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The Genomic Landscape of Pheochromocytoma and Paraganglioma: From Molecular Classification to Precision Therapy

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ABSTRACT

Pheochromocytoma and paraganglioma (PPGL) constitute a uniquely complex group of neuroendocrine tumors in which rare incidence contrasts sharply with disproportionate clinical impact. Despite their low prevalence, PPGLs pose a persistent diagnostic and therapeutic challenge due to their high genetic heterogeneity, unpredictable clinical behavior, and potential for life-threatening catecholamine-mediated complications. Over the past decade, advances in genomic profiling have overturned the traditional view of PPGL as largely sporadic and benign, revealing that up to 40% of cases are driven by germline pathogenic variants, with additional somatic alterations shaping tumor aggressiveness and metastatic risk.

Nevertheless, major unresolved gaps remain, including incomplete genotype–phenotype correlations, variable penetrance even within the same mutation, and the absence of universally accepted algorithms for integrating genetic data into routine clinical decision-making. These uncertainties directly affect risk stratification, surveillance intensity, and selection of emerging targeted and radionuclide therapies.

This review critically examines current evidence on the molecular architecture, biochemical phenotypes, and genotype-guided management of PPGLs, highlighting areas of consensus as well as ongoing controversies. By synthesizing recent translational and clinical insights, we aim to clarify why a genetics-centered, precision-based framework is no longer optional but essential for improving outcomes in PPGL.

Keywords: Pheochromocytoma; Paraganglioma; Genetic Susceptibility; Precision Medicine; Targeted Therapy

INTRODUCTION

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors arising from neural crest–derived chromaffin cells and represent a biologically heterogeneous disease spectrum with distinctive genetic, biochemical, and clinical features. Pheochromocytomas originate from the adrenal medulla and account for approximately 80–85% of PPGLs, whereas sympathetic paragangliomas arise from extra-adrenal sympathetic ganglia located along the thorax, abdomen, and pelvis, constituting about 15–20% of cases. In contrast, head and neck paragangliomas (HNPGLs) derive from parasympathetic paraganglia and are typically non- or weakly secretory in nature [1–3].

A defining hallmark of PPGLs is their ability to synthesize and secrete catecholamines, resulting in distinct biochemical phenotypes that closely reflect tumor origin and underlying molecular drivers. Approximately half of adrenal pheochromocytomas exhibit an adrenergic phenotype, characterized by epinephrine production with variable norepinephrine co-secretion. In contrast, most extra-adrenal sympathetic paragangliomas display a noradrenergic phenotype, producing predominantly or exclusively norepinephrine. A subset of PPGLs, particularly head and neck tumors and aggressive or metastatic lesions, demonstrate a dopaminergic phenotype, marked by dopamine production and elevated 3-methoxytyramine levels, reflecting altered catecholamine biosynthetic enzyme activity [4–6].

Beyond their secretory behavior, PPGLs are notable for having the highest heritable fraction among all human tumors. Large genomic studies have established that up to 40% of patients harbor germline pathogenic variants, with additional somatic alterations detected in a substantial proportion of sporadic cases. These genetic drivers cluster into biologically coherent signaling pathways, including pseudohypoxia, kinase, and Wnt

pathways, which together explain much of the observed diversity in tumor location, biochemical profile, metastatic risk, and clinical outcome [7–9].

Despite their rarity, pheochromocytomas and paragangliomas (PPGLs) remain among the most diagnostically and therapeutically challenging endocrine tumors due to their heterogeneous clinical presentation and the potentially life-threatening effects of catecholamine excess. Although advances in genomic profiling and functional imaging have reshaped their biological classification, critical gaps persist particularly incomplete genotype–phenotype correlations, variable mutation penetrance, and the absence of standardized frameworks for integrating molecular data into routine clinical practice thereby constraining the full implementation of precision medicine.

This review adopts a translational and clinically focused perspective, aiming to bridge molecular insights with patient-centered management. We critically examine the genomic architecture and biochemical phenotypes of PPGLs and discuss how molecular stratification informs risk assessment, surveillance, surgical decision-making, and the selection of radionuclide and targeted systemic therapies. By integrating current genetic and clinical evidence, we underscore the necessity of a structured, genetics-driven framework to guide individualized care and improve long-term outcomes in PPGL.

Adrenergic Phenotype

Adrenergic PPGLs are defined by predominant epinephrine production, clinically captured by disproportionate elevations of metanephrine (MN) (often with variable accompanying normetanephrine, NMN), reflecting intratumoral conversion of epinephrine from norepinephrine. In practice, a biochemical profile characterized by marked MN elevation (plasma free or urinary fractionated metanephrines) strongly suggests an adrenergic catecholamine phenotype and should be interpreted within standardized pre-analytical conditions recommended for PPGL diagnostics [3].

From a molecular taxonomy standpoint, the adrenergic phenotype aligns most consistently with kinase-signaling PPGLs (TCGA “cluster 2”), driven by activation of pathways such as RAS/RAF/ERK, PI3K/AKT, and mTOR. Germline or somatic alterations in RET (MEN2), NF1, TMEM127, and HRAS are canonical in this group. These tumors are typically well-differentiated adrenal pheochromocytomas and, compared with pseudohypoxia-driven PPGLs, tend to show lower metastatic propensity overall (with important gene-specific exceptions) [10–14].

A mechanistic hallmark that explains both the biochemistry and the usual anatomic distribution is phenylethanolamine N-methyltransferase (PNMT), the enzyme catalyzing norepinephrine → epinephrine conversion. PNMT expression is physiologically promoted by the adrenocortical–medullary microenvironment (including local glucocorticoid exposure), which is why tumors with a strongly adrenergic biochemical signature are most often intra-adrenal. Nevertheless, adrenergic secretion can be encountered outside the adrenal in select molecular contexts (notably some TMEM127-associated tumors) and should not be used as an absolute locator rule when imaging or staging [13,15–17].

