models significantly reduced tumor burden.²³² Although previous results with everolimus, an mTORC1 inhibitor, have been disappointing, dual mTORC1/2 inhibitors could overcome compensatory mechanisms that may be activated upon reduction in one mTORC due to targeted treatment.²³¹

Heat shock proteins, molecular chaperones thought to play a role in protein folding and degradation, have been investigated as potential treatment targets in various tumor types. Preliminarily promising results of inhibitors of a specific protein, Hsp90, have been seen in multiple cancers, including melanoma, leukemia, prostate cancer, lung cancer, multiple myeloma, and breast cancer.²³³ Hsp90 is of particular interest due to its overexpression in metastatic PHEO/PGL.¹⁶⁰ A study of two Hsp90 inhibitors, 17-AAG and ganetespib, found

that cell proliferation and migration were reduced *in vitro* with Hsp90 inhibitors in available mouse and rat PHEO cell lines and in primary human PHEO/PGL tissue cultures. In addition, metastatic tumor burden was reduced in a mouse model of metastatic PHEO/PGL after treatment with Hsp90 inhibitors.²³⁴ A second study on rat PHEO cell lines also confirmed reduced cell proliferation after 17-AAG treatment and also reported increased apoptosis.²³⁵

Other potential targets for therapy will be discovered as more insight is gained into PHEO/PGL pathogenesis. A recent study on insulin-like growth factor 1 (IGF1) found a link between circulating levels of IGF1 and PHEO/PGL tumor development and progression in mice, suggesting this as a possible therapeutic target.²³⁶ An *in vitro* study of NVP-AEW541, an IGF1 receptor antagonist, found significantly decreased cell viability in mouse PHEO/PGL cell lines with high doses, although compensatory upregulation of other cellular pathways was also observed.²³⁷ Drugs targeting *RET*, which have been successfully used in MTC, may be of value in PHEO/PGL, particularly Cluster 2 tumors.²³¹ Another receptor tyrosine kinase, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ERBB2, Her2/Neu), has been found to lead to PHEO formation in mice when overexpressed²³⁸; high levels have also been found in metastatic human PHEO/PGL.²³⁹ Although no studies of this target have been done, several existing drugs target this protein and could be introduced into clinical trial for patients with metastatic PHEO/PGL.²³¹

Fatty acids have also been suggested to play a role in apoptosis induction in several cancers. One such fatty acid, eicosapentaenoic acid (EPA), has been found to induce apoptosis in rat PHEO cells. This is thought to result at least partially from lipid peroxidation.²⁴⁰ Whether this could be used as a treatment modality for PHEO/PGL remains to be seen, but its limited side effects make this an appealing possibility.²³¹

Another potential target is the previously mentioned N-terminal truncated splice isoform of carboxypeptidase E, which has been found to be present in high copy numbers in metastatic PHEO/PGL.¹⁶⁴ The protein product, CPE-deltaN, of this truncated mRNA was found to upregulate the expression of genes associated with metastases formation in melanoma.¹⁶⁴ Using siRNA targeted to this splice isoform reduced tumor growth and invasion in mice injected with highly metastatic human liver cells.¹⁶⁴ As previously mentioned, carboxypeptidase E copy numbers are also thought to be a potential biomarker of malignant potential in benign tumors, though further investigation is needed.^{164,231}

Another mechanism for treatment involves increasing apoptosis in tumor cells. Several drugs have been found to have this ability *in vitro* and in animal models, but are still awaiting introduction into clinical trials. One such treatment is the use of histone deacetylase (HDAC) inhibitors. Two HDAC inhibitors were tested in mouse PHEO cell lines, and both showed inhibition of cell proliferation. However, perhaps more interesting, both also increased the uptake of ¹³¹I-MIBG into metastatic PHEOs in a mouse model, suggesting a possible role for HDAC inhibitors as a pretreatment enhancer for patients undergoing MIBG therapy.²⁴¹ The use of HDAC inhibitors has also been proposed to prevent the degradation of mutant SDHB protein, allowing it to be transported to the mitochondria.²⁵ Similarly, a nuclear factor kappa B (NFκB) inhibitor was found to induce apoptosis in mouse and rat

PHEO cell lines, reduce metastases in a mouse model, and increase the levels of the norepinephrine transporter system, which thereby increases the available entrance sites for ^{131}I -MIBG treatment.²⁴² Topoisomerase inhibitors have also been proposed as treatment targets in cancer, due to their role in unraveling DNA supercoiling and in apoptosis.²⁴³

