Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline

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Objective: The aim was to formulate clinical practice guidelines for pheochromocytoma and paraganglioma (PPGL).

Participants: The Task Force included a chair selected by the Endocrine Society Clinical Guidelines Subcommittee (CGS), seven experts in the field, and a methodologist. The authors received no corporate funding or remuneration.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence. The Task Force reviewed primary evidence and commissioned two additional systematic reviews.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, European Society of Endocrinology, and Americal Association for Clinical Chemistry reviewed drafts of the guidelines.

Conclusions: The Task Force recommends that initial biochemical testing for PPGLs should include measurements of plasma free or urinary fractionated metanephrines. Consideration should be given to preanalytical factors leading to false-positive or false-negative results. All positive results require follow-up. Computed tomography is suggested for initial imaging, but magnetic resonance is a better option in patients with metastatic disease or when radiation exposure must be limited. ^{123}I-metaiodobenzylguanidine scintigraphy is a useful imaging modality for metastatic PPGLs. We recommend consideration of genetic testing in all patients, with testing by accredited laboratories. Patients with paraganglioma should be tested for *SDHx* mutations, and those with metastatic disease for *SDHB* mutations. All patients with functional PPGLs should undergo preoperative blockade to prevent perioperative complications. Preparation should include a high-sodium diet and fluid intake to prevent postoperative hypotension. We recommend minimally invasive adrenalectomy for most pheochromocytomas with open resection for most paragangliomas. Partial adrenalectomy is an option for selected patients. Lifelong follow-up is suggested to detect recurrent or metastatic disease. We suggest personalized management with evaluation and treatment by multidisciplinary teams with appropriate expertise to ensure favorable outcomes. (*J Clin Endocrinol Metab* 99: 1915–1942, 2014)

Abbreviations: CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FDOPA, ^{18}F-fluorodihydroxy-phenylalanine; LC-ECD, liquid chromatography with electrochemical detection; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MEN2, multiple endocrine neoplasia type 2; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; PET, positron emission tomography; PPGL, pheochromocytoma and paraganglioma; ROC, receiver operating characteristic; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau; VMA, vanillylmandelic acid; VUS, variant of unknown significance.

SUMMARY OF RECOMMENDATIONS

1.0 Biochemical Testing for Diagnosis of Pheochromocytoma and Paraganglioma (PPGL)

1.1 We recommend that initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractionated metanephrines. (1|⊕⊕⊕⊕)

1.2 We suggest using liquid chromatography with mass spectrometric or electrochemical detection methods rather than other laboratory methods to establish a biochemical diagnosis of PPGL. (2|⊕⊕○○)

1.3 For measurements of plasma metanephrines, we suggest drawing blood with the patient in the supine position and use of reference intervals established in the same position. (2|⊕⊕○○)

1.4 We recommend that all patients with positive test results should receive appropriate follow-up according to the extent of increased values and clinical presentation. (1|⊕⊕○○)

2.0 Imaging Studies

2.1 We recommend that imaging studies to locate PPGL should be initiated once there is clear biochemical evidence of a PPGL. (1|⊕⊕○○)

2.2 We suggest computed tomography (CT) rather than magnetic resonance imaging (MRI) as the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis. (2|⊕⊕⊕○)

2.3 We recommend MRI in patients with metastatic PPGL, for detection of skull base and neck paragangliomas, 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, patients with known germline mutations, and those with recent excessive radiation exposure). (1|⊕⊕⊕○)

2.4 We suggest the use of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy as a functional imaging modality in patients with metastatic PPGL detected by other imaging modalities when radiotherapy using ^{131}I-MIBG is planned, and occasionally in some patients with an increased risk for metastatic disease due to large size of the primary tumor or to extra-adrenal, multifocal (except skull base and neck PPGLs), or recurrent disease. (2|⊕○○○)

2.5 We suggest the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT scanning in patients with metastatic disease. ^{18}F-FDG PET/CT is the preferred imaging modality over ^{123}I-MIBG scintigraphy in patients with known metastatic PPGL. (2|⊕⊕⊕○)

3.0 Genetic Testing

3.1 We recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing. (1|⊕⊕⊕○)

3.2 We recommend the use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations. (1|⊕⊕⊕○)

3.3 We suggest that patients with paraganglioma undergo testing of succinate dehydrogenase (SDH) mutations and that patients with metastatic disease undergo testing for *SDHB* mutations. (2|⊕⊕⊕○)

3.4 We recommend that genetic testing for PPGL be delivered within the framework of health care. Specifically, pretest and post-test counseling should be available. All tests for PPGL genetic testing should be performed by accredited laboratories. (Ungraded recommendation)

4.0 Perioperative Medical Management

4.1 We recommend that all patients with a hormonally functional PPGL should undergo preoperative blockade to prevent perioperative cardiovascular complications. (1/⊕⊕○○) We suggest α-adrenergic receptor blockers as the first choice. (2|⊕⊕○○)