Clinically, kinase-signaling/adrenergic PPGLs are frequently associated with episodic catecholamine symptoms (paroxysmal hypertension, palpitations, diaphoresis, headaches), and their phenotype has practical implications for both perioperative risk and individualized imaging/management in cluster-informed care. Importantly, although adrenergic tumors are often straightforward biochemically, results must still be contextualized against known confounders (medications, posture, stress, sampling conditions), and positive tests require confirmatory follow-up per guideline-based workflows [3,13].

Genetic evaluation is essential because PPGLs have a high hereditary fraction and genotype increasingly guides surveillance and family counseling. While historical practice often used phenotype-guided prioritization (e.g., high MN prompting early consideration of RET/MEN2 and NF1), contemporary expert reviews and multidisciplinary guidance increasingly favor broad germline testing (multigene panels/NGS) for most patients—especially those diagnosed young, with bilateral/multifocal disease, recurrent/metastatic presentation, or suggestive family history, because stepwise testing can miss actionable variants. That said, in an adrenergic biochemical context with classic syndromic cues, RET and NF1 remain high-yield starting points in differential diagnosis, with TMEM127 and MAX considered when first-line etiologies are excluded or when tumor patterns suggest these genes [11,15,18,19].

MAX also warrants particular attention because it can blur the biochemical boundary within kinase-signaling PPGLs. Although cluster 2 tumors are classically associated with an adrenergic biochemical profile, MAX-related PPGLs may exhibit an intermediate catecholamine secretion pattern, showing overlapping adrenergic and noradrenergic features. Consequently, MAX should remain an integral part of the genetic differential diagnosis in patients with apparently sporadic adrenal pheochromocytoma, especially when more common susceptibility genes have been excluded or when clinical and pathological features raise suspicion of an underlying hereditary predisposition [15,20,21].

Noradrenergic Phenotype

Noradrenergic PPGLs are defined by predominant norepinephrine production, which is biochemically reflected by elevated NMN (often with increased norepinephrine, depending on the assay and sampling conditions) and low or absent MN. This phenotype is typically established using plasma free or urinary fractionated metanephrines as recommended first-line tests; interpretation must account for pre-analytical factors (posture, stress, medications) to reduce false positives and ensure appropriate follow-up of abnormal results [3,19].

At the molecular level, the noradrenergic phenotype is most strongly associated with pseudohypoxia-driven PPGLs (TCGA "cluster 1"), a group enriched for pathogenic variants that activate hypoxia signaling or mimic hypoxic transcriptional programs. Cluster 1 includes (i) Krebs cycle/oncometabolite

genes such as SDHx (SDHA/SDHB/SDHC/SDHD), SDHAF2, FH, and MDH2, and (ii) hypoxia pathway genes such as VHL and EPAS1/HIF2A, with additional regulators (e.g., PHD1/PHD2) implicated in pseudohypoxic tumorigenesis. These alterations converge on HIF pathway activation (notably HIF-2α signaling), promoting chromaffin/paraganglionic tumorigenesis and clinically distinct patterns of secretion, imaging, and recurrence risk [13,22].

A key biological explanation for this biochemical profile is reduced capacity for epinephrine synthesis. Compared with kinase-signaling (cluster 2) tumors, pseudohypoxia, related PPGLs frequently show lower PNMT expression/activity, limiting conversion of norepinephrine to epinephrine and thereby favoring a noradrenergic (NMN-predominant) pattern. This is classically demonstrated in VHL-associated pheochromocytomas, which typically exhibit a distinctly noradrenergic phenotype relative to MEN2/RET-associated tumors [23,24].

From an anatomic and clinical perspective, noradrenergic secretion is common in sympathetic paragangliomas, which are frequently extra-adrenal (thoraco-abdominal, pelvic sympathetic chain) and are overrepresented among SDHx, driven disease. However, important exceptions exist: in VHL syndrome, tumors can be confined to the adrenal and still remain predominantly noradrenergic, so "noradrenergic = extra, adrenal" is a useful clue but not an absolute rule [24,25].

A frequently under, emphasized but clinically crucial add-on is the dopaminergic signal within pseudohypoxic disease. Some SDHB-associated tumors (and metastatic PPGL more broadly) may produce dopamine, captured by elevated plasma/urinary 3-methoxytyramine (3-MT), either alone or alongside NMN elevation. Contemporary European guidance highlights that 3-MT elevation can correlate with metastatic risk in SDHB-associated tumors, and cohort data consistently identify SDHB as a major risk factor for metastatic PPGL, many of which are noradrenergic sympathetic PGLs [13,25].

Finally, while phenotype, guided testing remains informative (e.g., high NMN ± 3-MT prioritizing evaluation of SDHx/VHL/EPAS1-related etiologies), modern practice increasingly supports broad germline testing (multigene panels/NGS) in most patients because PPGLs have substantial heritability and genotype determines surveillance intensity, metastatic risk stratification, and family cascade testing. Phenotype should therefore be presented as a probability, weighting tool, not a replacement for comprehensive genetic evaluation when indicated [13,25,26].

Dopaminergic Phenotype

Dopaminergic PPGLs are characterized by predominant dopamine production, occurring either in isolation or together with only mild norepinephrine/normetanephrine increases, and are best biochemically captured by elevated 3-MT, the O-methylated metabolite of dopamine. Because circulating dopamine can be low or fluctuate (and may be analytically less reliable), 3-MT provides higher diagnostic yield for identifying a dopaminergic secretory pattern, especially when MN and NMN are not markedly increased [3,27,28].

