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PHEOCHROMOCYTOMA AND PARAGANGLIOMA

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Updated July 21, 2025

ABSTRACT

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or neural crest progenitors located outside of the adrenal gland, respectively. These tumors are derived from either sympathetic tissue in the adrenal or extra-adrenal abdominal locations (sympathetic PPGLs) or parasympathetic tissue in the thorax, head, and neck (parasympathetic PPGLs). The clinical presentation is so variable that a PPGL has been described as "the great masquerader"(1). The extensive signs and symptoms of PPGLs arise from the hemodynamic and metabolic effects of the catecholamines that these tumors produce, store, and secrete. Therefore, a thorough understanding of these tumors' physiology, genetics, and pathophysiology is vital for providing optimal care, as discussed in detail in this chapter. Recent advances have greatly enhanced our understanding of PPGLs, providing a new viewpoint on their metastatic features, a classification of these tumors according to their genetic profiles, and, most recently, an analysis of their immune characteristics. Additionally, there has been a better understanding of catecholamine metabolism, its clinical implications for particular tumor phenotypes, and the development of specific imaging features. The newer targeted therapies for metastatic PPGLs are based on our improved understanding of tumor biology and the design of new PPGL-specific compounds with fewer side effects. There has been extensive research in the field of PPGLs in the last decade that has shed new light on genetics and multiple possible metabolic and other pathways that participate in the pathogenesis of these tumors. This article details the current literature on diagnosing and managing PPGLs, focusing on recent advancements in the field.

INTRODUCTION

Pheochromocytomas and paragangliomas (PPGLs) are highly vascular neuroendocrine tumors that produce catecholamines and metabolites (2)(3). They originate from chromaffin cells of the adrenal medulla or their neural crest and likely other progenitors outside the adrenal gland, respectively (4). PPGLs are estimated to occur in about 2–8 of 1 million people per year, and approximately 0.1% of hypertensive patients harbor a PPGL—about 10% of patients with PPGL present with adrenal incidentaloma (5,6). According to the 2022 WHO classification of tumors (fifth edition), based on their location/origin, these neuroendocrine neoplasms are classified as tumors of the adrenal medulla and extra-adrenal paraganglia (2).

Catecholamines are primarily metabolized in the cytoplasm of tumor cells, but only about 70% of PPGLs release them into circulation (7,8). In the remaining 30% of tumors, catecholamines are efficiently metabolized in the cytoplasm to either metanephrines or 3-methoxytyramine, and only these metabolites are released (7,8). As discussed further in this chapter, these tumors reuptake released catecholamines using the cell membrane norepinephrine transporter into the tumor cell, allowing the re-storage or metabolism of catecholamines, which are essential mechanisms to be considered for drug interactions.

Pheochromocytomas represent about 80% of the tumors and originate from medullary chromaffin tissue, now also referred to as intra-adrenal paragangliomas (4,9). The remaining 20% of tumors come from extra-adrenal paraganglia, referred to as paragangliomas (1). Paragangliomas are classified based on their origin: those that arise from parasympathetic ganglia of the skull base and neck region, as well as the anterior mediastinum (e.g., along the vagal nerve, glomus, carotid, jugular, and tympanic areas), and those that originate from the sympathetic ganglia in the abdomen, less commonly from the pelvis and rarely from posterior mediastinum or any other body location (9).

According to the WHO, all pheochromocytomas and paragangliomas have metastatic potential, as they can metastasize many years after successfully eradicating a primary tumor without evidence of residual disease or recurrence on early (3-6 months) postoperative imaging (2). Currently, metastatic PPGLs are defined by the presence of the disease only in the bones and lymph nodes (2). Most PPGLs represent sporadic tumors, and about 40% of PPGLs are of familial origin, with about 25 known susceptibility genes, making them the most hereditary among all human tumors (10,11). PPGLs can be classified into three broad clusters based on currently known PPGL mutations and their pathogenetic pathways. Cluster 1 includes genes belonging to the Krebs cycle and the hypoxia signaling pathway. Cluster 2 mutations entail abnormal activation of kinase signaling pathways like PI3Kinase/AKT, RAS/RAF/ERK, and mTOR pathways (12). Cluster 3 includes activating mutations of the Wnt-signaling pathway (Wnt receptor signaling and Hedgehog signaling) (1,13,14). This activation of Wnt and Hedgehog signaling is secondary to somatic mutations of the *CSDE1* (cold shock domain containing E1) and *MAML3* (Mastermind-like transcriptional coactivator 3) genes (14). On the other hand, according to the catecholamine secretory patterns, PPGLs can be characterized into three different phenotypical categories – noradrenergic phenotype (predominant norepinephrine secreting), adrenergic phenotype (predominant epinephrine producing), and dopamine secreting (1). These distinct biochemical phenotypes of PPGL lead to a constellation of symptoms and signs based on the predominant hormone secreted, resulting in different clinical manifestations (3).

CLINICAL FEATURES

The clinical presentation is so variable that a PPGL has been termed "the great masquerader." The varied signs and symptoms of PPGLs mainly reflect the hemodynamic and metabolic actions of the catecholamines produced and subsequently secreted by the tumors (10,15)(3). However, the presence of signs and symptoms of catecholamine excess remains the principal reason for initial suspicion of PPGLs; not all PPGLs exhibit these manifestations. The main reason is that an increasing proportion of these tumors are now being discovered incidentally during imaging procedures for unrelated conditions or during routine periodic screening in patients with identified mutations that predispose to the tumor (16,17). In such patients, the clinical presentation, if any present, may differ considerably (based on the biochemical phenotype) compared to patients in whom the tumor is suspected based on signs and symptoms.

PPGLs can synthesize, metabolize, reuptake, and release catecholamines, including norepinephrine, epinephrine, and/or dopamine. While the former two exert organ-specific effects after binding to adrenoreceptors, dopamine is hemodynamically inert unless secreted at very high levels, which results in hypotension (1). Catecholamines bind to active α- and β-adrenoceptors throughout the body, profoundly impacting the cardiovascular system and leading to specific clinical features. Hypertension is the most common indicator and can be chronic or episodic, with the episodic form being the more usual presentation occurring alongside normal blood pressure or ongoing hypertension. The effects of catecholamines on α1-adrenoceptors in the vessels and pre-capillary sphincters result in vasoconstriction and a subsequent increase in blood pressure (1,18). The action of catecholamines on the β1-adrenoceptors in the cardiac conduction system leads to overactivation of the sinoatrial and atrioventricular nodes, causing tachycardia; the β-adrenoceptor action also increases cardiac output, resulting in further elevation of blood pressure (1,18). PPGL may also present with hypotension, postural hypotension, or alternating episodes of high and low blood pressure due to the epinephrine stimulation of β2-adrenoceptors on the peripheral arteries and the resulting vasodilation (1,18,19).

Norepinephrine, with its higher affinity towards α1- followed by β1-adrenoceptor, is continuously released (rather than episodic release) and mediates vasoconstriction, leading to sustained hypertension (20). Thus, patients with the noradrenergic phenotype can have hypertensive encephalopathy that sometimes leads to ischemic attack/stroke, intestinal ischemia leading to intestinal necrosis, followed by sepsis, renal failure, muscle necrosis, and myoglobinuria (1,18,21–23). Less frequent clinical manifestations include fever of unknown origin (hypermetabolic state) and constipation (21). Catecholamine-induced hypertension (CIH) is a unique cause of secondary hypertension due to norepinephrine and epinephrine excess (20). On the contrary, patients with the adrenergic phenotype may sometimes present with hypotension resulting in tachycardia and even cardiogenic shock due to the vasodilatory effects of epinephrine, mediated by prominent β2-adrenoceptor overstimulation (10, 16, 20, 22, 23). Furthermore, patients with the adrenergic phenotype have commonly the episodic release of epinephrine from the tumor. Thus, these patients more often present with paroxysmal tachycardia and hypertension, or much less frequently hypotension.

Headache occurs in up to 90% of patients with PPGL. In some patients, catecholamine-induced headache may be similar to tension headache. Excessive, most commonly truncal, sweating occurs in approximately 60-70% of patients; however, since many tumors are now found as incidentalomas, sweating is much less common. Another sign of excess catecholamine is also pallor, observed in approximately 27% of patients, while only a few patients may have flushing (24). The presence of the 3 Ps triad, including headache (pain), palpitations, and generalized inappropriate sweating (perspiration) in patients with hypertension, should lead to immediate suspicion for a PPGL. In the recent study by Geroula et al. (25), presentations like hyperhidrosis, tremor, and pallor were 66% to 102% more prevalent in patients with PPGLs compared to those without any tumor, showing a consistent significance. Furthermore, palpitations were 28% more common, while muscle weakness and constipation were 23% to 60% more prevalent among those with these tumors. However, no significant differences were noted for headaches, flushing, or panic/anxiety between the two groups (25).