4.2 We recommend preoperative medical treatment for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate. Treatment should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction preoperatively to prevent severe hypotension after tumor removal. (1|⊕⊕○○)

4.3 We recommend monitoring blood pressure, heart rate, and blood glucose levels with adjustment of associated therapies in the immediate postoperative period. (1|⊕⊕○○)

4.4 We suggest measuring plasma or urine levels of metanephrines on follow-up to diagnose persistent disease. We suggest lifelong annual biochemical testing to assess for recurrent or metastatic disease. (2|⊕⊕○○)

5.0 Surgery

5.1 We recommend minimally invasive adrenalectomy (eg, laparoscopic) for most adrenal pheochromocytomas. (1|⊕⊕○○) We recommend open resection for large (eg, >6 cm) or invasive pheochromocytomas to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence. (1|⊕○○○) We suggest open resection for paragangliomas, but laparoscopic resection can be performed for small, noninvasive paragangliomas in surgically favorable locations. (2|⊕○○○)

5.2 We suggest partial adrenalectomy for selected patients, such as those with hereditary pheochromocytoma, with small tumors who have already undergone a contralateral complete adrenalectomy to spare adrenal cortex to prevent permanent hypocortisolism. (2|⊕○○○)

6.0 Personalized Management

6.1 In recognition of the distinct genotype-phenotype presentations of hereditary PPGLs, we recommend a personalized approach to patient management (ie, biochemical testing, imaging, surgery, and follow-up). (Ungraded recommendation)

6.2 We recommend that patients with PPGLs should be evaluated and treated by multidisciplinary teams at centers with appropriate expertise to ensure favorable outcome. In particular, patients should be referred to such centers should there be pregnancy, metastatic disease, or issues concerning the complexity or difficulty in biochemical diagnosis; localization; performance and interpretation of genetic testing; preoperative preparation; surgical treatment; and follow-up. (Ungraded recommendation)

METHOD OF DEVELOPMENT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis of pheochromocytoma and paraganglioma a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphic descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number **1**, and weak recommendations use the phrase "we suggest" and the number **2**. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more

careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks,* a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Definition, Prevalence, and Clinical Significance of Pheochromocytoma and Paraganglioma

Definition of pheochromocytoma and paraganglioma (PPGL)

A *pheochromocytoma* is a tumor arising from adrenomedullary chromaffin cells that commonly produces one

Table 1. Clinical Settings for Testing for PPGL

Signs and symbols of PPGL, in particular if paroxysmal
PPGL symptoms provoked by use of medications associated
  with adverse effects (see Table 2)
Adrenal incidentaloma, with or without hypertension
Hereditary predisposition or syndromic features suggesting
  hereditary PPGL
Previous history of PPGL

or more catecholamines: epinephrine, norepinephrine, and dopamine. Rarely, these tumors are biochemically silent. A *paraganglioma* is a tumor derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. Paragangliomas also arise from parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and at the base of the skull (3); these do not produce catecholamines. These last paraganglioma in the neck and at the base of the skull receive minimal coverage in this guideline. About 80 to 85% of chromaffin-cell tumors are pheochromocytomas, whereas 15 to 20% are paragangliomas (4). Together they will be referred to here as PPGL.

The prevalence of PPGL

The prevalence of PPGL in patients with hypertension in general outpatient clinics varies between 0.2 and 0.6% (5–8). Diagnosis of PPGL may be missed during life; autopsy studies demonstrate undiagnosed tumors in 0.05–0.1% of patients (9–11). In children with hypertension, the prevalence of PPGL is approximately 1.7% (12). Nearly 5% of patients with incidentally discovered adrenal masses on anatomical imaging prove to have a pheochromocytoma (13, 14).

At least one-third of all patients with PPGLs have disease-causing germline mutations (inherited mutations present in all cells of the body). The prevalence of PPGL in individuals carrying a germline mutation in PPGL susceptibility genes may be around 50%. Patients with hereditary PPGLs typically present with multifocal disease and at a younger age than those with sporadic neoplasms (15, 16).

The clinical importance of PPGL

It is important to suspect, confirm, localize, treat, and resect these tumors for several reasons. Most of these tumors hypersecrete catecholamines, and if untreated, cardiovascular morbidity and mortality are high (17–21). Also, PPGLs enlarge with time and may cause mass-effect symptoms by encroaching upon or extending into adjacent tissues and organs.

Another reason to encourage case detection is that, for familial disease, detection of a tumor in the proband may result in earlier diagnosis and treatment in other family members. Finally, some PPGLs have malignant potential. Malignancy is defined as the presence of metastases in nonchromaffin tissue; the prevalence varies between 10 and 17% (22). Mutations in the gene encoding SDH subunit B (*SDHB*) can lead to metastatic disease in 40% or more of the patients (23, 24).