Immunotherapy is a novel but increasingly popular potential treatment modality in many cancers. Through the use of vaccines targeted to specific cancer molecules, the patient's immune system can recognize and attack these molecules.²⁴⁴ The challenge is identifying molecules that would be specific to the tumor cells and still be capable of recognition. One proposed target in PHEO/PGL is CgA. A study in mice with vaccines targeted to CgA found that cytotoxic T-cells were successfully produced in response to the vaccines and were capable of recognizing CgA and inducing lysis in PHEO cells. Vaccinated mice also exhibited less tumor growth in the liver.²⁴⁵ This preliminary study suggests that exploring immunotherapy as a treatment option in PHEO/PGL, with CgA or other potential target molecules, could be an effective therapy.

The use of MIBG in combination with other therapies, such as chemotherapy or DOTA-peptide radionuclides, has been proposed, but so far these techniques have not been reported in the literature.^{171,206,246} Combinations of multiple targeted molecular therapies directed toward multiple pathways may overcome compensatory mechanisms of PHEO/PGL cells, reduce necessary doses and therefore reduce the risk of resistance development, and overall lead to greater therapeutic success.^{171,231} Combined treatment with NVP-BEZ235, a dual PI3K/mTORC1/2 inhibitor, and lovastatin, a drug known to reduce ERK signaling, showed a significant additive effect leading to reduced cell viability in mouse PHEO/PGL cells, supporting the use of combination therapies in overcoming compensatory upregulation of other pathways and increasing treatment efficacy.²³⁷

Conclusions

The application of novel techniques and improved understanding of PHEO/PGL pathogenesis have led to a great deal of progress in this field in recent years. However, successful long-term treatments for patients who develop metastatic disease are still lacking. Several promising options have been identified and need to be introduced into clinical trials. These targeted treatment options will not only provide insight into the molecular mechanisms of PHEO/PGL pathogenesis, but also improve the quality of life for patients who suffer from this devastating disease.

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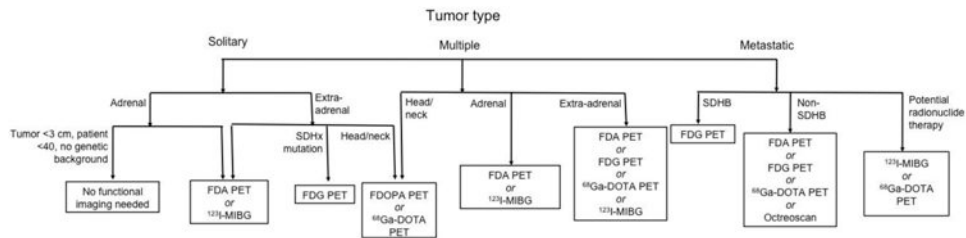


Figure 1.

Recommended genetic testing algorithm for patients with PHEO/PGL. (Adapted from Karasek et al. 2013)

*If both normetanephrine and methoxytyramine are elevated, follow the algorithm for methoxytyramine. If both normetanephrine and metanephrine are elevated, follow the algorithm for metanephrine.

**In patients with elevated normetanephrine with clinical features that do not clearly indicate which gene to test, perform immunohistochemistry for SDHB and SDHA.

+If tumor is adrenal, TMEM127 testing may be considered.

Abbreviations: DA: dopamine; HIF2A: hypoxia-inducible factor 2-alpha; HNP: head and neck PGL; h/o: history of; MAX: myc-associated factor X; MEN2: multiple endocrine neoplasia type 2; MTY: methoxytyramine; NF1: neurofibromatosis type 1; RET: rearranged during transfection; SDHA: succinate dehydrogenase subunit A; SDHB: succinate dehydrogenase subunit B; SDHC: succinate dehydrogenase subunit C; SDHD: succinate dehydrogenase subunit D; TMEM127: transmembrane protein 127; VHL: von Hippel-Lindau