Anatomically, a dopaminergic profile is frequently encountered in HNPGLs (e.g., carotid body, jugulotympanic, vagal), which are often non or minimally adrenergic; in these tumors, dopamine excess may be present even when classic catecholamine symptoms are absent or atypical, and measurement of dopamine metabolites can support diagnosis and follow, up. Although less common, dopamine-producing adrenal pheochromocytomas have also been reported, underscoring that "dopaminergic phenotype = head/neck" is a strong association rather than an absolute rule [27,29].

Clinically, dopaminergic secretion has important risk-stratification implications, as increased 3-MT is repeatedly linked with metastatic or aggressive disease biology, particularly in the context of SDHB (and to a lesser extent SDHD/SDHC) pathogenic variants. Large cohort analyses have shown that plasma 3-MT adds independent information to established risk markers (tumor size, location, SDHB status) for estimating metastatic likelihood, and European guidance incorporates elevated 3-MT as a trigger for more intensive staging imaging (e.g., FDG PET/CT) in specific clinical contexts [30–32].

Mechanistically, the dopaminergic phenotype is commonly attributed to impaired conversion of dopamine to norepinephrine due to reduced activity/expression of dopamine β, hydroxylase (DBH), leading to dopamine accumulation and relatively lower norepinephrine output. This enzymatic immaturity has been hypothesized to reflect proliferation of poorly differentiated progenitor-like tumor cells, which is consistent with the observed enrichment of dopaminergic (3-MT–positive) profiles among metastatic PPGLs and SDHB/SDHD-associated disease. While sporadic case reports describe dopaminergic PPGLs in syndromic backgrounds such as NF1, VHL, and MEN2, the strongest and most reproducible association in the broader literature remains with SDHx, related pseudohypoxia biology and metastatic risk [19,27,33].

Incidence

PPGLs (pheochromocytoma and paraganglioma) are rare neuroendocrine tumors with an estimated population incidence of ~2–8 cases per million persons per year and an overall prevalence of ~1:2,500 to 1:6,500. In the United States, this corresponds to approximately 500–1,600 newly diagnosed cases annually, although estimates vary by methodology and case ascertainment [34–36].

The true incidence is likely higher than clinically recognized because PPGLs can remain undiagnosed until death, particularly when symptoms are mild, intermittent, or attributed to other causes. Supporting this under-detection, a large coronial autopsy series from Australia/New Zealand reported previously unrecognized pheochromocytoma in ~0.05% of autopsies (≈1 per 2,031 autopsies), highlighting the contribution of missed diagnoses to epidemiologic underestimation [37].

Among patients evaluated for hypertension, PPGL is an uncommon but clinically critical cause of secondary hypertension. Prospective screening data in hypertensive cohorts have reported prevalences around ~0.6% in selected outpatient populations, and major endocrine references

commonly cite a prevalence range of roughly ~0.2–0.6%among hypertensive patients, reflecting differences in screening strategies and referral patterns [37–39]. With respect to tumor distribution and "incidental" discovery, adrenal pheochromocytomas constitute the majority of PPGLs (often cited ~80–85%), yet pheochromocytoma represents only a small fraction of adrenal incidentalomas, commonly around ~5–7% in clinical series and reviews. This point is important for manuscript framing: PPGLs are a minority of incidental adrenal masses, but missing the diagnosis has disproportionate perioperative and cardiovascular risk [39–42].

Demographically, PPGL incidence peaks between the third and fifth decades (mean/median age in many series near the early to mid 40s), while pediatric disease accounts for a minority (frequently cited ~10–20%), and is more likely to be associated with an underlying hereditary predisposition than adult-onset sporadic presentations [34,43].

Signs and Symptoms

Clinical manifestations of PPGL are highly heterogeneous and largely determined by

- The catecholamine profile (epinephrine, norepinephrine, and/or dopamine, predominant)
- The pattern of secretion (continuous vs episodic)
- Host factors such as receptor sensitivity and concomitant cardiovascular disease

Accordingly, patients may present with classic adrenergic spells, sustained hypertension, atypical complaints, or even minimal/no symptoms despite biochemically active tumors [44,45].

A characteristic feature, particularly for catecholamine-secreting sympathetic PPGLs, is paroxysmal symptom clusters reflecting episodic hormone release, most commonly including headache, palpitations, diaphoresis, tremor, pallor, anxiety/panic, like episodes, and flushing; nausea, chest discomfort, and dyspnea may also occur. These paroxysms can arise spontaneously or be precipitated by physiologic or mechanical stimuli (e.g., exercise, abdominal pressure, postural changes), emotional stress, smoking, alcohol, or catecholamine-releasing/interactional exposures [45,46].

A clinically important, and often overlooked, element is the role of exogenous triggers, including medications and tyramine-rich foods. Reported precipitants include certain glucocorticoids, ACTH/glucagon, sympathomimetics (e.g., ephedrine/phenylephrine), dopamine antagonists (notably metoclopramide), phenothiazines, tricyclic antidepressants/ other agents interfering with catecholamine handling, and high, osmolality contrast or peri, anesthetic stressors; dietary tyramine (classically in aged cheeses and some fermented foods/drinks) can also provoke hypertensive episodes in susceptible settings. These triggers matter both for clinical suspicion and for preventing iatrogenic crises during procedures [12,46–49].

Beyond episodic adrenergic symptoms, PPGLs can present with life-threatening cardiovascular events driven by catecholamine excess, including hypertensive crisis, acute coronary syndromes/ myocardial infarction (often via vasospasm and demand ischemia), brady- and tachyarrhythmias, acute heart failure, and catecholamine-induced cardiomyopathy, including Takotsubo syndrome. Importantly, some patients manifest labile blood pressures or, more rarely, hypotension and shock, including pheochromocytoma multisystem crisis characterized by hemodynamic instability and multiorgan dysfunction, situations in which PPGL should be considered when conventional etiologies do not fully explain the presentation [50–52].