Reasons to suspect PPGL

The most important step for diagnosis of PPGL is to first recognize the possibility of the tumor. As reviewed in detail elsewhere (4, 7, 25, 26), it is key to recognize the signs and symptoms and other manifestations or clinical

Table 2. Medications That Are Implicated in Adverse Reactions in Patients with Pheochromocytoma and That Can Precipitate a Crisis

Class of Drugs	Examples
Dopamine D2 receptor antagonists (including some antiemetic agents and antipsychotics)	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol
β-Adrenergic receptor blockers[a]	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, pseudoephedrine, fenfluramine, methylphenidate, phentermine, dexamfetamine
Opioid analgesics	Morphine, pethidine, tramadol
Norepinephrine reuptake inhibitors (including tricyclic antidepressants)	Amitriptyline, imipramine,
Serotonin reuptake inhibitors (rarely reported)	Paroxetine, fluoxetine
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids	Dexamethasone, prednisone, hydrocortisone, betamethasone
Peptides	ACTH, glucagon
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

[a] Although most case reports on β-adrenergic receptor blockers pertain to nonselective blockers, selective β_1-blockers may also precipitate a crisis because at higher doses they may lose β_1-selectivity.

settings that might signal a need for biochemical testing for PPGL (Tables 1 and 2). Biochemical testing is also warranted in syndromic forms of PPGL, which may be indicated by specific clinical stigmata (Table 3).

1.0 Biochemical Testing for Diagnosis of Pheochromocytoma and Paraganglioma

Available tests and test performance

Recommendation

1.1 We recommend that initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractionated metanephrines. (1⊕⊕⊕⊕)

1.1 Evidence

There is compelling evidence that measurements of plasma free or urinary fractionated metanephrines are superior to other tests of catecholamine excess for diagnosis of PPGLs; the theoretical basis for this is provided by improved understanding of catecholamine metabolism (27–29). According to this understanding, the free metanephrines are produced within adrenal chromaffin cells (or the tumors derived from these cells) by membrane-bound catecholamine O-methyltransferase. Lack of this enzyme in sympathetic nerves, the major site of initial norepinephrine metabolism, means that the O-methylated metabolites are relatively specific markers of chromaffin tumors. Most importantly, these metabolites are produced continuously within tumors by a process that is independent of exocytotic catecholamine release, which for some tumors occurs at low rates or is episodic in nature.

The superior sensitivity of urine metanephrines over catecholamines and vanillylmandelic acid (VMA) for diagnosis of PPGLs was first suggested from a meta-analysis by Manu and Runge (30). This analysis was followed by

reports revealing false-negative results for measurements of urine catecholamines and VMA and improved accuracy with measurements of urinary metanephrines (31–36).

Initial evidence that measurements of plasma free metanephrines provide advantages for diagnosis of PPGLs over other tests was first outlined by Lenders et al (37). Diagnostic specificity was equivalent to other tests, but diagnostic sensitivity was superior. A second National Institutes of Health (NIH) study involving patients screened for hereditary PPGLs established excellent sensitivity of 97%, well in excess of the 47 to 74% for other tests (38). The final NIH report, with cumulative experience in over 800 patients, established that the superiority of plasma metanephrines for the diagnosis remained significant, even when compared with combinations of other tests (39).

The high diagnostic accuracy of measurements of plasma free metanephrines has now been confirmed by 15 independent studies (39–53) (Table 4).

Areas under receiver operating characteristic (ROC) curves reported in nine of these studies ranged from 0.965 to 1. Among studies involving comparisons with other biochemical tests, all except two indicated both improved sensitivity and specificity for plasma metanephrines than for plasma (n = 4) and urine (n = 7) catecholamines or VMA (n = 1). These exceptions included one study in which the combination of urinary catecholamines and total metanephrines (normetanephrine and metanephrine measured in combined form by spectrophotometry) was assessed by areas under ROC curves to offer similar diagnostic accuracy to measurements of plasma metanephrines (41).

Five of the 15 studies involved comparisons of plasma free with urine fractionated metanephrines (39, 42, 46, 48, 53). The results suggest higher specificity of the plasma than the urine test (Table 5); however, all five studies had

Table 3.   Clinical Findings Associated with Syndromic PPGL

Multiple endocrine neoplasia type 2A	Medullary thyroid cancer, primary hyperparathyroidism, and cutaneous lichen amyloidosis
Multiple endocrine neoplasia type 2B	Medullary thyroid cancer, mucocutaneous neuromas, skeletal deformities (eg, kyphoscoliosis or lordosis), joint laxity, myelinated corneal nerves, and intestinal ganglioneuromas (Hirschsprung disease)
von Hippel-Lindau syndrome	Hemangioblastoma (involving the cerebellum, spinal cord, or brainstem), retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumors and serous cystadenomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament
Neurofibromatosis type 1	Neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, central nervous system gliomas, macrocephaly, and cognitive deficits