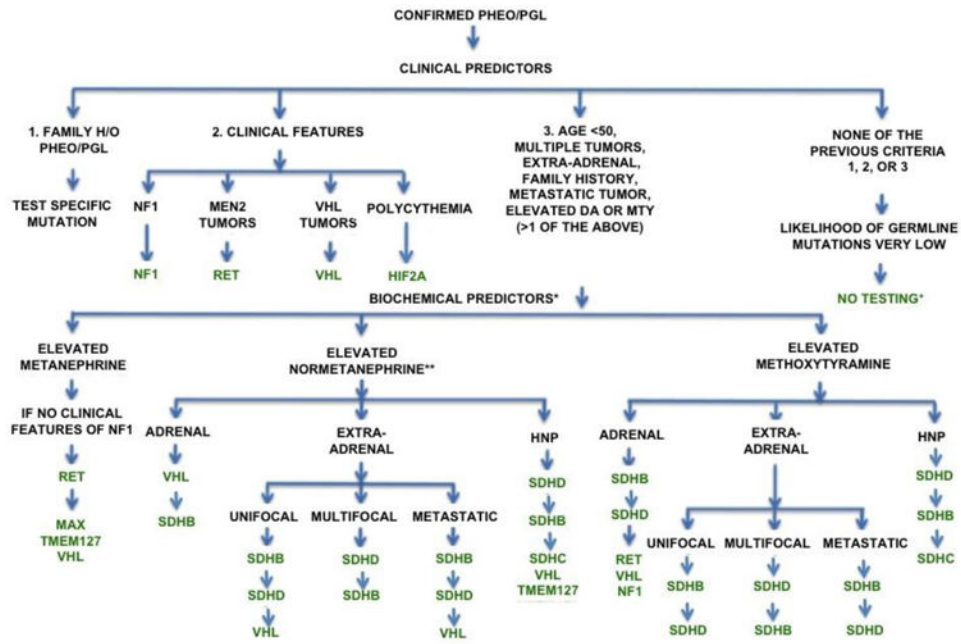


Figure 2.

Recommended functional imaging algorithm for patients with PHEO/PGL.

Abbreviations: FDA: ¹⁸F-fluorodopamine; FDG: ¹⁸F-fluorodeoxyglucose; FDOPA: ¹⁸F-fluorodopa; ⁶⁸Ga-DOTA: ⁶⁸Ga-DOTA-peptides; ¹²³I-MIBG: ¹²³I-metaiodobenzylguanidine; PET: positron emission tomography;; SDHB: succinate dehydrogenase subunit B; SDHx: succinate dehydrogenase mutation

Table 1

Clinical characteristics of genetic mutations associated with PHEO/PGL.

GENE	PROTEIN FUNCTION	SYNDROME	GERMLINE/SOMATIC	PHEO/PGL Penetrance	DE NOVO MUTATIONS	MEAN AGE	BIOCHEMICAL PHENOTYPE	COMMON PHEO/PGL SITES	BILATERAL PHEO	MALIGNANCY	OTHER ASSOCIATED CLINICAL CHARACTERISTICS/TUMORS
<i>VHL</i>	E3 ubiquitin ligase	VHL	Both reported	10-20%	20%	30	Nonadrenergic	Adrenal PHEOs (rarely sympathetic or head and neck PGLs)	50%	<5%	<ul style="list-style-type: none"> • Hemangioblastomas • Renal cell carcinoma • Islet cell tumors of pancreas
<i>RET</i>	Receptor tyrosine kinase	MEN2	Both reported	50%	5% (MEN2A), 50% (MEN2B)	30-40	Adrenergic	Adrenal PHEOs	50-80%	Rare	<ul style="list-style-type: none"> • Medullary thyroid carcinoma (95% MEN2A, 100% MEN2B) • MEN2A: hyperparathyroidism (15-30%) • MEN2B: marfanoid habitus; mucosal ganglioneuromas
<i>NFI</i>	GTPase activating protein	NFI	Both reported	<6%	50%	42	Adrenergic	Adrenal PHEOs (rarely sympathetic PGLs)	16%	~12%	<ul style="list-style-type: none"> • Café-au-lait spots • Neurofibromas • Freckles • Bony iris hamartomas • Optic-nerve gliomas • Spheroid bone dysplasia/pseudarthrosis
<i>SDHB</i>	Catalytic subunit of succinate dehydrogenase (mitochondrial complex II)	PGL4	Both reported	30-100%	Further study needed	30	Nonadrenergic and/or dopaminergic (Rarely biochemically silent)	Sympathetic PGLs (rarely adrenal PHEOs and head and neck PGLs)	Rare	31-71%	<ul style="list-style-type: none"> • Renal cell carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas • Possibly breast carcinoma • Possibly papillary thyroid carcinoma
<i>SDHD</i>	Membrane anchoring subunit of succinate dehydrogenase	PGL1	Both reported	73-90% (paternal transmission)	Further study needed	35	Nonadrenergic, dopaminergic, or silent	Head and neck PGLs, commonly multiple (extra-adrenal abdominal PGLs or adrenal PHEOs)	Rare	<5%	<ul style="list-style-type: none"> • Renal cell carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas
<i>SDHC</i>	Membrane anchoring subunit of succinate dehydrogenase	PGL3	Germline	Further study needed	Further study needed	40-50	Nonadrenergic, dopaminergic, or silent	Head and neck PGLs, sometimes multiple (rarely sympathetic PGLs or adrenal PHEOs)	Further study needed	Rare	<ul style="list-style-type: none"> • Renal cell carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas
<i>SDHA</i>	Catalytic subunit of succinate dehydrogenase (mitochondrial complex II)		Germline	Further study needed	Further study needed	40	Further study needed	Adrenal PHEOs or extra-adrenal PGLs	Further study needed	0-14%	<ul style="list-style-type: none"> • Homozygous patients: Leigh syndrome • Renal cell carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas
<i>SDHAF2</i>	Assembly factor for succinate dehydrogenase (mitochondrial complex II)	PGL2	Germline	100% (paternal transmission)	Further study needed	30-40	Further study needed	Head and neck PGLs, sometimes multiple	No known cases of PHEO	Further study needed	
<i>MAX</i>	Transcription factor		Both reported	Further study needed (paternal transmission likely)	Further study needed	32	Adrenergic and nonadrenergic	Adrenal	67%	20-25%	