Other common (but non-specific) complaints are severe anxiety, tremulousness, vomiting, weakness, fatigue, dyspnea, weight loss despite normal appetite (caused by catecholamine-induced glycogenolysis and lipolysis), visual problems during an attack, and profound tiredness and polyuria, most experienced after an attack (1). Most patients also present with severe episodes of anxiety, nervousness, or panic attacks. Attacks (spells) of signs and symptoms may

occur weekly, several times daily, or as infrequently as once every few months. Most last less than an hour (sometimes even a few minutes), but very rarely more than several days. Attacks may be precipitated by palpitation of the tumor, changes in posture, physical exertion, anxiety, trauma, pain, consumption of foods or beverages containing tyramine (certain cheeses, beers, and wines), use of specific drugs (histamine, glucagon, tyramine, phenothiazine, metoclopramide, adrenocorticotropic hormone), intubation, induction of anesthesia, chemotherapy, endoscopy, catheterization, and micturition or bladder distention (with a bladder PGL) (1).

Patients with the dopaminergic phenotype may have some very non-specific manifestations as described above in this section, e.g., nausea and vomiting (possibly due to some stimulation of the D2 receptor in the brain), diarrhea (stimulation of D1 receptors in the intestinal tract) and hypotension (due to vasodilatory effects of dopamine) (26). Except for the clinical signs and symptoms described so far, patients with PPGL can, in up to 54% of cases, have tumor-related pain due to large primary tumors or due to metastatic lesions, most often bone metastases (27).

Highly variable symptomatology in patients with PPGL can reflect variations in the nature and types of catecholamines secreted, as well as co-secretion of neuropeptides: vasoactive intestinal peptide, corticotropin, neuropeptide Y, atrial natriuretic factor, growth hormone-releasing factor, somatostatin, parathyroid hormone-related peptide, calcitonin, and adrenomedullin. The classic example is PPGL with ectopic secretion of corticotropin or corticotropin-releasing factor, resulting in the presentation of Cushing syndrome (28, 29). PPGLs have also been described as secreting excessive amounts of vasoactive intestinal peptide, resulting in the presentation of watery diarrhea and hypokalemia (30).

As described above, neglecting the secretory status of these tumors predisposes patients to serious and life-threatening cardiovascular complications due to excess catecholamines, including severe hypertension, acute myocardial infarction, cardiac arrhythmias, pulmonary edema, heart failure due to aseptic cardiomyopathy, and shock (31).

GENETICS

PPGLs are neuroendocrine tumors with a heritable rate of approximately 40%, and a significant number arise from somatic mutations in over 25 susceptible genes (13,14,24–26). Given the high prevalence of somatic mutations in these tumors, somatic mutation analysis is always advised when tumor samples are accessible. While genetic panels specifically for pheochromocytomas and paragangliomas are still commonly utilized and provide a convenient means for practical genetic evaluation in clinical settings (12 of the most prevalent susceptibility genes are found in many patients), the reduction in costs, broad availability, and comprehensive coverage of all known susceptibility genes offered by next-generation sequencing technology is becoming much more desirable (1). Dependence only on germline mutation testing will miss 40% of somatic mutations that could be found in the tumors. Identifying these somatic mutations is crucial for future treatments, especially in cases of locally advanced disease or metastatic progression.

The classification of the susceptibility genes is into three primary clusters as described earlier: Cluster 1 includes genes associated with the Krebs cycle and the hypoxia signaling pathway, with the most significant genes being the succinate dehydrogenase gene family (subunits A-D), fumarate dehydrogenase, *EPAS1* (or *HIF2A*: hypoxia-inducible factor 2α), and von Hippel-Lindau (*VHL)*; cluster 2 involves genes tied to the kinase signaling pathway, primarily *RET*, *NF1*, *TMEM127*, and MAX, and cluster 3 consists of the *CSDE1* and *UBTF-MAML3* genes.

Tumors in cluster 1 typically manifest as extra-adrenal PGLs (except VHL) and usually display the

noradrenergic biochemical profile, while to a lesser extent, particularly those linked to *SDH* mutations, may also exhibit the dopaminergic biochemical profile (10). Tumors classified as Cluster 1 are frequently very aggressive and metastatic and present with a high rate of multiplicity and recurrence (1). Among the *SDH* gene family, PPGLs associated with *SDHA* mutations show the highest metastatic potential (up to 70%, this % may vary based on different studies and populations of patients), followed by *SDHB* mutations (up to 40%), and both *SDHC* and *SDHD* mutations exhibit an equal metastatic potential of up to 20%, based on clinical observations (1,27–29). The lifetime penetrance for PPGLs linked to *SDHB* mutations is estimated to be around 45%, with males showing a greater penetrance (5.2% and 35% by ages 20 and 60, respectively, whereas for females, it is 1.8% and 20% by the same ages; some studies indicate a lower penetrance of 22%) (35). In terms of size, *SDH* tumors exceeding 3.5–4 cm are linked to a more significant metastatic potential compared to other hereditary and non-hereditary tumors, which usually measure 6 cm or larger, and children diagnosed with these tumors generally have better survival rates than adults (30–34). For identifying these tumors as cluster 1 PPGLs, except *EPAS1* and *VHL*, the ^{68}Ga-DOATATE PET/CT is the preferred functional imaging method for primary, recurrent, multiple, and metastatic tumors in pediatric and adult populations (28,32–38). For PPGLs that have *EPAS1* and *VHL* mutations, the ^{18}F-fluorodopa PET/CT is the recommended functional imaging method. Recent research has shown that improved monitoring of *SDHB* carriers can lead to better clinical results, especially by facilitating the early identification of small tumors when their likelihood of metastasis is minimal (39,40).

Tumors in Cluster 2 typically appear as pheochromocytomas, characterized by the adrenergic biochemical phenotype, which may involve solely epinephrine or a mix of epinephrine and norepinephrine (1). These tumors are generally benign, except for *MAX* tumors, which tend to have a more significant potential for metastasis, and they also show a high rate of multiplicity and recurrence (27,41). Recent findings also indicate that the rate of metastatic pheochromocytoma in individuals with *NF1* is roughly 7.3% (10, 36). A table detailing the genes from both clusters, including when to start screening and the screening method, is provided in figure 2. A more recent update on the genetics of PPGL comes from Tothill et al., whose integrated single-nuclei RNA sequencing and bulk-tissue gene-expression analysis confirmed the presence of seven distinct gene-expression subtypes of PPGL, each with significant associations with specific genetic mutations and clinical characteristics (42). The most recent study from 2025 further advanced this understanding through multi-omic profiling of 94 *SDHB* tumors from 79 patients, identifying that *TERT* and *ATRX* mutations correlate with metastatic progression, along with an elevated mutational burden and altered telomere architecture (43).