Table 4. Summary Characteristics of 15 Diagnostic Studies Involving Measurements of Plasma Free Normetanephrine and Metanephrine for Diagnosis of PPGL

First Author, Year (Ref.)	Analytical Method	Sampling Position	URL NMN, nmol/L	URL MN, nmol/L	Diagnostic Sensitivity	Diagnostic Specificity	Area Under ROC Curve	Analytical Test Comparisons
Raber, 2000 (40)	LC-ECD	Supine	0.66	0.30	100% (17/17)	100% (14/14)	nd	UC
Lenders, 2002 (39)	LC-ECD	Supine	0.61	0.31	99% (211/214)	89% (575/644)	0.985	UFM, UTM, UC, UV, PC
Sawka, 2003 (41)	LC-ECD	Seated	0.90	0.50	97% (30/31)	85% (221/261)	0.965	UTM, UC
Unger, 2006 (42)	RIA	Seated	0.69[a]	0.19[a]	96% (23/24)	79% (54/68)	nd	UFM, UC, PC
Giovanella, 2006 (43)	LC-ECD	Not stated	0.50	Sum NMN & MN	95% (42/44)	94% (140/148)	nd	CgA
Vaclavik, 2007 (44)	LC-ECD	Supine	0.61	0.31	100% (25/25)	96.7% (1194/1235)	nd	None
Gao, 2008 (45)	EIA	Supine	0.73	0.47	97% (29/30)	86% (44/51)	0.965	None
Hickman, 2009 (46)	LC-ECD	Not stated	0.90	0.60	100% (22/22)	98% (40/41)	0.993	UFM, UC, UV, PC
Procopiou, 2009 (47)	EIA	Not stated	1.09	0.46	91% (20/22)	100% (156/156)	0.987	UC
Grouzmann, 2010 (48)	LC-ECD	Supine	1.39	0.85	96% (44/46)	89% (102/114)	0.993	UFM, PC
Peaston, 2010 (49)	LC-MS/MS	Seated	1.18	0.51	100% (38/38)	96% (108/113)	1.000	PM by EIA
Mullins, 2011 (50)	EIA	Seated	0.98	0.46	100% (13/13)	88% (51/60)	0.969	PM by LC-MS/MS
Sarathi, 2011 (51)	EIA	Seated	0.98	0.46	94% (32/34)	94% (62/66)	nd	None
Christensen, 2011 (52)	EIA	Seated	1.09	0.46	91% (10/11)	99% (172/174)	0.970	UC
Unger, 2012 (53)	EIA	Seated	0.91[a]	0.13[a]	90% (17/19)	90% (54/60)	nd	UFM, CgA

Abbreviations: CgA, chromogranin A; EIA, enzyme immunoassay; MN, plasma free metanephrine; nd, no data; NMN, plasma free normetanephrine; PC, plasma catecholamines; PM, plasma metanephrines; RIA, radioimmunoassay; UC, urine catecholamines; UFM, urine fractionated metanephrines; URL, upper reference limit; UTM, urine total metanephrines; UV, urine VMA.

[a] URL determined from ROC curves, package inserts of EIA kits.

limitations, and none involved head-to-head comparisons of mass spectrometric-based measurements.

As shown by Perry et al (54), measurements of urine fractionated metanephrines by mass spectrometry provide excellent sensitivity (97%) and specificity (91%) for diagnosis of PPGLs, with an area under the ROC curve of 0.991 in par with measurements of plasma metanephrines determined by other studies (Table 4). Thus, until there are data available directly comparing plasma and urinary measurements by "gold standard" mass spectrometric methods, there can be no recommendation that one test is superior to the other. This includes measurements of urinary free fractionated metanephrines as an alternative test (55–57). Thus, all measurements of fractionated metanephrines remain recommended as initial screening tests.

1.1 Values and preferences

The committee recognizes the importance of high diagnostic sensitivity as a primary consideration to avoid missed diagnoses of potentially lethal tumors and the need to minimize additional testing (eg, imaging) when initial test results are negative. Our recommendation that initial testing should always include measurements of plasma free or urinary fractionated metanephrines does not exclude the use of additional biochemical tests during initial testing. Despite the convenience of a spot urine sample, there is no evidence to suggest that this should replace the standardized 24-hour urine collection method.

1.1 Remarks

When measuring the 24-hour urinary excretion of fractionated metanephrines, urinary creatinine should be measured to verify completeness of the urine collection.