Recent evidence also clarifies that classic symptom patterns are less universal than historically assumed. A meta-analysis summarized in contemporary reviews reported headache, palpitations, and sweating in only ~60%, 59%, and 52% of patients, respectively, with other symptoms occurring at lower frequencies. Moreover, a prospective, feature-based study found that no single symptom occurred in >65% of PPGL patients, even among those tested because clinicians suspected catecholamine excess, highlighting limited sensitivity and specificity of symptom-based screening alone [45,49,53].

It should be noted, a meaningful subset of PPGLs are asymptomatic (silent) and discovered incidentally on imaging or during surveillance of genetically predisposed individuals. This phenomenon reinforces the need to integrate symptoms with biochemical testing (metanephrines ± 3-methoxytyramine in selected contexts) and appropriate imaging rather than relying on the classic triad alone [44,45,54].

Diagnosis

The diagnosis of PPGL requires biochemical evidence of catecholamine excess, because clinical presentation alone is insufficiently sensitive and specific. In patients evaluated because of hypertension and suggestive symptoms, the pre-test prevalence is low (~0.5%), and it is similarly modest among individuals with incidentally discovered adrenal masses (~5% in many series) (55,56). This low baseline probability, combined with imperfect test specificity, creates a diagnostic setting in which false positives are common, yet false negatives are unacceptable because missed PPGL can lead to catastrophic cardiovascular outcomes [3,57,58].

The clinical imperative for reliable testing is underscored by older but influential autopsy, based observations: among patients in whom pheochromocytoma was discovered post-mortem, a large proportion died suddenly from myocardial infarction or cerebrovascular events, and a substantial subset experienced collapse during or shortly after unrelated minor procedures, consistent with unrecognized catecholamine surges under stress/anesthesia [59]. While modern detection has improved, these data remain central to the rationale for systematic biochemical confirmation before interventions that might trigger crisis.

First-Line Biochemical Testing

Current international recommendations state that initial biochemical testing (Table 1) should be performed using either plasma free metanephrines or urinary fractionated

metanephrines. These metabolites outperform direct catecholamine measurements because PPGLs continuously metabolize catecholamines to metanephrines within tumor tissue, so metanephrines remain elevated even when catecholamine release is episodic [3].

Pre-analytical Conditions and Common Pitfalls (often under-emphasized)

Because diagnostic specificity is strongly affected by sampling conditions, guidelines emphasize controlling pre-analytical variables. For plasma metanephrines, supine sampling after a period of rest is preferred, and clinicians must account for factors that increase sympathetic tone (pain, anxiety, acute illness), as well as medications and substances that can produce borderline elevations or analytic interference. When these issues are ignored, mildly elevated results frequently represent false positives, particularly in low-prevalence screening contexts [3,60].

Interpreting Positive and Borderline Results

Positive results should be interpreted by the magnitude and pattern of elevation. Marked increases (commonly operationalized as several, fold above the upper reference limit) are far more predictive of PPGL than borderline elevations, which often require repeat testing under optimized conditions or additional confirmatory steps. The Endocrine Society guideline explicitly recommends structured follow, up of all positive tests according to the extent of elevation and clinical context [3].

In patients with equivocal normetanephrine elevations, especially when sympathetic activation is suspected, confirmatory approaches may be used in specialized settings (e.g., reassessment under strict conditions and selected suppression testing strategies), but the most evidence-based first response remains repeat measurement with optimized posture/rest and careful review of confounders [3,60].

Adding 3-Methoxytyramine (3-MT) when appropriate

A key often forgotten component is that some PPGLs, particularly those with dopaminergic output or aggressive biology, may be best captured by 3-MT, the O-methylated dopamine metabolite. Contemporary diagnostic discussions highlight 3-MT as useful when dopamine secretion is suspected (e.g., head and neck PGL, SDHx disease) and for risk enrichment in selected contexts [45,60].

Imaging after Biochemical Confirmation

Once biochemical evidence supports PPGL, anatomic imaging is typically the next step. The Endocrine Society guideline suggests CT for initial localization in most patients, while MRI is preferred when radiation exposure should be minimized or when metastatic disease is suspected/being staged. Functional imaging (e.g., MIBG or PET-based approaches) is then selected based on tumor location, genotype/phenotype, and the clinical question (localization vs. staging vs. theranostic planning) [3].

Genetic Testing Integrated into Diagnosis

Because PPGLs have a high heritable fraction and genotype influences surveillance and staging strategy, modern diagnostic algorithms increasingly incorporate early genetic evaluation (often via multigene panels) rather than relying solely on stepwise phenotype-guided testing. Phenotype still helps prioritize likelihood (e.g., pseudohypoxia/noradrenergic patterns vs. kinase/adrenergic patterns), but it should complement, not replace, comprehensive genetic assessment when indicated [3,45].

Test	Sensitivity (%)	95% Confidence interval	Specificity (%)	95% Confidence interval
Plasma free metanephrines	99	96–100	89	87–92
Urinary fractionated metanephrines	97	92–99	69	64–72
Plasma catecholamines	84	78–89	81	78–84
Urinary catecholamines	86	80–91	88	85–91
Urinary total metanephrines	77	68–85	93	89–97
Urinary vanillylmandelic acid	64	55–71	95	93–97

Table 1: Comparison of sensitivity and specificity of tests commonly used for the evaluation of patients with suspected pheochromocytoma [61]

Genetic Approach

PPGLs represent the most highly heritable group of human neoplasms, with a uniquely strong genetic determinism that directly informs diagnosis, risk stratification, surveillance intensity, and family counselling (Table 2). Contemporary series and reviews consistently show that ~30–40% (and in many cohorts ~40%) of patients harbor a germline pathogenic/likely pathogenic variant in a PPGL susceptibility gene, while an additional ~30–40% of apparently sporadic tumors contain somatic driver alterations, often affecting the same pathways and, in some cases, the same genes implicated in hereditary disease [62–68].