Gene	Locus	Associated Syndrome(s)	Inheritance	Penetrance	PCC or PGL	Bilaterality or Multifocality	Metastatic Potential	Biochemical Phenotype	Associated Features
Cluster 1A									
SDHA	5p15.33	PGLS, CSS, 3PA	AD	Less than 5%	PGL	More data needed	Up to 70%	NA or DA	ccRCC, GIST*, PC*, PA**
SDHB	1p36.13	PGL4, CSS, 3PA	AD	30-60%	PGL, sometimes PCC	Commonly multifocal, rarely bilateral adrenal	Up to 75%	NA or DA	ccRCC, GIST*, PC*, PA**, NB
SDHC	1q23.3	PGL3, CSS, 3PA	AD	< 10%	PGL, sometimes PCC	More data needed	Rare	NA or DA	ccRCC, GIST*, PC*, PA**
SDHD	11q23.1	PGL1, CSS, 3PA	AD, paternal	80% if paternal inheritance	PGL, sometimes PCC	More data needed	15-20%, more data needed	NA or DA	ccRCC, GIST*, PC*, PA**
SDHAF2	11q12.2	PGL2	AD, possibly paternal	More data needed	PGL	More data needed	More data needed	NA or DA	
FH	1q43	Also in HLRCC	AD	About 1-3%	Both	Moderate	Moderate/high	NA	HLRCC: cutaneous and uterine leiomyoma, type 2 papillary RCC
IDH1/2	2q34 (IDH1), 15q26.1 (IDH2)	Also in Ollier disease and Maffucci syndrome	Mosaic	Variable by mosaicism	PGL	More data needed	More data needed	More data needed	Enchondromas, chondrosarcomas, spindle cell hemangiomas, many other soft tissue sarcomas
SLC25A11	17p13.2	PGL6	AD	More data needed	PGL	More data needed	High	NA	
DLST	14q24.3	PGL7	AD	More data needed	PGL, sometimes PCC	Likely moderate to high, more data needed	Likely low, more data needed	NA	PA (prolactinoma) and endometrial carcinoma (single reports)
Cluster 1B									
VHL	3p25.3	von Hippel-Lindau syndrome	AD	10-30%	PCC, PGL is rare	50%	5-7%	NA	Retinal angiomas, CNS HB, RCC, PNET, ELST, cystic lesions (pancreatic, uterine broad ligament, or epididymal)
EPAS1 (HIF2A)	2p21	Pacak-Zhuang syndrome	Mosaic, rarely AD (germline)	Variable by mosaicism; unknown (germline)	PGL, sometimes PCC	100% (somatic)	> 50% (somatic)	NA	Polycythemia, duodenal ampullar somatostatinoma, ocular anomalies, CNS venous anomalies, CCHD
Cluster 2									
RET	10q11.21	Multiple endocrine neoplasia, type 2A	AD	50%	PCC, rarely PGL	50-80%	< 5 %	A	MTC, hyperparathyroidism, Hirschsprung disease, and cutaneous lichen amyloidosis
RET	10q11.21	Multiple endocrine neoplasia, type 2B	AD, 75% de novo	50%	PCC, rarely PGL	50-80%	< 5 %	A	MTC, marfanoid habitus, (sub)mucosal and other (ganglio)neuromas
NF1	17q11.2	Neurofibromatosis type 1	AD, 50% de novo	Up to 13% (may be asymptomatic)	PCC, rarely PGL	16%	7%	A	Cafe-au-lait spots, axillary or inguinal freckling, Lisch nodules, optic pathway glioma, peripheral nerve sheath tumors, neurofibromas, astrocytoma, medullary thyroid cancer, carcinoid tumors, spina bifida, scoliosis
TMEM127	2q11.2		AD	33%	PCC	25% bilateral adrenal	Low	A	
MAX	14q23.3	Some cases of 3PA	AD, possibly paternal	More data needed	PCC, sometimes PGL	Frequently bilateral adrenal as well as multifocal	Around 10%	A	Ganglioneuroma, NB, PA**, parathyroid adenoma, chondrosarcoma, and pulmonary adenocarcinoma
HRAS	11p15.5		Sporadic	More data needed	PCC, rarely PGL	Low	More data needed	S	Ganglioneuroma
H3F3A	1q42.12		Mosaic	More data needed	PCC, PGL	Present, limited reports	More data needed	More data needed	Giant cell tumors of bone

FIGURE 1. Genes and features of pheochromocytoma and paraganglioma-associated syndromes. Genetic and clinical features of genes described for PPGL syndromes, modified from Pacak 2022 (10). CCHD, cyanotic congenital heart disease; CNS, central nervous system; CSS, Carney-Stratakis syndrome; ELST, endolymphatic sac tumor; HB, hemangioblastoma; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; MTC, medullary thyroid carcinoma; NB, neuroblastoma; PA, pituitary adenoma; PC, pulmonary chondroma; PNET, pancreatic neuroendocrine tumor; ccRCC, clear cell renal cell carcinoma; GIST, gastrointestinal stromal tumor; PCC, pheochromocytoma; PGL, paraganglioma; NA, noradrenergic; DA, dopaminergic; A, adrenergic; *Associated with Carney-Stratakis syndrome or Carney triad. **Included in three P Association (3PA).

Gene	When to Start Screening	Clinical Screening	Biochemical and Laboratory Screening	Imaging Screening
Cluster 1A				
SDHA, *SDHC*, *SDHD*-pi	10-15y	Annual: symptom questionnaire and blood pressure measurement.	Every 2 years: Plasma free or urinary	Every 2-3 years: MRI-HN and MRI-TAP.
	Adulthood	Continue as above.	Annual: plasma free metanephrines.	MRI as above. Once: PET/CT (^{68}Ga-DOTA-BSA preferred).
SDHB	6-10y	Annual: symptom questionnaire and blood pressure measurement.	Every 2 years: Plasma free or urinary	Every 2-3 years: MRI-HN and MRI-TAP.
	Adulthood	Continue as above.	Annual: plasma free metanephrines.	MRI as above. Once: PET/CT (^{68}Ga-DOTA-BSA preferred).
FH	8y	Annual: dermatology evaluation (8y).		Baseline: MRI Abdomen (8y). Every 6 months: US Abdomen (12y).
	Adulthood	Continue as above. Annual: gynecologic evaluation (21y).		Annual: CT or MRI Abdomen (start at 18y). Annual: US Pelvis (start at 21y).
	Diagnosis		Annual: plasma free (or urinary) metanephrines.	
Cluster 1B				
VHL	Before 1y	Every 6-12 months: dilated eye exam.		
	1y	Continue as above. Annual: history and physical examination.		
	2y	Continue as above, include BP and pulse on exam.		
	5y	Continue as above.	Annual: plasma free metanephrines.	
	11y	Continue as above. Every 2 years: audiogram.	Continue as above.	Every 2 years: MRI Brain and Spine w/wo contrast.
	15y	Continue as above.	Continue as above.	Continue as above. Every 2 years: MRI Abdomen w/wo contrast. Once: MRI Internal Auditory Canal.
	30y	Annual: history and physical examination, vital signs (BP and pulse), and dilated eye exam. Every 2 years: audiogram.	Continue as above.	Every 2 years: MRI Brain and Spine w/wo contrast and MRI Abdomen w/wo contrast.
	40y	Annual: history and physical examination, vital signs (BP and pulse), and dilated eye exam.		
	Pregnancy	Preconception: history and physical examination and vital signs (BP and pulse). Preconception and every 6-12 months: dilated eye exam.	Preconception: plasma free metanephrines.	Preconception: MRI Brain and Spine w/wo contrast and MRI Abdomen w/wo contrast.
EPAS1/*HIF2A*	5y	Annual: history and physical examination and vital signs (blood pressure and pulse) measurements. Ophthalmology evaluation at diagnosis.	Annual: plasma free or urinary metanephrines. Monitor hemoglobin and hematocrit (unspecified interval).	Every 1-2 years: MRI-HN and MRI-TAP (at minimum, MRI abdomen). Echocardiogram at diagnosis.
	20y	Continue as above. Assess for symptoms of somatostatinoma and other neuroendocrine tumors (e.g., gastrinoma).	Continue as above. Somatostatin level (unspecified interval).	Continue as above. Negative enteric contrast CT or endoscopy for somatostatinoma (unspecified interval).
Cluster 2				
RET (MEN2A)	3-5y (ATA-MOD)	Every 6-12 months: physical examination. Timing of prophylactic thyroidectomy based on screening data and shared decision-making for ATA-MOD but refer by 5y for ATA-H.	Every 6-12 months: serum calcitonin (those without thyroidectomy).	Every 6-12 months: US Neck (those without thyroidectomy).
	11y (ATA-H) or 16y (ATA-MOD)	Continue as above.	Annual: plasma free metanephrines or 24-hour urinary fractionated metanephrines, ionized (or albumin-corrected) calcium level a serum intact PTH, and serum calcitonin.	Continue as above. If metanephrine screening positive: MRI or CT Adrenals.
RET (MEN2B)	Before 1y (ATA-HST)	Routine physical examinations. Refer for prophylactic thyroidectomy.	Every 6-12 months: serum calcitonin (those without thyroidectomy, start at 6mo).	Every 6-12 months: US Neck (those without thyroidectomy).
	1y (ATA-HST)	Routine physical examinations.	Annual: plasma free metanephrines or 24-hour urinary fractionated metanephrines.	If metanephrine screening positive: MRI or CT Adrenals.
NF1	1-12 months	At diagnosis: physical examination (especially cardiac, neurologic, dermatologic, and skeletal). Annual: ophthalmologic examination. Pediatric standards (timing varies): growth curves and developmental evaluation.		As needed based on physical examination findings.
	1-5y	Annual: measure HC and BP, physical examination (especially neurologic, dermatologic, and skeletal), ophthalmologic examination, assess for precocious puberty. Pediatric standards (timing varies): growth curves and developmental evaluation.		As needed based on physical examination findings.
	5y-Puberty	Annual: monitor growth, measure HC and BP, physical examination (especially neurologic, dermatologic, and skeletal), ophthalmologic examination, assess for precocious puberty. At least once: developmental evaluation and discuss reproductive planning.		As needed based on physical examination findings.
	Adolescence	Annual: blood pressure measurement, physical examination (especially neurologic, dermatologic, and skeletal). At least once: developmental evaluation and discuss reproductive planning. As needed: ophthalmologic examination.	Every 3 years: plasma free (or 24-hour urinary fractionated) metanephrines (start at 10-14y).	If metanephrine screening positive: MRA/MRI +AP (add functional imaging [MIBG or F-DOPA PET/CT] if negative).
	Adults	Annual: NF1-focused medical history and physical examination, blood pressure measurement.	Continue metanephrine screening as above (also check if symptomatic and hypertensive). Monitor and supplement to maintain 25-hydroxyvitamin D levels in sufficient range.	Consider baseline MRI for plexiform neurofibromas. Hypertensive (if > 30y, pregnant, or abdominal bruits): MRA abdomen. If metanephrine screening positive: MRA/MRI-AP (add functional imaging [MIBG or F-DOPA PET/CT] if negative). Annual (females): mammography (starting at 30y) and consider MRI Breast with contrast (30-65y).
MAX	Diagnosis	Annual: history and physical examination.	At diagnosis: plasma (or urinary) metanephrines, anterior pituitary endocrine panel, ionized (or albumin-corrected) calcium level, serum intact PTH.	At diagnosis: MRI-HN, MRI-TAP. Consider functional imaging (^{68}Ga-DOTATATE or F-DOPA PET/CT).
TMEM127	22y	Annual: history and physical examination.	Annual: plasma free (or 24-hour urinary fractionated) metanephrines.	Every 1-3 years: MRI-AP.
MET	18y	Annual: history and physical examination.		Baseline: CT or MRI abdomen, then every 2 years (by 39y or sooner).
H3F3A	Diagnosis, for p.(G34W)	Annual: history and physical examination.	At diagnosis: plasma (or urinary) metanephrines.	At diagnosis: MRI-AP and skeletal survey.