Measurement methods

Recommendation

1.2 We suggest using liquid chromatography with mass spectrometric or electrochemical detection methods rather than other laboratory methods to establish a biochemical diagnosis of PPGL. (2|⊕⊕○○)

1.2 Evidence

Fractionated metanephrines may be measured by liquid chromatography with electrochemical or fluorometric de-

Table 5. Comparison of Diagnostic Performance of Plasma Free Versus Urinary Fractionated Metanephrines from 5 Available Studies

First Author, Year (Ref.)	Sensitivity		Specificity	
	Plasma	Urine	Plasma	Urine
Lenders, 2002 (39)	98.6% (211/214)	97.1% (102/105)	89.3% (575/644)	68.6% (310/452)
Unger, 2006 (42)	95.8% (23/24)	93.3% (14/15)	79.4% (54/68)	75.0% (39/52)
Hickman, 2009 (46)[a]	100.0% (14/14)	85.7% (12/14)	97.6% (40/41)	95.1% (39/41)
Grouzmann, 2010 (48)	95.7% (44/46)	95.0% (38/40)	89.5% (102/114)	86.4% (121/140)
Unger, 2012 (53)	89.5% (17/19)	92.9% (13/14)	90.0% (54/60)	77.6% (38/49)

[a] Data restricted to that available from Table 4 of those studies where all measurements were made.

tection (LC-ECD), liquid chromatography with tandem mass spectrometry (LC-MS/MS), or immunoassay methods. Accumulating evidence indicates that the diagnostic performance of these methods varies to an extent that this should be considered in the choice of diagnostic tests. This evidence includes comparisons of the results of the eight studies to date employing LC-ECD or LC-MS/MS with the seven other studies employing immunoassays (Table 4). These data reveal lower diagnostic sensitivity of the latter than the former measurement methods.

Other evidence includes results of interlaboratory quality assurance programs establishing that immunoassays not only suffer from imprecision compared with LC-ECD and LC-MS/MS, but also substantially underestimate plasma concentrations of metanephrine and normetanephrine (58, 59). Poorer diagnostic performance of immunoassay than LC-MS/MS measurements has been further indicated by two other studies (49, 50). The first confirmed the lower measured values of plasma normetanephrine by immunoassay than by LC-MS/MS and highlighted in two patients with pheochromocytoma repeatedly false-negative measurements by immunoassay compared with elevated levels by LC-MS/MS (49).

1.2 Values and preferences

The committee recognizes that the availability of different measurement methods varies regionally. Therefore, our recommendation that the choice of biochemical test for diagnosis of PPGL should take into account the method of measurement pertains mainly to locations where there is a choice in available methods. Where choice is limited, consideration should be given to upgrading to more accurate and precise measurement methods or referring patients or specimens to specialist centers where such methods are available.

Preanalytical sampling conditions and reference intervals

Recommendation

1.3 For measurements of plasma metanephrines, we suggest drawing blood with the patient in the supine position and use of reference intervals established in the same position. (2|⊕⊕○○)

1.3 Evidence

Measurements of plasma metanephrines for diagnosis of PPGLs were established using blood samples collected in the supine position; this recognizes the rapid circulatory clearances of the metabolites, the strong influence of sympathetic activation and upright posture to stimulate release of norepinephrine and metabolism to normetanephrine, and likely the lack of response in patients with PPGLs (37–39, 60, 61). Lack of response of plasma normetanephrine to upright posture in patients with PPGLs was confirmed by Raber et al (40), but was misinterpreted to support sampling without consideration of postural or other influences on sympathetic outflow and plasma normetanephrine (62, 63).

Recognizing the problem of seated sampling, Lenders et al (64) took blood samples from 60 patients with primary hypertension in the seated position and after 30 minutes of supine rest, at which stage consistent decreases in plasma normetanephrine were noted. Using data from a further 872 patients tested for PPGLs, it was calculated that drawing blood in the seated position would result in a 2.8-fold increase in false-positive results.

Higher concentrations of plasma metanephrines in upright positions of blood sampling than in supine positions have been confirmed in other studies (65, 66), explaining why upper cutoffs of reference intervals determined from blood collected in the seated position (48, 62, 63, 67) are up to 2-fold higher than those determined in the supine position (38). Thus, in the study by Lenders et al (64), it was estimated that the use of upper limits of reference intervals determined from samples collected in the seated instead of the supine position would result in a drop in diagnostic sensitivity associated with a 3-fold increase in false-negative results. Because patients with PPGLs do not show significant posture-associated increases in metanephrines (40), the associated danger of missing the diagnosis with seated reference intervals applies equally to patients sampled in both supine and seated positions.

The potential for misdiagnoses associated with seated rather than supine sampling is evident from examination of data available from five and seven respective studies involving supine and seated sampling (Table 4), in which seated sampling is associated with reduced diagnostic accuracy. It is therefore suggested that for diagnosis of PPGLs, blood should be preferably taken with the patient in the supine position; when blood taken in the seated position yields a positive result, the test should be repeated in the supine position. Furthermore, for interpretation of results, reference intervals should be utilized that do not compromise diagnostic sensitivity. Age adjustments for upper cutoffs to both maintain diagnostic sensitivity and minimize false-positives associated with higher plasma concentrations of normetanephrine in older patients provide one approach (68).