Genetic Cluster	Common Genes	Biochemical Phenotype	Tumor Location	Malignancy Risk	Preferred Imaging / Therapy
Pseudohypoxia	SDHx, VHL, EPAS1/HIF2A, FH, MDH2	Noradrenergic/ Dopaminergic	Extra-adrenal / adrenal	High (esp. SDHB)	68Ga-DOTATATE PET; PRRT; intensive follow-up
Kinase-Signaling	RET, NF1, TMEM127, MAX, HRAS	Adrenergic	Adrenal (often bilateral)	Low–moderate	MIBG imaging; surgery; TKI in select cases
Wnt / Fusion-driven	MAML3, CSDE1	Variable	Adrenal / Thoracoabdominal	Aggressive / metastatic	Emerging targeted therapies; clinical trial consideration

Table 2: Schematic overview of integrating genomic information into diagnostic and therapeutic decisions

The major germline susceptibility genes span three biologically coherent molecular groups: (i) pseudohypoxia/Krebs cycle–related genes, most prominently SDHx (SDHA, SDHB, SDHC, SDHD) and SDHAF2, as well as VHL, EPAS1/HIF2A, FH, and MDH2; (ii) kinase-signaling genes, including RET (MEN2), NF1, TMEM127, MAX, and HRAS; and (iii) Wnt, altered tumors, which include CSDE1 and recurrent MAML3 fusion events (e.g., UBTF–MAML3) (Table 3). This molecular framework is clinically meaningful because genotype correlates with tumor location, biochemical phenotype, metastatic propensity, and preferred functional imaging/theranostic strategies [7,63,69–72].

Given this high heritable burden, multiple practice guidelines recommend that all patients with PPGL be considered for genetic testing, ideally supported by pre, and post-test genetic counselling in accredited settings. The Endocrine Society guideline explicitly recommends consideration of genetic testing in all PPGL patients and highlights genotype, directed priorities such as SDHx testing for paraganglioma and SDHB-assessment in metastatic disease. Similarly, the European Society of Endocrinology long, term follow-up guideline recommends that all PPGL patients be considered for genetic testing as part of standardized post, operative care [3,32].

In current clinical practice, phenotype, guided single-gene testing has largely been superseded by multigene panel testing (NGS), because it improves diagnostic yield, reduces time to result, and limits missed diagnoses in patients without obvious syndromic stigmata. Nevertheless, clinical variables remain useful for prioritizing interpretation and counselling, including age at onset, tumor site (adrenal vs extra, adrenal; head/neck vs thoracoabdominal), multifocality, metastatic presentation, and biochemical profile (adrenergic vs noradrenergic vs dopaminergic/3-methoxytyramine elevation). This pragmatic integration of phenotype with comprehensive genotyping is emphasized in recent genetics, focused syntheses and consensus, oriented reviews [73,74].

Tumor, based molecular profiling complements germline analysis, particularly in patients with negative germline panels or in advanced disease where prognostic refinement and therapeutic planning are needed. Large, scale genomic characterization has identified recurrent somatic drivers (e.g., HRAS, RET, EPAS1, NF1) and additional oncogenic events including MAML3 fusions that define biologically aggressive subsets. Importantly, several "second, hit/late" alterations, most notably telomerase activation (TERT, related alterations) and ATRX loss/mutation, are repeatedly associated with metastatic behavior and poorer outcomes, supporting their role as clinically relevant prognostic modifiers in appropriate contexts [7,75–78].

Special consideration is warranted in pediatric and adolescent PPGL, where heritability is markedly higher; international consensus work reports that a majority of childhood PPGL (often ~70–80%) are hereditary, reinforcing the need for early genetic evaluation and structured family, based surveillance. In all age groups, identification of a pathogenic variant should trigger cascade testing and tailored longitudinal screening for associated neoplasms (e.g., MEN2 features with RET; VHL spectrum; NF1 manifestations; SDHx, associated paraganglioma syndromes), implemented through multidisciplinary pathways that integrate endocrinology, genetics, oncology, nuclear medicine, and surgery [3,32,79].

In summary, because germline and somatic alterations together explain a substantial fraction of PPGL biology and directly affect prognosis and management, genetic counselling and comprehensive germline testing should be offered to every patient with PPGL, with tumor sequencing considered when germline testing is negative, when metastatic disease is present, or when additional prognostic/theranostic biomarkers (e.g., ATRX/TERT, MAML3 fusions) would change clinical decision, making.

Gene	Locus	Syndrome	Hormonal secretion profile	Risk of malignancy	Clinical features and associated tumors
RET	10q11.2	MEN2	Adrenergic	Low (1–5%)	Usually benign, frequently bilateral pheochromocytomas ; MEN2A: medullary thyroid carcinoma (~95%) and hyperparathyroidism (15–30%); MEN2B: marfanoid habitus, mucosal ganglioneuromas.
NF1	17q11.2	NF1	Adrenergic	~12%	Predominantly unilateral benignpheochromocytomas ; café-au-lait spots, neurofibromas, Lisch nodules, optic gliomas, axillary/inguinal freckling, skeletal dysplasia.
VHL	3p25.5	VHL	Noradrenergic	<5%	Often bilateral benign pheochromocytomas ; hemangioblastomas, retinal angiomas, RCC, pancreatic NETs.
SDHA	5p15	–	Unknown	0–14%	Pheochromocytomas and paragangliomas; Leigh syndrome in homozygotes.
SDHAF2	11q13.1	PGL2 (paternal)	Unknown	Unknown	Head and neck paragangliomas.
SDHB	1p36.13	PGL4	Noradrenergic / Dopaminergic	30–72%	Often malignant; GIST, RCC, breast cancer, papillary thyroid carcinoma, neuroblastoma.
SDHC	1q21	PGL3	Noradrenergic / Silent	<5%	Mostly benign head and neck paragangliomas.
SDHD	11q23	PGL1 (paternal)	Noradrenergic / Silent	<5%	Multiple head and neck paragangliomas.
MAX	14q23.3	–	Adrenergic / Noradrenergic	~25%	Frequently bilateral pheochromocytomas .
TMEM127	2q11.2	–	Adrenergic / Noradrenergic	Low (~1%)	Pheochromocytomas ; papillary thyroid carcinoma; breast cancer.
HIF2A	2p21	Pacak–Zhuang	Noradrenergic / Adrenergic	Unknown	Multiple pheochromocytomas / paragangliomas; polycythemia; somatostatinomas.