Figure 2. Recommended screening for PPGL syndromes according to genetic classification. Adapted with permission from Kuo and Pacak 2025 (44). **ATA-H, American Thyroid Association (ATA) high risk; ATA-HST, ATA highest risk; ATA-MOD, ATA moderate risk; BP, blood pressure; HC, head circumference; MRI-AP, MRI of abdomen and pelvis; MRI-HN, MRI of head and neck; MRI-TAP, MRI of thorax, abdomen, and pelvis; PTH, parathyroid hormone; *SDHD*-pi, paternally inherited *SDHD* pathogenic variant; MEN, multiple neuroendocrine neoplasia; CS, Carney syndrome; CSS, Carney-Stratakis syndrome; 3PA, 3 P association; NF1, neurofibromatosis type 1; TSC, tuberous sclerosis complex.**

BIOCHEMICAL TESTING

Missing a PPGL can have a detrimental outcome. Therefore, biochemical evaluation should include highly sensitive tests to exclude a PPGL safely. Depending on their biochemical phenotype, PPGLs can secrete any combination of catecholamines, including all, none, or some of the following: epinephrine, norepinephrine, dopamine. These Catecholamines are produced and stored in intratumoral vesicles, leading to concentrations that typically exceed normal plasma levels by more than a thousand times (37). This is particularly critical in scenarios that may trigger a massive release of catecholamines into circulation, leading to life-threatening cardiovascular complications. Such situations include manipulation of the tumor during surgery, accidents, manual palpations, obstetric procedures, or cases of tumor instability due to ischemia, hemorrhage, or rupture (10). Additionally, the displacement of catecholamines is also possible due to certain foods or drugs like tyramine-rich food, amphetamines, or other stimulants (16). Moreover, catecholamines are efficiently metabolized within the tumor cell cytoplasm into their metabolites (primarily metanephrines). As a result, about 30% of these tumors may not present with elevated levels of catecholamines in their blood or urine (10). As the secretion of catecholamines from a PPGL is episodic, a single estimation of plasma or urinary epinephrine and norepinephrine most likely misses the biochemical diagnosis. In contrast, the metabolites of catecholamines (epinephrine is metabolized to metanephrine, and norepinephrine is metabolized to normetanephrine) are constantly released into circulation (38). This intra-tumoral process occurs independently of catecholamine release, which can occur intermittently or at low rates. In line with these concepts, numerous independent studies have confirmed that measurements of initially fractionated metanephrines (i.e., normetanephrine and metanephrine measured separately; currently free metanephrine and normetanephrine are measured either in plasma or urine) in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines (39). Consequent to the above considerations, although current, outdated US Endocrine Society guidelines recommend plasma or urinary free metanephrines as initial screening tests (40). There is a notable difference in the secretion patterns: tumors with a noradrenergic phenotype release about 50% of their norepinephrine content on a daily basis, while epinephrine tumors release only 3-5% per day (1). As a result, PPGLs with the norepinephrine phenotype are more likely to present with sustained hypertension, with or without tachycardia. In contrast, PPGLs with the adrenergic phenotype more often present with episodic symptoms and signs (refer to the clinical presentation section). In resting conditions, about 70% of catecholamines released by the tumor are taken back by the cell membrane norepinephrine transporter system via the catecholamine reuptake process (1). This is of clinical significance because certain medications, like most tricyclic antidepressants and monoamine oxidase inhibitors, can block catecholamine reuptake, causing a false elevation in catecholamine and metanephrine levels (24). A detailed list of medications that can interfere with testing is listed in figure 3. One should consider withholding these medications (only if the patient's clinical condition permits) that can lead to false-positive test results. The kidneys typically eliminate 14-16% of plasma metanephrines, while nearly all catecholamines are also cleared by the kidneys (20). In individuals with renal failure, there are significantly elevated levels of plasma catecholamines in comparison to free metanephrines. Therefore, plasma catecholamine concentrations should not be utilized for patients with kidney failure needing evaluation for PPGLs; instead, free metanephrines should be assessed. Consequently, a modified cutoff for plasma free metanephrines in patients with renal failure should be established, approximately 25-30% higher than that for those without kidney issues (45). Additionally, an updated recommendation suggests that the analysis of plasma or urine metanephrines

and 3-methoxytyramine should be performed using liquid chromatography tandem mass spectrometry (LC-MS/MS), which avoids most analytical interferences from medications, is cost-efficient, and highly precise (46–48). It is important to note that measuring dopamine and 3-methoxytyramine in urine for assessing PPGL is no longer advisable (49). Recently, age-specific reference intervals have been established, particularly noting that infants up to six months of age show increased levels of free normetanephrine and 3-methoxytyramine, which then decline sharply; in infants younger than one year, these values are considerably lower compared to those later in childhood (50).

A high diagnostic sensitivity for detecting these tumors is achieved if blood measurements are collected in the supine position, especially after an overnight fast and after a patient has been recumbent in a stress-free environment for at least 20 to 30 minutes before sampling (43). Urinary metanephrine, with measurement of urinary creatinine for collection verification, can be used as an alternative option, especially in centers where supine blood sampling is not feasible. Caffeine, smoking, and alcohol intake, as well as strenuous physical activity, should be withheld for approximately 24 hours before testing to avoid false-positive results. A 3-fold increase in normetanephrine, metanephrine, or 3-methoxytyramine levels above the upper limit of the age-adjusted reference is rarely a false-positive result, except when patients are on antidepressants and psychostimulants. Levels of catecholamine metabolites within the reference range typically exclude the tumors, while equivocal results (<2-3-fold above the upper limit) require additional tests if reference intervals are appropriately established and measurement methods are accurate and precise (44, 45). False-negative metanephrine could be observed in tumors that are smaller than 1 cm, dopamine-secreting head and neck tumors (recommend measuring 3-Methoxytyramine), or nonfunctional tumors (7). Also, it is important to note that urine dopamine levels should never be used in the diagnostic workup, as most of the dopamine in mammalian urine is formed in renal cells, rendering this test unacceptable for evaluating PPGLs (42).

Drug Category	Drug	Metanephrine (MN)	Normetanephrine (NMN)	Mechanism/Notes
Pain medications	Acetaminophen	–	↑↑	Analytical interference with some HPLC methods.
Pain medications	Sulfasalazine / Mesalamine	–	↑↑	Analytical interference.
Antidepressants	Tricyclic antidepressants	–	↑↑	Pharmacodynamic interference increasing NMN.
Antidepressants	MAO inhibitors	↑↑	↑↑	Inhibit monoamine breakdown → elevated MN & NMN. Avoid 5 days pre-test.
Sympathomimetics	Sympathomimetics	↑	↑	Increase catecholamine release by displacing them from storage vesicles.
Addiction-related	Cocaine	–	↑↑	Increases catecholamines → raised NMN.
Parkinson's drugs	Levodopa	↑	↑	Increases dopamine & methoxytyramine, which interfere in non-mass spectrometry assays.
Antihypertensives	α-Methyldopa	–	↑↑	Analytical interference in LC-ECD assays.
Antihypertensives	Labetalol	–	↑↑	Plasma unaffected; urinary NMN & MN ↑↑.
Antihypertensives	Sotalol	–	↑↑	Plasma unaffected; urinary NMN & MN ↑↑.
Antihypertensives	Phenoxybenzamine	–	↑	Pharmacodynamic effect – raises NMN mildly.
Anxiolytics	Buspirone	↑	–	Raises MN in plasma and urine mildly.
Other Interferents	Sulfasalazine	–	↑↑	See above – interferes with NMN only.