1.3 Values and preferences

The committee recognizes that at most clinical centers, phlebotomists routinely sample blood with patients in the

seated position. Sampling in the supine position takes extra time and effort and entails additional cost. Thus, blood may be taken in the seated position, but with recognition that this entails an increased likelihood of false-positive results and a need for follow-up with sampling in the supine position. In situations where this requirement cannot be followed, measurements of urinary fractionated metanephrines provide a useful alternative, or patients may be referred to specialist centers experienced with recommended procedures.

The committee also recognizes that reference intervals for plasma free metanephrines are often reported from blood samples taken from seated subjects or according to the package inserts of commercial kits (Table 4). For both situations, clinicians should be aware of the increased likelihood of false-negative results.

1.3 Remarks

For drawing blood in the supine position for measurement of plasma metanephrines, patients should be fully recumbent for at least 30 minutes before sampling.

Interpretation of test results and follow-up

Recommendation

1.4 We recommend that all patients with positive test results should receive appropriate follow-up according to the extent of increased values and clinical presentation. (1|⊕⊕○○)

1.4 Evidence

Although the high diagnostic sensitivity of plasma free or urine fractionated metanephrines means that almost all cases of symptomatic catecholamine-producing tumors can be detected by positive results, this does not imply that all positive results indicate the presence of a tumor. The usually less than 1% pretest prevalence of PPGLs combined with suboptimal diagnostic specificity means that false-positive results far outnumber true-positive results. As reported in a retrospective analysis of laboratory results from 1896 patients by Yu and Wei (69), false-positive results are common, with a rate of 19–21% for both plasma free and urine fractionated metanephrines. However, in an audit of patients with positive test results, it was shown that only 28% of patients received appropriate follow-up (70).

More than 75% of all PPGLs can be easily recognized from the extent and nature of increased results (39, 71). For example, elevations of both normetanephrine and metanephrine are rare as false-positives but occur in at least half of all patients with adrenal pheochromocytomas. Such findings should therefore be treated with a high level of suspicion. Similarly, findings of solitary increases in either normetanephrine or metanephrine elevated 3-fold or more above upper cutoffs are also rare as false-positives and should be followed up in most cases by imaging to locate the tumors.

The larger problem for interpreting positive test results concerns those that are borderline, which involves a quarter of all patients with PPGLs, hidden among a much larger proportion of patients without tumors and similarly elevated test results. In most situations this is due to inappropriate sampling and is easily dealt with by repeat sampling in the supine position. If results remain elevated, the clonidine suppression test with measurements of plasma normetanephrine provides one method to distinguish true-positive from false-positive borderline elevations of that metabolite (71, 72). This test has a purported diagnostic specificity of 100% with a sensitivity of 97%, but as yet it has not been validated in any prospective study (Table 6). Others have proposed the combination of measurements of chromogranin and urinary fractionated metanephrines as follow-up tests for elevations of plasma metanephrines (73). In situations of borderline positive test results and low probability of a tumor, a wait-and-retest approach can illuminate increased likelihood of an enlarging small tumor when mild initial elevations are followed by continued increases after 6 months or more.

Medications that directly interfere with measurement methods (eg, acetaminophen, mesalamine, sulfasalazine in LC-ECD methods) or interfere with the disposition of catecholamines (eg, tricyclic antidepressants) can result in mildly to markedly raised values for biochemical test results (Table 7) (74–77). Physiological stress associated with extreme illness, as in intensive care settings, and laboratory error are examples that should be considered in interpreting marked elevations of plasma or urine metanephrines (69, 78). In such situations, confirmatory testing after exclusion of these sources of false-positives is useful.

For plasma free metanephrines, dietary considerations are only relevant when measurements include the dopamine metabolite 3-methoxytyramine (65). For such measurements, sampling should be done after an overnight fast.

1.4 Values and preferences

The committee recommends that all positive results should be followed up. However, the nature of this and whether to first follow-up with additional comprehensive or involved biochemical testing procedures, adopt a wait-

Table 6.   Protocol for Clonidine Suppression Test

Principle	Clonidine is an α_2-adrenoreceptor agonist that inhibits neuronal norepinephrine release in patients without PPGL but not in patients with autonomous tumoral secretion of catecholamines by a PPGL.
Indication	To discriminate patients with mildly elevated test results for plasma normetanephrine due to increased sympathetic activity from patients with elevated test results due to a PPGL.
Pretest condition	Withdraw sympatholytic drugs before testing (eg, β-blocker) at least 48 h before testing. The test is carried out with patient in the supine position. The test is cancelled if baseline blood pressure is <110/60 mm Hg or in volume-depleted patients.
Procedure	A venous cannula is placed in an antecubital vein. After 20 min of supine rest, a first blood sample is drawn. Clonidine is administered orally at a dose of 300 μg/70 kg body weight. Blood pressure and heart rate are measured at regular intervals before and during the test. Three hours after drug administration, a second blood sample is drawn. The tubes with blood samples are immediately placed on ice. Blood samples are analyzed for plasma normetanephrine.
Interpretation	An abnormal test result indicating a PPGL includes an elevation of plasma normetanephrine at 3 h after clonidine administration and a less than 40% decrease in levels compared with baseline.