GENE	PROTEIN FUNCTION	SYNDROME	GERMLINE/SOMATIC	PHEO/PGL Predisance	DE NOVO MUTATIONS	MEAN AGE	BIOCHEMICAL PHENOTYPE	COMMON PHEO/PGL SITES	BILATERAL PHEO	MALIGNANCY	OTHER ASSOCIATED CLINICAL CHARACTERISTICS/TUMORS
<i>TMEM127</i>	Further study needed		Germline	Further study needed	Further study needed	43	Adrenergic and nonadrenergic	Adrenal	33%	<5%	<ul style="list-style-type: none"> • Possibly linked to breast carcinoma • Possibly linked to papillary thyroid carcinoma
<i>HIF2A</i>	Hypoxia-inducible factor	Pacak-Zhuang	Mostly somatic; germline reported	N/A	Somatic mutations		Nonadrenergic	Extra-adrenal PGLs, usually multiple or PHEOs, possibly bilateral	Further study needed	None reported	<ul style="list-style-type: none"> • Multiple somatostatinomas • Polycythemia
<i>IDH</i>	Metabolic enzyme in Krebs cycle		Somatic (one case)	N/A	N/A	N/A	Not specified	Carcoid PGL	No known cases of PHEO	None reported	Glioblastoma multiforme
<i>FH</i>	Metabolic enzyme in Krebs cycle		Germline (one case)	N/A	N/A	N/A	Nonadrenergic	Adrenal PHEO	None reported	Patient had metastatic tumor	<ul style="list-style-type: none"> • Leontomyomatosis • Renal cell carcinoma
<i>KIF1Bβ</i>	Kinesin family protein (transport protein)		Germline	N/A	N/A	N/A	Further study needed	Further study needed	Further study needed	None reported	
<i>PHD2</i>	Proly hydroxylase		Germline (one case)	N/A	N/A	N/A	Not specified	Multiple PGLs	No known cases of PHEO	None reported	Erythrocytosis
<i>HAS</i>	GTPase		Somatic	N/A	Somatic mutations	N/A	Adrenergic and/or nonadrenergic	Both PHEO and PGL	None reported	None reported	

Table 2

Frequency of signs and symptoms in patients with PHEO/PGL.

Signs	Symptoms
Hypertension	Headaches
Sustained hypertension	Palpitations
Paroxysmal hypertension	Anxiety/nervousness
Postural hypotension	Tremulousness
Tachycardia or reflex bradycardia	Weakness, fatigue
Excessive sweating	Nausea/vomiting
Pallor	Pain in chest/abdomen
Flushing	Dizziness or faintness
Weight loss	Paresthesias
Fasting hyperglycemia	Constipation (rarely diarrhea)
Decreased gastrointestinal motility	Visual disturbances
Increased respiratory rate	

Frequency: highest (++++) to lowest (+). Adapted from Eisenhofer *et al.* (76).