IDH	2q33.3	–	Unknown	Unknown	Carotid body paragangliomas; glioblastoma multiforme.
FH	1q43	–	Noradrenergic	Potentially high	Associated with leiomyomatosis and RCC.
KIF1Bβ	1p36.2	–	Unknown	Unknown	Neuroblastoma, ganglioneuroma, medulloblastoma, lung adenocarcinoma.
PHD2	1q42.1	–	Unknown	Unknown	Paragangliomas associated with erythrocytosis.
HRAS / KRAS	11p15 / 12p12	–	Adrenergic / Noradrenergic	Unknown	Pheochromocytomas and paragangliomas.
BAP1	3p21.1	–	Unknown	Unknown	Paragangliomas; meningioma; melanoma; mesothelioma.
ATRX	Xq21.1	–	Unknown	Unknown	Pheochromocytomas and paragangliomas.
PHD1	19q13.2	–	Unknown	Unknown	Paragangliomas associated with polycythemia.
MDH2	7q11.23	–	Noradrenergic	Unknown	Multiple metastatic paragangliomas.

Table3: Genotype–Phenotype correlations in pheochromocytomas and paragangliomas [62,66,68,80]

MEN2: Multiple Endocrine Neoplasia type 2; NF1: Neurofibromatosis type 1; VHL: von Hippel–Lindau syndrome; PGL: Paraganglioma syndrome; RCC: Renal cell carcinoma; NET: Neuroendocrine tumor; GIST: Gastrointestinal stromal tumor; HIF2A: Hypoxia-inducible factor 2 alpha (EPAS1); FH: Fumarate hydratase; IDH: Isocitrate dehydrogenase; PHD: Prolyl hydroxylase domain protein; MDH2: Malate dehydrogenase 2.

Hormonal secretion profile refers to the predominant catecholamine phenotype (adrenergic: epinephrine-predominant; noradrenergic: norepinephrine-predominant; dopaminergic: dopamine/3-methoxytyramine–associated).

Risk of malignancy reflects approximate lifetime metastatic risk based on available cohort data and may vary across studies.

Paternal transmission indicates parent-of-origin–dependent tumor development due to genomic imprinting (e.g., SDHD, SDHAF2).

Clinical features listed represent the most characteristic associated manifestations and should not be considered exhaustive.

Genetic Counseling

PPGL are characterized by an exceptionally high degree of heritability. Large contemporary cohorts demonstrate that approximately 30–40% of patients carry pathogenic germline variants in known PPGL susceptibility genes, a proportion that exceeds that of most other solid tumors. Clinical features such as early age at onset, multifocal or bilateral disease, recurrent tumors, metastatic presentation, and a positive family history substantially increase the likelihood of identifying a germline pathogenic variant [3,10].

In this context, genetic counseling is a critical and integral component of PPGL care and should be offered to all patients, regardless of apparent sporadic presentation. Counseling should include a structured discussion of the potential clinical implications of genetic testing, limitations of current assays, possible incidental findings, and the impact of results on long-term surveillance and family members. Multiple international guidelines now recommend consideration of genetic testing for every patient with PPGL, reflecting both the high prevalence of heritable disease and the direct influence of genotype on management and follow-up strategies [3,32].

When a pathogenic variant is detected in tumor tissue, confirmation of germline versus somatic origin is essential. This requires parallel testing of non-tumor DNA, typically obtained from peripheral blood or saliva. Distinguishing germline from somatic alterations is crucial for accurate risk assessment, family counseling, and cascade testing. Gene selection for testing should prioritize well-established PPGL

susceptibility genes, with particular emphasis on RET, SDHB, SDHD, VHL, and NF1, which together account for a substantial proportion of hereditary cases and have well-defined clinical and prognostic associations [7].

NGS-Based Genetic Testing and Diagnostic Approach

Germline Genetic Testing

NGS–based multigene panel testing has become the preferred first-line approach for germline evaluation in PPGL. Current clinical practice guidelines and expert consensus statements recommend germline testing in all patients with paraganglioma and in most patients with pheochromocytoma, given the reported germline mutation rate of ~35–40% [3,68]. Modern panels typically include SDHx genes (SDHA, SDHB, SDHC, SDHD, SDHAF2), VHL, RET, NF1, TMEM127, MAX, and other less frequent susceptibility genes, enabling comprehensive and time-efficient evaluation while minimizing missed diagnoses.

Somatic Genetic Analysis

Somatic genomic profiling using targeted NGS panels or whole-exome sequencing (WES) complements germline testing, particularly in patients with negative germline results, metastatic disease, or atypical presentations. Somatic analyses can identify actionable alterations, including EPAS1 (HIF2A) mutations, HRAS alterations, MAML3 fusion events, and secondary prognostic markers such as ATRX loss or TERT-related changes, which may inform risk stratification and therapeutic decision-making [7,10].