Figure 3. Medications that interfere with the testing of plasma or urinary metanephrines. Adapted from Hannah-Schmouni et al (24) and Lenders et al (51). LC-ECD, liquid chromatography with electrochemical or fluorometric detection; HPCL, High Performance Liquid Chromatography.

As the underlying genetic mutation leads to variable expression of catecholamine biosynthetic enzymes, there is a profound difference in the types and amount of catecholamines produced by these tumors (46). Moreover, regulatory and constitutive secretory pathways, which are also genotype dependent, contribute to variations in the catecholamine content displayed by tumors (46). Hence, a greater understanding of the genetic background will allow physicians to further advance diagnostic approaches (and thus treatment options). Approaching genetic testing using an individual patient's clinical presentation is considered cost-effective, timely, and valuable for early and effective treatment of patients, especially with hereditary PPGLs.

Tumor localization should usually only be initiated once the clinical evidence and biochemical proof of a PPGL is established. In patients with a hereditary predisposition, a previous history of a PPGL, or other PPGL syndromic presentations where the pre-test probability of a PPGL is relatively high, less-compelling biochemical evidence might justify the use of imaging studies. Imaging also plays a key role in screening patients with genetic predispositions to PPGL development. For carrier screening and biochemical evaluations, a CT or MRI is often recommended every few years to detect tumors in early stages, if at all. Adding whole-body imaging is particularly important for *SDH* mutation carriers, as these tumors are sometimes missed by only biochemical evaluations (54).

LOCALIZATION STUDIES

Either computed tomography (CT) or magnetic resonance imaging (MRI) is recommended for initial PPGL localization (more than 95% of PPGLs are found) (3, 55). Compared to MRI, CT has a better spatial resolution and is hence used as the first-choice imaging modality. Though both CT and MRI have equal sensitivity in localizing PPGLs, use of T2-weighted MRI imaging is recommended especially in patients with metastatic PPGL, for detection of skull base and neck PGLs, patients with surgical clips, in patients with an allergy to CT contrast and for patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations, and those with recent excessive radiation exposure) (1).

On CT, the measurement of Hounsfield units (HU) plays a significant role, particularly in non-contrast series. An attenuation of less than 10 HU almost entirely (99.9%) excludes the presence of these tumors. Conversely, an attenuation range of 10–30 HU is often considered a grey zone, necessitating further investigation (1). In non-contrast/contrast-enhanced imaging series, tumors may exhibit an attenuation exceeding 100 HU. The sensitivity of these imaging approaches typically ranges from 80% to 95% (1). Reduced sensitivity may arise in cases with previous surgical interventions, anatomical abnormalities, or tumors located in atypical regions, such as the gastrointestinal tract, which may require additional diagnostic methods such as endoscopy (1). Conversely, MRI, particularly with gadolinium as a contrast agent, is acknowledged as a very dependable imaging technique, providing sensitivity rates similar to those of Computed Tomography (CT). Importantly, MRI often proves more effective than contrast-enhanced CT in specific clinical scenarios, such as assessing liver and cardiac lesions (1). Current clinical guidelines recommend the use of non-contrast MRI for patient follow-up in cases of these tumors, as well as in individuals with genetic predispositions to pheochromocytoma and paraganglioma (52).

The article by Pacak (2022) (1) discusses the significant financial burden placed on patients and highlights the time-consuming nature of certain medical procedures that cannot be completed in a single visit. It also addresses the lower reliability of MRI in detecting small lesions, including metastases, except in cases involving the liver and heart. This unreliability is attributed to MRI's inferior spatial resolution and the presence of various artifacts compared to CT scans. Although MRI does not expose patients to radiation, the author points out an unknown risk related to the use of gadolinium contrast agents, particularly concerning their accumulation in the brain. The long-term implications of this accumulation are still being evaluated, especially in pediatric patients. In cases of adrenal tumors, MRI may demonstrate a bright T2-weighted signal intensity known as the "light-bulb sign," which can be absent in up to one-third of patients (53). Additionally, a relative washout of less than 40% and an absolute washout of less than 60% observed in adrenal washout CT scans further suggest the presence of these tumors (53). We express a preference for CT imaging over MRI in specific scenarios: during preoperative patient preparation (excluding liver and cardiac surgeries), for staging or restaging in complex or critical cases (such as those displaying symptoms/signs of catecholamine excess and positive biochemical laboratory results without a clearly located tumor), in treatment planning for metastatic disease, and in detecting multiple tumors in individuals with hereditary conditions linked to PPGL (1). Nevertheless, noncontrast MRI is very useful for follow-up of patients who underwent successful PPGL surgical removal or carriers of PPGL susceptibility genes, in some children and pregnant women.

Although CT and MRI have almost equal and excellent sensitivity for detecting most PPGLs, these anatomical imaging approaches lack the specificity required to unequivocally identify a mass as a PPGL. The higher specificity of functional imaging modalities offers an approach that overcomes the limitations of anatomical imaging, providing justification for the coupling of the

two approaches. Upon CT or MRI lesion confirmation, a patient's biochemical phenotype, tumor size, family history, syndromic presentation, and metastatic potential play a key role in determining the need for functional imaging. The patients with a single, epinephrine-producing or metanephrine-secreting adrenal tumor that is less than 5 cm will most likely not benefit from additional functional imaging, since these tumors are almost always confined to the adrenal gland and present with a small likelihood of metastases, even if a hereditary component is present (58). On the contrary, functional imaging is necessary for lesions that produce norepinephrine or secrete normetanephrine and are larger than 5 cm or associated with a hereditary tumor syndrome (as these characteristics determine the metastatic potential). Functional imaging also allows for the determination of the extent of disease, including the presence of multiple tumors or metastases, which is information that can be important for appropriately guiding subsequent management and treatment (59).

Historically, functional imaging has been performed with ^{123}I- or ^{131}I-metaiodobenzylguanidine (MIBG) scintigraphy. Though ^{123}I-MIBG SPECT has high sensitivity for detection of adrenal pheochromocytoma, it has unacceptably low sensitivity for the detection of extra-adrenal PGLs (56% to 75%) and metastases, especially in the presence of *SDHx* mutations (60). Moreover, certain medications, such as opioids, tricyclic antidepressants, and perhaps anti-hypertensives like labetalol, can also affect MIBG uptake, leading to less intense or false-negative scans. Nonetheless, ^{123}I-MIBG is useful to identify patients with metastatic PPGL because MIBG avid lesions indicate that these patients may benefit from treatment with therapeutic doses of ^{131}I-MIBG. Given the low sensitivity of MIBG imaging, the US Endocrine Society Guidelines recommend using ^{18}F-FDG PET scan as a preferred functional imaging modality in patients with metastatic disease (40). However, many recent studies have shown that metastatic lesions were missed on ^{18}F-FDG PET scan (61, 62). As PPGLs express somatostatin receptors (SSTRs), imaging modalities based on SSTR (DOTA peptides, particularly ^{68}GaDOTA(0)-Tyr(3)-octreotate (^{68}Ga-DOTATATE) are now viewed as gold standard for the detection of PPGLs.