Refs. 71 and 216.

and-retest approach, or proceed directly to imaging studies remains a matter of clinical judgment based on the pretest probability of the tumor and the extent and pattern of increases in test results in relation to the presentation of patients and other preanalytical considerations impacting test interpretation.

Table 7.   Major Medications That May Cause Falsely Elevated Test Results for Plasma and Urinary Metanephrines

	Plasma		Urine	
	NMN	MN	NMN	MN
Acetaminophen[a]	++	−	++	−
Labetalol[a]	−	−	++	++
Sotalol[a]	−	−	++	++
α-Methyldopa[a]	++	−	++	−
Tricyclic antidepressants[b]	++	−	++	−
Buspirone[a]	−	++	−	++
Phenoxybenzamine[b]	++	−	++	−
MAO-inhibitors[b]	++	++	++	++
Sympathomimetics[b]	+	+	+	+
Cocaine[b]	++	+	++	+
Sulphasalazine[a]	++	−	++	−
Levodopa[c]	+	+	++	+

Abbreviations: MAO, monoamine oxidase; MN, metanephrine; NMN, normetanephrine; ++, clear increase; +, mild increase; −, no increase.

[a] Analytical interference for some but not all methods employing LC-ECD.

[b] Pharmacodynamic interference leading to increased levels affecting all analytical methods.

[c] Analytical interference with some LC-ECD assays, and also pharmacodynamic interference increase the dopamine metabolite 3-methoxytyramine affecting all analytical methods.

2.0 Imaging Studies

Recommendation

2.1 We recommend that imaging studies to locate PPGLs should be initiated once there is clear biochemical evidence of a PPGL. (**1**|⊕⊕◯◯)

2.1. Evidence

There are no randomized controlled studies to support restricting the use of imaging to patients with clear biochemical evidence of PPGLs. Rather the strength of this recommendation is based on the high diagnostic sensitivity of modern biochemical tests when correctly implemented, as outlined in the preceding sections.

There are nevertheless situations that clinicians should be aware of where PPGL can be biochemically negative, even when collections of specimens and biochemical measurements are correctly employed: 1) skull base and neck paragangliomas, often biochemically silent and for which imaging represents the principal means for diagnosis; and 2) paragangliomas in patients with *SDHx* mutations. Emerging evidence indicates that some of these paragangliomas lack the biosynthetic machinery for catecholamine production and may present with biochemically silent features (80, 81). The tumors consequently can reach a large size. Thus, only imaging studies can detect the presence of these tumors.

2.1. Values and preferences

For a cost-effective approach and to avoid unnecessary radiation, there is a need for biochemical proof of PPGL before imaging studies are performed. The committee rec-

ognizes that currently there is insufficient evidence to formulate guidelines about when and how to perform imaging studies in patients at risk for biochemically silent PPGL.

Recommendation

2.2 We suggest CT rather than MRI as the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis. (2|⊕⊕⊕○)

2.2 Evidence

CT with contrast provides an excellent initial method for the localization of PPGLs, with sensitivity between 88 and 100% (82–90). CT has excellent tomographical resolution but, as with MRI, lacks specificity. On CT, PPGLs may be homogeneous or heterogeneous, necrotic with some calcifications, solid, or cystic. Although between 87 and 100% of PPGLs exhibit a mean attenuation of more than 10 Hounsfield units on unenhanced CT, PPGLs can occasionally have more than 60% washout of contrast agents on 15-minute delayed scanning (91–94). A high signal intensity (bright) T2-weighted MRI image may be of value for the detection of PPGLs; however, a recent study showed that in pheochromocytomas this finding is relatively uncommon (95).

The use of nonionic contrast is safe, and therefore, contrast CT can be performed in patients without adrenergic receptor blockade (96, 97). Modern CT scans can detect tumors 5 mm or larger. Because most PPGLs are located in the abdomen, a CT scan of the abdomen and pelvis should be the first option. Some studies showed that sensitivity of CT for extra-adrenal, residual, recurrent, or metastatic tumors can be as low as 57% and inferior to MRI (83, 86, 98–102). CT is preferred to MRI for detection of lung metastatic lesions (84). For skull base and neck paraganglioma, the sensitivity of MRI is between 90 and 95% (81). Use of ultrasound is usually not recommended due to its suboptimal sensitivity.