Molecular Biomarkers and Emerging Approaches

Beyond DNA-based testing, transcriptomic profiling and DNA methylation analyses are increasingly recognized as valuable adjuncts for PPGL classification. These approaches have demonstrated the ability to distinguish biologically distinct molecular clusters and may improve prognostic assessment by identifying aggressive tumor subtypes that are not fully captured by conventional histopathology or single-gene testing. Although not yet part of routine clinical practice, such molecular biomarkers are expected to play an expanding role in integrated diagnostic algorithms and precision medicine strategies for PPGL in the near future [7,68].

Treatment

The management of PPGL is fundamentally multidisciplinary, with surgical resection remaining the cornerstone of curative therapy for localized disease. "When feasible, complete tumor excision, including total adrenalectomy for adrenal pheochromocytoma, provides excellent long-term biochemical control and survival outcomes [3].

Surgical Strategies and Adrenal Preservation

In recent years, partial (cortical-sparing) adrenalectomy has emerged as a validated alternative to total adrenalectomy in carefully selected patients, particularly those with bilateral, multifocal, or hereditary PPGL syndromes. The principal rationale is to preserve endogenous adrenal cortical function and to avoid lifelong glucocorticoid and mineralocorticoid replacement. Chronic adrenal insufficiency is associated with substantial long-term morbidity, including hypertension, diabetes mellitus, osteoporosis, weight gain, and impaired quality of life [81,82].

"Evidence from hereditary cohorts, especially VHL, MEN2 (RET), and NF1, indicates that the risk of malignancy is relatively low, and that cortical-sparing surgery can achieve excellent functional outcomes with acceptable oncologic control, particularly when tumors are small and confined. In patients with a solitary adrenal gland or bilateral disease, preservation of sufficient adrenal cortex is often achievable when the dominant tumor is <4 cm, allowing maintenance of steroid independence in a large proportion of cases [82–86]. Minimally invasive approaches, including laparoscopic and robotic partial adrenalectomy, are now widely recommended, as they reduce perioperative morbidity while providing equivalent oncologic efficacy compared with open surgery in experienced centers.

Observation in Selected Hereditary Cases

In highly selected scenarios, most notably asymptomatic, small pheochromocytomas in VHL patients, active surveillance has been proposed as a reasonable option. Several longitudinal studies have shown that careful observation with biochemical and imaging follow-up may delay or avoid surgery without compromising oncologic outcomes, provided that tumors remain non-secretory or minimally secretory and demonstrate slow growth [87]. This strategy underscores the importance of individualized risk assessment rather than uniform surgical intervention.

Role of Genetic Information in Surgical Decision-Making

In patients without a prior diagnosis of a hereditary syndrome, identification of a germline mutation may directly influence surgical planning. This is particularly true for young individuals or those with bilateral or multifocal disease, where it can guide the choice between total and partial adrenalectomy. Conversely, detection of SDHB pathogenic variants, which are strongly associated with higher metastatic potential, generally favors a more aggressive surgical approach, including total adrenalectomy and intensified postoperative surveillance, given the increased risk of malignant behavior [7,10].

Advanced and Non-Surgical Therapies

For patients with unresectable, recurrent, or metastatic PPGL, treatment extends beyond surgery and may include radionuclide therapy, systemic agents, or targeted treatments guided by functional imaging and genotype. Although these modalities are discussed in detail elsewhere, their integration further highlights the necessity of genotype- and phenotype-driven therapeutic strategies within contemporary PPGL management.

Genotype, Guided Therapeutic Approach

Genetic stratification has moved from being purely diagnostic to directly shaping treatment selection in PPGL, particularly for (i) extent and timing of surgery, (ii) choice of functional imaging and theranostics, and (iii) selection of systemic therapies in unresectable/metastatic disease. This approach is

supported by integrated molecular frameworks (pseudohypoxia vs kinase-signaling vs Wnt, altered) and by clinical practice guidance that increasingly emphasizes genotype-informed multidisciplinary decision-making [3,13,79].

Management of SDHB Mutant (and selected SDHx) Tumors

Pathogenic SDHB variants are consistently associated with a high risk of metastatic disease and warrant earlier and more intensive staging, closer surveillance, and a lower threshold for systemic/theranostic escalation. Multiple expert syntheses and guideline documents highlight SDHB as a major determinant of aggressive clinical behavior, informing follow-up frequency and imaging strategy [3,13,88].

Theranostic selection should be individualized based on tumor biology and tracer avidity. In metastatic/unresectable PPGL, radionuclide options include high, specific, activity ^131I, MIBG for MIBG, avid disease and ^177Lu, DOTATATE PRRT for somatostatin receptor (SSTR)–positive tumors; the clinical logic is that genotype (often SDHx) correlates with functional imaging patterns and therefore can indirectly guide the most suitable radiopharmaceutical pathway [88,89].

For systemic therapy, temozolomide-based regimens have repeatedly been reported as clinically active in metastatic PPGL and appear to show higher response likelihood in SDHB/SDHx mutant tumors in retrospective series and contemporary reviews; mechanistically, MGMT-related biology has been proposed as a contributor to temozolomide sensitivity, though this remains imperfectly standardized for routine practice [88,90,91].

RET Mutant / MEN2-Associated Pheochromocytomas

In MEN2/RET-associated pheochromocytoma, the most actionable genotype, guided decisions are typically surgical and perioperative, rather than a proven RET-targeted systemic drug strategy for PPGL itself. MEN2 tumors are often adrenal, may be bilateral or metachronous, and therefore genotype status informs adrenal-preserving strategies (e.g., cortical, sparing adrenalectomy when appropriate) to reduce lifelong adrenal insufficiency while maintaining oncologic safety within individualized risk frameworks [3,13,92].