The first functional imaging specific to neuroendocrine tumors, including PPGLs, was ^{18}F-fluorodopa (^{18}F-FDOPA), an amino acid analog and catecholamine precursor that is taken up by the amino acid transporter. Initially, lower sensitivity was now improved by inhibiting DOPA decarboxylase by pretreatment with carbidopa, which enhances the tracer uptake by the tumor (63). From all PPGLs, ^{18}F-FDOPA PET is extremely sensitive for patients with head and neck PGLs, sometimes identifying small tumors missed by all other imaging techniques. This technique also appears to be particularly effective for patients with *SDH* mutations or biochemically silent PHEO/PGL or both and may be valuable as a screening technique, particularly for patients with *SDHD* mutations. ^{18}F-fluorodopamine (^{18}F-FDA), which is similar to dopamine and taken up by norepinephrine transporters. ^{18}F-FDA PET is another PPGL-specific tracer that offers excellent diagnostic sensitivity and spatial resolution, and appears particularly useful for the localization of some primary and metastatic PPGLs, but this imaging modality is not used often these days since it has been surpassed by ^{68}Ga-DOTATATE and ^{18}F-FDOPA PET. A prospective study demonstrated the superiority of ^{68}Ga-DOTATATE in a cluster of 22 patients, in which ^{68}Ga-DOATATE could localize 97.6% metastatic lesions whereas ^{18}F-FDG PET/CT, ^{18}F-FDOPA PET/CT, ^{18}F-FDA PET/CT, and CT/MRI showed detection rates of 49.2 %, 74.8 %, 77.7 %, and 81.6 % respectively ($p<0.01$) (64). King et al (50) and Janssen et al (61) reported that ^{18}F-FDOPA as well as ^{68}Ga-DOTATATE PET were equally good in the localization of head and neck *SDHx*-related and non-hereditary PPGLs. However, a prospective analysis by Archier et al (65) concluded that ^{68}Ga-DOTATATE was superior to ^{18}F-FDOPA in localizing small head and neck PPGLs, especially caused by *SDHD* mutation,

making it a preferred modality of imaging in head and neck PPGLs. Conversely, the study showed that small adrenal pheochromocytomas (usually seen with MEN2 and NF1 syndromes) are better detected with ^{18}F-FDOPA (65). This might be secondary to high physiological uptake of ^{68}Ga-DOTATATE in the adrenal gland, compared to ^{18}F-FDOPA. Recently, ^{64}Cu-DOTATATE, a novel tracer radiolabeled with copper-64, has been introduced for imaging neuroendocrine tumors (54). Compared to ^{68}Ga-DOTATATE, it offers: Improved spatial resolution and image quality, a longer half-life (12.7 hours vs. 1.1 hours), allowing delayed imaging up to 3 hours, enhanced tumor-to-background ratios, potential for individualized dosimetry, making it suitable for theranostic applications (54). Despite these advantages, head-to-head intraindividual comparisons between ^{64}Cu and ^{68}Ga-DOTATATE are lacking, though preliminary data suggest comparability (54). These functional imaging modalities form the cornerstone of theranostics, where diagnostic imaging with ^{68}Ga-DOTATATE is used to determine eligibility for peptide receptor radionuclide therapy (PRRT), offering targeted radiotherapy for inoperable or metastatic disease (55),(56). Figure 4 summarizes the current proposed PET radiopharmaceuticals for PPGL imaging according to genetic background (66).

Gene	Location	Other related tumor conditions	First-choice radiopharmaceutical	Second-choice radiopharmaceutical
SDHB	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	^{68}Ga-DOTA-SSAs	^{18}F-FDG
SDHD	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	^{68}Ga-DOTA-SSAs	^{18}F-FDG
SDHC	Adrenal/extradrenal	GISTs, RCCs	^{68}Ga-DOTA-SSAs	^{18}F-FDG
FH	Adrenal/extradrenal	Skin and uterine leiomyomas, RCCs, uterine leiomyosarcomas and ovarian mucinous cystadenomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
VHL	Adrenal/extradrenal	RCCs, CNS hemangioblastomas, pancreatic and testicular tumors	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
EPAS1/HIF2A	Adrenal/extradrenal	Somatostatinomas	^{18}F-FDOPA	^{18}F-FDG
MEN2	Adrenal/extradrenal	MTC, parathyroid adenomas, or hyperplasia	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
NF1	Adrenal/extradrenal	Neurofibromas, peripheral nerve sheath tumors, and gliomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
TMEM127	Adrenal/extradrenal	RCCs	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs
MAX	Adrenal/extradrenal	Renal oncocytomas	^{18}F-FDOPA	^{68}Ga-DOTA-SSAs

Figure 4. Current proposed PET radiopharmaceuticals for PPGL imaging based on genetic background. Adapted from Taïeb et al (66).

METASTATIC POTENTIAL OF PPGL

According to the WHO, all PPGLs have metastatic potential, as they can metastasize many years after successfully eradicating the primary tumor without evidence of residual disease or recurrence on postoperative imaging (1). The patterns of metastatic behavior vary between cluster 1 and cluster 2 tumors, particularly evident in the occurrence rates of 20–30% and 2–7% in patients, respectively. The most common sites for metastasis are the lymph nodes, followed by the bones, and then the liver and other organs. Patients with soft tissue lesions are typically classified as high-risk and have a shorter survival rate compared to those without such lesions (1). Additionally, it has been found that pheochromocytomas present a lower risk of metastasis compared to sympathetic PGLs (usually located outside the head and neck), with rates of approximately 5–20% versus 15–35%, respectively (10). Recent research has indicated a correlation between the development of metastases and *SDHB* mutations, high levels of norepinephrine and dopamine, increased levels of 3-methoxytyramine and normetanephrine, the size of the primary tumor, its multiplicity, and an extra-adrenal location (27, 67-69).

The risk factors include the age at which the primary diagnosis is made, the tumor location—where

parasympathetic tumors are typically the least likely to metastasize—the presence of multiple or recurrent tumors, genetic factors, elevated oncometabolite levels (such as succinate and fumarate in mutations of the *SDH* and fumarate hydratase genes, respectively), high levels of 3-methoxytyramine, and established genetic abnormalities (like TERT structural rearrangements, copy number gains, and *ATRX* mutations), all of which serve as reliable predictors of tumor behavior over the course of the disease (10). Ultimately, the most effective imaging technique for identifying metastatic lesions is ^{68}Ga/^{64}Cu-DOTATATE, which should be conducted for both initial staging and re-staging following therapeutic procedures (38,57–61).

MANAGEMENT OF PPGLs

PPGLs are rare tumors that are represented in only a few specialized centers worldwide. In 2021, the North American Neuroendocrine Tumor Society established a consensus guideline for surveillance and management of metastatic or unresectable PPGL (62). According to this guideline, there is now consensus on the therapies for metastatic PPGL or locally advanced PPGL. Treatment for unresectable tumors should focus on stabilizing tumor growth (which can include complete or partial responses, as well as stable disease) and/or controlling catecholamine production and secretion (62). Surgical management of metastatic PPGL is usually not recommended unless there is tumor mass effect or there is appropriate justification for removal of a tumor (e.g., primary tumor or usually a large metastatic lesion) such as a particularly large tumor which upon resection would lead to a significant decrease in circulating catecholamine concentrations, whose end-organ effects cannot be well controlled by various drugs.

The definitive treatment of PPGL is surgical excision of the tumor. Laparoscopic surgery is commonly the technique of first choice for resection of adrenal and extra-adrenal PPGLs when oncologic principles can be followed (70). Exposure to high levels of circulating catecholamines during surgery may cause hypertensive crises and arrhythmias, which can occur even when patients are preoperatively normotensive and asymptomatic. All patients with PPGL should therefore receive appropriate preoperative medical management to block the effects of released catecholamines (40). Hence, it is of utmost importance that the preparation of the patient for surgery requires adequate preoperative medical treatment to minimize operative and postoperative complications. Exceptions to this rule include endocrine emergencies like necrotic PPGL leading to severe hypotension, other surgical emergencies (71) or the tumors that secrete high amounts of dopamine or epinephrine.

Pre-Operative Medical Management (Blockade)

As described above, once diagnosed with PPGL, patients should be placed on antihypertensive medications, preferentially α followed by β-adrenoceptor blockade (3). Figure 5 summarizes the list of available drugs and suggested doses. The first choice should be an α-adrenoceptor blocker. A β-adrenoceptor blocker may be used for preoperative control of arrhythmias, tachycardia, or angina. However, loss of β-adrenergic-mediated vasodilatation in a patient with unopposed catecholamine-induced vasoconstriction via α-adrenoceptors can result in dangerous increases in blood pressure, sometimes a hypertensive crisis. Therefore, β-adrenoceptor blockers usually should not be employed without first blocking α-adrenergic-mediated vasoconstriction. Labetalol (more potent β than α-antagonist activities with α: β of 1:5-7) should not be used as the initial therapy because it can result in paradoxical hypertension due to its high affinity to β-adrenoceptors. Phenoxybenzamine, a long-acting α-adrenoceptor blocker, is commonly the preferred drug in patients who have elevated blood pressures. Short acting α_1-adrenoceptor blockers like prazosin, terazosin, and doxazosin are used when phenoxybenzamine is not available or when a patient's hypertension is not severe enough to warrant the use

of a long-acting α-adrenoceptor blocker, or simply as good alternative to phenoxybenzamine that is not available in many countries (72). As there is a high chance that these medications can cause orthostatic hypotension, they should be started at night (72). The doses should be titrated to achieve normo-tension or mild tolerable hypotension. The patients should also be advised to maintain adequate water and salt intake to maintain adequate intravascular volume. Calcium channel blockers (CCBs) can be added if a goal blood pressure control is not achieved with adequate α- and β-adrenoceptor blockade. CCBs can also be used as initial agents of choice in patients who have normo-tension/mild hypertension, and/or who could not tolerate an α-blocker due to hypotension (usually seen in PPGLs that secrete dopamine predominantly). Patients with non-secreting head and neck tumors with normal blood pressure may not be placed on pre-procedural blockade (37).