Table 3
Medications contraindicated in patients with known or suspected PHEO/PGL

Drug class	Relevant clinical uses
β-Adrenergic blockers ¹	May be used to treat conditions that result from catecholamine excess (e.g. hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia and cardiac dysrhythmias)
Dopamine D2 receptor antagonists	Control of nausea, vomiting, psychosis, hot flashes and for tranquilizing effect
Tricyclic antidepressants	Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely)
Other antidepressants (serotonin and NE reuptake inhibitors)	Depression, anxiety, panic attacks, antiobesity agents
Monoamine oxidase inhibitors	Non-selective agents rarely used as antidepressants (due to “cheese effect”).
Sympathomimetics ¹	Control of low blood pressure during surgical anesthesia; decongestants; antiobesity agents
Chemotherapeutic agents ¹	Antineoplastic actions; treatment of malignant pheochromocytoma
Opiate analgesics ¹	Induction of surgical anesthesia
Neuromuscular blocking agents ¹	Induction of surgical anesthesia
Peptide and steroid hormones ¹	Diagnostic testing

¹ These drugs have therapeutic or diagnostic use in pheochromocytoma, but usually only alter pretreatment with appropriate antihypertensives (e.g. α-adrenoceptor blockers).

Table 4

Sensitivities and specificities of imaging modalities

Imaging modality	Primary (non-metastatic)		Adrenal PHEO	Extra-adrenal PGL	Head/neck PGL	SDHx carriers	Metastatic	SDHB metastatic	Non-SDHB metastatic	Bone metastases
	Sensitivity	Specificity								
CT/MRI	66-100%	40-90%	---	---	80-92%	85.7-87.5%	45-100%	78-96%	71%	37.8-96%
FDA PET	77-88%	90%	---	---	40-46%	---	76-97%	76-88%	76%	79-100%
FDG PET	58-88%	90%	---	---	69-80%	---	74-91.4%	74-100%	62-67.3%	76-93.7%
FDOPA PET	67-93%	95-100%	93.9%	47.1-90%	96.5-100%	---	45-100%	20-45%	93%	---
MIBG	52-87%	75-100%	85-87%	58-67%	18-50%	42.70%	38-92.4%	44-80%	59-66%	20.75-76%
Octreoscan	25-54%	75%	---	---	64-100%	69.50%	68.5-88.9%	59-81%	---	---
⁶⁸ Ga-DOTA peptides	80-100%	85.7%	---	---	100%	60%	91.70%	---	---	100%

Table 5

Medications used for symptom management and pre-procedural blockade.

Drug	Classifications	Doses	Recommended Use
<p><i>Alpha blockers</i></p> <p>Phenoxybenzamine (Dibenzylime)</p>	<p>long-lasting; irreversible; noncompetitive</p>	<p>10 mg 1-3 times daily</p>	<p>First choice for alpha-adrenoceptor blockade</p> <ul style="list-style-type: none"> When phenoxybenzamine is not available For patients who cannot tolerate phenoxybenzamine For patients with mild hypertension
<p>Prazosin (Minipress)</p> <p>Terazosin (Hytrin)</p> <p>Doxazosin (Cardura)</p>	<p>short-acting; specific; competitive</p> <p>short-acting; specific; competitive</p> <p>short-acting; specific; competitive</p>	<p>2-5 mg 2-3 times daily</p> <p>2-5 mg per day</p> <p>2-8 mg per day</p>	
<p><i>Beta blockers</i></p> <p>Atenolol (Tenormin)</p> <p>Metoprolol (Lopressor)</p> <p>Propranolol (Inderal)</p>	<p>cardioselective</p> <p>cardioselective</p> <p>non-selective</p>	<p>12.5-25 mg 2-3 times daily</p> <p>25-50 mg 3-4 times daily</p> <p>20-80 mg 1-3 times daily</p>	<p>To control tachyarrhythmia caused by catecholamines or alpha blockade</p>
<p><i>Calcium channel blockers</i></p> <p>Amlodipine (Norvasc)</p>		<p>10-20 mg per day</p>	<ul style="list-style-type: none"> To provide additional blood pressure control for patients on alpha blockers For patients who cannot tolerate alpha blockers For patients with intermittent hypertension
<p>Nicardipine (Cardene)</p> <p>Nifedipine (Adalat)</p> <p>Verapamil (Covera-HS, Calan-SR)</p>	<p>extended-release action</p> <p>extended-release action</p>	<p>60-90 mg per day</p> <p>30-90 mg per day</p> <p>180-540 mg per day</p>	
<p><i>Catecholamine synthesis inhibitors</i></p> <p>Metyrosine (Demser)</p>		<p>250 mg every 8-12 h for a total dose of 1.5-2 g per day</p>	<p>To provide additional blood pressure control for patients on adrenoceptor blockade</p>