While RET, directed multi-kinase inhibitors (e.g., vandetanib, cabozantinib) are established in medullary thyroid carcinoma, evidence for genotype, specific efficacy in PPGL is limited; instead, targeted agents such as sunitinib or cabozantinib have been explored in metastatic PPGL in broader (non-RET-restricted) settings and are generally considered in selected progressive cases, preferably within trials, rather than as a routine RET, driven standard of care for PPGL [13,93].

VHL-Mutant Disease and Hypoxia Pathway Targeting (belzutifan)

VHL-associated PPGL is frequently early-onset and may be multifocal, which reinforces the importance of genotype-guided planning (surveillance, timing of intervention, and organ, sparing strategies when feasible) [3,13].

A major recent advance is direct pathway targeting of pseudohypoxia signaling: the HIF-2α inhibitor belzutifan received FDA approval (May 14, 2025) for adults and pediatric patients ≥12 years with locally advanced, unresectable, or metastatic PPGL, establishing the first FDA-approved oral systemic therapy specifically indicated for advanced PPGL. This approval provides a clear genotype-anchored therapeutic rationale rooted in pseudohypoxia biology, particularly within the VHL/HIF signaling axis. Nevertheless, patient selection should be guided by regulatory indications, disease status, and multidisciplinary assessment [94,95].

Wnt/β-catenin–altered subsets (MAML3 fusions and related events)

A minority of PPGLs fall into Wnt-altered molecular categories, including tumors characterized by MAML3 fusion events and other Wnt-pathway dysregulation. These tumors have been associated with more aggressive clinical behavior in molecular profiling studies, but validated Wnt, targeted therapies are not yet established for routine PPGL care; therefore, the most actionable genotype-informed recommendation is tight oncologic follow, up and enrollment in clinical trials whenever feasible, particularly for progressive or metastatic disease [13,88].

CONCLUSIONS AND RECOMMENDATIONS

Recent advances in molecular genetics, biochemistry, and functional imaging have fundamentally reshaped the understanding and clinical management of pheochromocytoma and paraganglioma (PPGL). Collectively, contemporary data indicate that PPGLs are no longer best viewed as a single disease entity, but rather as a spectrum of biologically and genetically defined tumors with distinct developmental pathways, clinical behaviors, and therapeutic vulnerabilities. Integrated analyses demonstrate that germline pathogenic variants are present in approximately 30–40% of patients, with an additional 30–40% harboring relevant somatic driver alterations, underscoring the central role of genetic dysregulation in PPGL pathogenesis.

From a clinical perspective, the convergence of tumor location, catecholamine secretion pattern, metastatic propensity, and molecular genotype provides a framework for individualized care that extends beyond traditional symptom-based paradigms. Accumulating evidence supports a genotype-informed approach in which diagnostic algorithms, surveillance strategies, and therapeutic decisions are adapted to molecular risk categories rather than applied uniformly across all patients. This is particularly relevant for pseudohypoxia-driven tumors (e.g., SDHx and VHL-related disease), which display higher rates of multifocality and metastasis and therefore require intensified follow-up and earlier consideration of advanced imaging and systemic therapies.

Importantly, genetic testing has emerged as a cornerstone of PPGL management, not only for affected individuals but also for at-risk relatives. Identification of a pathogenic germline variant enables tailored long-term surveillance, informs surgical planning (including organ-sparing approaches in selected genotypes), and facilitates cascade testing for early detection in family members. Given the substantial heritable burden and the limitations of phenotype-only risk stratification, routine incorporation of comprehensive multigene testing with

appropriate genetic counseling should be considered standard of care for all PPGL patients, regardless of age, tumor location, or apparent sporadic presentation. Therapeutically, the field is transitioning toward precision-oriented management, in which genotype and functional phenotype guide the selection of radionuclide therapies, systemic agents, and emerging targeted treatments. The recent availability of pathway-directed therapies for advanced disease exemplifies how mechanistic insights into PPGL biology can be translated into clinically meaningful options for patients with previously limited treatments. Nevertheless, many genotype–therapy associations remain incompletely defined, highlighting the need for prospective trials that stratify patients by molecular subgroup and incorporate standardized outcome measures.

Looking forward, several priorities should guide future research and clinical practice. First, refinement of genotype–phenotype correlations through large, international, harmonized cohorts will be essential to improve prognostic accuracy and personalize follow, up intensity. Second, integration of tumor-based molecular profiling with germline testing may uncover additional biomarkers of progression, treatment response, and malignant transformation. Finally, embedding genetic and molecular data into routine clinical workflows, supported by multidisciplinary expertise, will be critical to realizing the full potential of precision medicine in PPGL.

In conclusion, PPGL exemplifies a tumor group in which genetics, biology, and clinical care are inseparably linked. A comprehensive, genetics-centered strategy, encompassing diagnosis, treatment, and lifelong surveillance, offers the most rational path toward improving outcomes, reducing preventable morbidity, and enabling truly personalized management for patients and their families.

DECLARATIONS

Ethics approval and consent to participate

Not applicable, as this study did not involve human participants, animals, or identifiable personal data.

CONSENT FOR PUBLICATION

Not applicable, this manuscript does not contain any individual person's data in any form.

AVAILABILITY OF DATA AND MATERIALS

Not applicable, this review did not generate new datasets. All sources cited are publicly available in the referenced literature.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

B.K.G. and H.CH. carried out Investigation, served as the senior author, data collection, and preparation of tables and figures, and contributed to conceptualization, writing original draft.

Ş.B.T. contributed to study design, validation, data interpretation, overall supervision, and writing review & editing.

All authors reviewed the manuscript critically, provided feedback, and approved the final submitted version.

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