Drug	Classification	Doses	Recommended use
Phenoxybenzamine (Dibenzyline)	α-adrenoceptor blocker	10 mg 1–3 times daily	First choice for α-adrenoceptor blockade.
Prazosin (Minipress)	α-adrenoceptor blocker	2–5 mg 2–3 times daily	When phenoxybenzamine is not available. Another alternative to Doxazosin.
Terazosin (Hytrin)	α-adrenoceptor blocker	2–5 mg/d	For patients who cannot tolerate phenoxybenzamine. Another alternative to Doxazosin.
Doxazosin (Cardura)	α-adrenoceptor blocker	2–8 mg/d	For patients with mild hypertension a very good choice for patients, in many countries as first choice for α-adrenergic blockade.
Atenolol (Tenormin)	β-Blocker	12.5–25 mg 2–3 times daily	To control tachyarrhythmia caused by catecholamines or α-adrenoceptor blockade and very occasionally α-adrenoceptor blockade.
Metoprolol (Lopressor)	β-Blocker	25–50 mg 3–4 times daily	To control tachyarrhythmia caused by catecholamines or α-adrenoceptor blockade and very occasionally α-adrenoceptor blockade.
Propranolol (Inderal)	β-Blocker	20–80 mg 1–3 times daily	To control tachyarrhythmia caused by catecholamines or α-adrenoceptor blockade and very occasionally α-adrenoceptor blockade.
Amlodipine (Norvasc)	Calcium channel blocker	5-10 mg/d	Use as add-on to α-adrenoceptor blockade or in patient with mild hypertension.
Nicardipine (Cardene)	Calcium channel blocker	60–90 mg/d	Use as add-on to α-adrenoceptor blockade or in patient with mild hypertension.
Nifedipine (Adalat)	Calcium channel blocker	30–90 mg/d	Use as add-on to α-adrenoceptor blockade or in patient with mild hypertension.
Verapamil (Covera-HS and Calan-SR)	Calcium channel blocker	180–540 mg/d	Use as add-on to α-adrenoceptor blockade or in patient with mild hypertension. Can also cause bradycardia.
Metyrosine (Demser)	Catecholamine synthesis inhibitor	250 mg every 6–12 h for a total dose of 1.5–2 g/d	To provide additional blood pressure control for patients on adrenoceptor blockade.

Figure 5. Medications used for symptom management and preoperative blockade for PPGLs. Adapted from Martucci et al (63).

In patients who did not achieve adequate blood pressure control despite being on optimized doses of α and β-adrenoceptor blockade, metyrosine (a competitive inhibitor of tyrosine hydroxylase) can be added to prevent catecholamine synthesis. Metyrosine acts by decreasing catecholamine synthesis, and its main side effects include depression, anxiety, and sleepiness due to its effects on the central nervous system (as it can cross the blood-brain barrier) (37).

In some patients, blood pressure can reach very high values, and such a situation is termed a hypertensive crisis when it is life-threatening or compromises vital organ function. The hypertensive crises are the result of a rapid and marked release of catecholamines from the tumor. Patients may experience hypertensive

crises in different ways. Some report severe headaches or diaphoresis, while others have visual disturbances, palpitations, encephalopathy, acute myocardial infarction, congestive heart failure, or cerebrovascular accidents. Therefore, it is crucial to start proper antihypertensive therapy immediately. Management of a hypertensive crisis, short-acting intravenous (IV) agents are preferred over oral medications because splanchnic vasoconstriction can impair absorption, and oral agents may have prolonged effects that can be dangerous if subsequent hypotension develops (64). Continuous IV infusions are ideal. In contrast, IV bolus medications e.g. diuretics (unless heart failure is present) should be avoided due to the potential risk of intravascular volume depletion caused by chronic α_1-adrenoceptor-mediated vasoconstriction (23). α-Adrenoceptor blockers would be cornerstone of treatment, although their availability is limited and therefore, impractical (for example, IV phentolamine or oral/IV phenoxybenzamine) (23). β-Blockers should never be used without adequate α-blockade because of the risk of unopposed α-stimulation, which could worsen hypertension (23). Calcium channel blockers like nicardipine, clevidipine, and nitroprusside can be utilized, but each has potential side effects, such as cyanide toxicity with nitroprusside (23). Verapamil is preferred among calcium channel blockers when concurrent tachyarrhythmias are present. Additionally, magnesium sulfate may be beneficial, especially in cases of arrhythmias or during pregnancy (23). Fenoldopam is rarely used but may offer renal-protective effects. Once blood pressure is controlled, a transition to oral α-blockers (such as doxazosin) should be initiated, followed by β-blockers (like metoprolol) if tachycardia persists (23).

Certain medications are to be avoided in patients with PPGLs. The effects of some drugs are more obvious due to their mechanism of action, such as the dopamine D2 receptor antagonist metoclopramide (51,65). More recently, peptide and corticosteroid hormones, including corticotropin, glucagon, and glucocorticoids (intravenous), have been shown to have adverse reactions in this patient population unless patient are on appropriate adrenergic blockade (51,65). Other classes of drugs relatively contraindicated in patients with PPGL are tricyclic antidepressants, antidepressants that are serotonin or norepinephrine reuptake inhibitors like Cymbalta and Effexor, again, unless these patients are on appropriate adrenergic blockade (51,65). Furthermore, displacement of catecholamines from storage can have devastating sequelae. Many drugs for obesity management fall in this category, such as phentermine (Adipex, Fastin, and Zantryl), phendimetrazine (Bontril, Adipost, and Plegine), sibutramine (Meridia), methamphetamine (Desoxyn), and phenylethylamine (Fenphedra). Other over-the-counter medications, such as nasal decongestants containing ephedrine, pseudoephedrine, or phenylpropanolamine, can also lead to drug interference (51,65).

Surgery

As described earlier, surgical resection is the treatment of choice. A less invasive surgical method should be chosen based on the skill level of the surgical team. There are currently no prospective clinical trials that directly compare laparoscopic and open adrenalectomy techniques for PPGL in either adult or pediatric patients (66). An open surgical approach may be considered for patients who present with tumor size greater than 5-10 cm in diameter, multifocal tumors in the same area, presence of regional lymph node metastases on preoperative scans, or tumors that are invading or closely located to adjacent organs or vascular structures (66). The risks of operative mortality are extremely low if performed by an experienced surgical team, including a skilled anesthesiologist to monitor for intraoperative hypertensive crises (37). Surgery can also be used as a curative treatment for recurrent or limited metastatic tumors; it can also be used as a debulking technique for patients with extensive metastatic disease to reduce symptoms/signs and imminent complications from tumor size (2). However, the long-term benefits

of debulking procedures for patients with metastatic disease may be limited (73).

Chemotherapy

In cases of rapidly growing tumors, chemotherapy is typically the preferred treatment strategy. Traditional chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has been used most extensively with progressive and widely metastatic PPGLs (81, 82). This regimen is administered over two days and repeated every 21 days. CVD chemotherapy is usually well tolerated for long periods, with an increased time between the doses can be tried in patients who develop toxicities. Clinicians using chemotherapy should be aware of potentially fatal complications arising from excessive catecholamine release as tumor cells are destroyed (usually within the first 24 hours), and patients should be closely monitored, preferably in an intensive care unit, especially in patients who have extensive disease and high baseline catecholamine levels.

Recent studies have indicated that the use of tyrosine kinase inhibitors has shown promise in treating these tumors (67). A meta-analysis assessing CVD chemotherapy revealed that 37% of patients with metastatic pheochromocytoma or paraganglioma experienced a partial response to this treatment (68). However, it is important to note that this analysis included patients with minimal or no progression of metastatic lesions prior to their enrollment in the CVD chemotherapy protocol. In contrast, a separate study focusing exclusively on patients with progressive metastatic disease reported a response rate of 33%, with a corresponding, albeit non-significant, improvement in overall survival (6.4 years for responders versus 3.7 years for non-responders)(69). When the genetics is taken into account, Cluster 1 metastatic PPGLs demonstrate a better response to CVD chemotherapeutic regimen compared to Cluster 2 tumors (70,71). This is particularly relevant for *SDHB* mutations, where complete or partial responses were observed in approximately 83% of cases (71). The potential response in other *SDH* mutations, such as A, C, and D, remains uncertain.

Tyrosine kinase inhibitors, including sunitinib, axitinib, and more recently, lenvatinib, cabozantinib, and pazopanib, provide additional treatment options for these patients, with overall response rates similar to CVD chemotherapy in about one-third of patients (except those with *SDH* mutations) (67,72,73). These inhibitors may also be particularly useful for patients with Cluster 2 tumors and those with von Hippel-Lindau (VHL) syndrome who have not responded to CVD or temozolomide chemotherapy, as summarized in recent clinical reviews (74,75).

Targeted Therapy

Lately, theranostic-based targeted radiotherapeutic approaches are gaining popularity as a favored treatment for patients with metastatic, locally invasive, or inoperable pheochromocytoma or paraganglioma, particularly when the overall tumor growth rate is slow to moderate. These treatment techniques emphasize the targeting of receptors and transporters found on tumor cells, such as somatostatin receptors and the norepinephrine transporter, enabling a more personalized therapy plan (55). An additional advantage is the ability to obtain whole-body scans, which not only help monitor tumor burden and treatment response but also assist clinicians in deciding whether a change in therapeutic strategy is necessary.

^{131}I-MIBG, a targeted radionucleotide therapy, is available in two strengths: low-specific activity (LSA) and high-specific activity (HSA) MIBG (Azedra®), which has received FDA approval (56). The HSA formula is nearly entirely composed of radiolabeled ^{131}I-MIBG, unlike the conventional or LSA formula, where 1 in 2000 MIBG molecules are radiolabeled with ^{131}I. As a result, HSA offers greater specificity and reduced side effects compared to LSA ^{131}I-MIBG (76,77). Typically, the single dose administered to

patients using HSA is higher in radiation (approximately 500 mCi or 8 mCi/kg for those weighing less than 62.5 kg and can be repeated once) than LSA ^{131}I-MIBG (with an average dose of about 200 mCi, usually given in three doses) (77). In the initial single-arm phase II study, patients diagnosed with metastatic or inoperable pheochromocytoma and paraganglioma were treated with one or two cycles of HSA ^{131}I-MIBG (77). Within the first year, 23% of patients showed an objective partial response, while 69% maintained stable disease (77). The median overall survival for the initial treatment was 36.7 months. Predictably, the administration of HSA ^{131}I-MIBG resulted in myelosuppression in around 72% of patients, with myelodysplastic syndrome in 4% and acute leukemia in 3% (77). Some severe hematologic side effects might be attributed to previous systemic cytotoxic interventions (such as chemotherapy) in a number of patients. Notably, there were no acute cardiovascular incidents reported with this treatment approach (77). However, HSA has been discontinued in April 2024 and is no longer available worldwide.

Another available radiotherapeutic option is PRRT (56), which utilizes either somatostatin receptor analogs DOTATATE or DOTATOC radiolabeled with ^{177}Lu or ^{90}Y; however, neither of these therapies is currently FDA-approved for these tumor types, although they have received approval from the European Medicines Agency (EMA). Among the various PRRT options, ^{177}Lu-DOTATATE (Lutathera®) is the most commonly used in medical institutions globally. In meta-analyses involving patients with metastatic or locally advanced pheochromocytoma or paraganglioma receiving either Lutathera® or ^{177}Lu/^{90}Y-DOTATATE/DOTATOC, 90% of individuals experienced either a partial response or stable disease (60,78). Consequently, the results associated with Lutathera® and Azedra® concerning partial responses and stable disease in patients with these tumors were almost indistinguishable. Furthermore, the risks of bone marrow suppression and myelodysplastic syndrome for Lutathera® were similar to those seen with Azedra®, though to a lesser extent (77–79). Unlike Azedra®, some patients receiving Lutathera® experienced an increase in catecholamines, leading to catecholamine crises, primarily affecting the cardiovascular system and resulting in other endocrine issues, although these potential effects may not have been thoroughly explored in patients treated with Azedra® (80,81) or LSA ^{131}I-MIBG.

The selection between ^{131}I-MIBG and ^{177}Lu-DOTATATE for treating specific tumors requires a careful clinical decision-making process, particularly when ^{123}I-MIBG and ^{68}Ga-DOTATATE show identical lesions. Key factors to consider include the availability of radiopharmaceuticals and their toxicity profiles based on patient age and bone marrow health. ^{131}I-MIBG is typically favored for younger patients with good bone marrow reserve and high catecholamine levels, while ^{177}Lu-DOTATATE is preferred for elderly patients with borderline bone marrow reserve and lower catecholamine levels (56). Liver or kidney impairment does not affect the selection of radiotherapy. Future advancements in radiopharmaceuticals may alter treatment strategies for these tumors.

Post-operative Management

While some patients experience hypotension shortly after surgery, the majority need treatment, most effectively addressed through fluid administration. Hypoglycemia immediately after tumor removal is another problem best prevented by infusion of 5% dextrose started immediately after tumor removal and continuing for several hours thereafter. Post-operative hypoglycemia is transient, whereas low blood pressure and orthostatic hypotension may persist for up to a day or more after surgery and require care with assumption of sitting or upright posture (57).

The long-term prognosis of patients after operation for PPGL is excellent, although nearly 50% may remain hypertensive after surgery. Biochemical testing should

be repeated after about 14-28 days from surgery to check for residual disease. Importantly, normal postoperative biochemical test results do not exclude remaining microscopic disease, so patients should not be misinformed that they are cured and that no further follow-up is necessary. On long-term follow-up, about 17% of tumors recur, with about half of these showing signs of metastatic disease. Individuals with *SDH* mutations have a perpetual risk of pheochromocytomas and paragangliomas (PPGL), requiring continuous monitoring, even if they show no symptoms at first. Regular follow-up for asymptomatic carriers (*SDHA*, *SDHB*, *SDHC*, *SDHD*) should include annual clinical examinations, biochemical tests every 2 years during childhood and annually in adulthood, and MRI imaging every 2–3 years (52). Ultrasound and functional imaging are not recommended as first-line follow-up methods (52). If a carrier has never developed a tumor and remains asymptomatic, screening can be delayed to every 5 years after age 70, with follow-up ceasing at age 80 (52). It is crucial to conduct thorough screening for pregnant individuals with *SDH* mutations due to the elevated risks of PPGL during pregnancy (82). Although follow-up is especially important for patients identified with mutations of disease-causing genes, there is currently no method based on pathological examination of a resected tumor to rule out the potential for malignancy or recurrence. Thus, long-term periodic follow-up is recommended for all cases of PPGL (7, 57).

CONCLUSIONS

1. PPGLs are neural crest-derived tumors, and currently, more than 40% have a known genetic cause. Thus, all patients with PPGLs should be considered for genetic testing.
2. Genetic testing should be based on several considerations: syndromic features, family history, age at diagnosis, multifocal and metastatic presentation, tumor location, and the dopaminergic biochemical phenotype.
3. PPGLs are tumors that are diagnosed based on the measurement of plasma or urinary free metanephrines and 3-methoxytyramine since 30% of these tumors do not secrete catecholamines.
4. All patients with metastatic disease should undergo appropriate genetic testing based on the biochemical profile and primary tumor location.
5. CT is an excellent imaging modality in patients with biochemically proven PPGL. MRI is recommended in patients with metastatic PPGL to liver, cardiac PGL, and also for detection of skull base and neck PGL; in patients with surgical clips that cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, and those with recent excessive radiation exposure).
6. ^{68}Ga DOTATATE scanning is the preferred functional modality in patients with metastatic disease and head and neck PGLs.
7. ^{123}I-MIBG scintigraphy is used as a functional imaging modality mainly in patients with metastatic PPGLs detected by other imaging modalities when radiotherapy using ^{131}I-MIBG is planned.
8. All patients with a biochemically positive PPGLs (except those with only elevated 3-methoxytyramine) should undergo preoperative adrenoceptor blockade with α-adrenoceptor blockade followed by β-blockers to prevent perioperative cardiovascular complications.
9. Minimally invasive (laparoscopic) surgery is recommended for most adrenal PPGLs, and open resection for large or locally invasive PPGLs to ensure complete resection and avoid local recurrence. *SDHB* pheochromocytoma should be always removed by total adrenalectomy.
10. Multidisciplinary teams at centers with appropriate expertise to ensure favorable outcomes should treat all patients with PPGL.

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