2.2 Values and preferences

The committee recognizes that the results of current and previous studies should be interpreted with caution, taking into consideration the type of CT or MRI scans and the design of the study, including its criteria, selection of patients, and controls. The committee recognizes that rarely there are PPGLs not detected by any anatomical imaging studies due to their small size or location, the presence of surgical clips, or postoperative changes, and that such tumors can only be detected by functional imaging modalities.

Recommendation

2.3 We recommend MRI in patients with metastatic PPGLs, for detection of skull base and neck paragangliomas, in patients with surgical clips causing 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, patients with known germline mutations, and those with recent excessive radiation exposure). (1|⊕⊕⊕○)

2.3 Evidence

See previous Section 2.2.

2.3 Values and preferences

MRI should not be performed in patients who have intracranial aneurysm clips.

See previous Section 2.2.

Recommendation

2.4 We suggest the use of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy as a functional imaging modality in patients with metastatic PPGLs detected by other imaging modalities when radiotherapy using ^{131}I-MIBG is planned and occasionally in some patients with an increased risk for metastatic disease due to large size of the primary tumor or to extra-adrenal, multifocal (except skull base and neck PPGLs), or recurrent disease. (2|⊕○○○)

2.4 Evidence

Because ^{123}I-MIBG has better sensitivity than ^{131}I-MIBG for detection of PPGLs (103- 106), only the former agent is recommended for imaging. Another advantage of [123]I- over ^{131}I-labeled MIBG is its utility for imaging by SPECT. Because up to 50% of normal adrenal glands demonstrate physiological uptake of ^{123}I-MIBG, false-positive results can be a problem (104, 107). Asymmetric uptake in normal adrenal glands can further lead to misinterpretation.

Sensitivity of ^{123}I-MIBG ranges between 85 and 88% for pheochromocytomas and between 56 and 75% for paragangliomas, whereas specificity ranges from 70–100% and 84–100%, respectively (108–111). Sensitivity for metastatic PPGLs is between 56 and 83% (109, 112), whereas for recurrent PPGLs it is approximately 75% (113). Results from a meta-analysis showed 90% sensitivity and specificity for pheochromocytomas, whereas sensitivities were 98% for paragangliomas, falling to 79% for malignant PPGLs (114). In another meta-analysis of 15 studies of ^{123}I-MIBG scintigraphy, sensitivity was 94% and specificity 92% (115). For *SDHx*-related PPGLs, and

in particular for *SDHB*-related PPGLs, overall sensitivity of ^{123}I-MIBG is less than 50% (81, 116). Similar results of suboptimal sensitivity have also been reported for the detection of skull base and neck, thoracic, bladder, or recurrent paragangliomas (107, 108, 111, 113, 117, 118).

^{123}I-MIBG SPECT is widely available, and recent studies suggest that its performance is similar to PET scanning using ^{18}F-fluorodopamine, ^{18}F-fluorodihydroxy-phenyl-alanine (^{18}F-FDOPA), or ^{18}F-FDG in the detection of pheochromocytoma (112, 119). For paragangliomas or metastatic disease including *SDHx*-related tumors, ^{123}I-MIBG is inferior to ^{18}F-FDG-PET, ^{18}F-FDOPA, or somatostatin receptor imaging with ^{111}In-diethylene triamine pentaacetic acid-pentetreotide (81, 118, 120–123).

2.4 Values and preferences

In making this recommendation, the committee has taken into account the findings of the Endocrine Society-sponsored systematic review of functional imaging in PPGL as well as the evidence outlined above that ^{123}I-MIBG scintigraphy has limited use due to relatively suboptimal sensitivity, particularly in patients with metastatic PPGLs and those with *SDHx*-related PPGLs (Brito, J. P., N. Asi, C. Undavali, et al., submitted for publication). Nevertheless, in patients with metastatic PPGLs in whom surgery is not an option, ^{123}I-MIBG scintigraphy is useful because, if positive, treatment with ^{131}I-MIBG may be considered. The recommendation for restricted use of MIBG to patients with or at risk for metastatic disease thus recognizes this therapeutic need, the widespread availability of this functional imaging modality, as well as its limited utility for identifying lesions not detected by conventional imaging.

2.4 Remarks

Accumulation of ^{123}I-MIBG can be decreased by several drugs: 1) sympathomimetics; 2) agents that block catecholamine transport via the norepinephrine transporter, such as cocaine and tricyclic antidepressants; and 3) agents such as calcium channel blockers and some combined α- and β-adrenergic receptor blockers such as labetalol (125). Therefore, most of these drugs should be withheld for about 2 weeks before ^{123}I-MIBG scintigraphy. Accumulation of ^{123}I-MIBG is also profoundly decreased in necrotic tumors (89). Use of ^{123}I-MIBG scintigraphy is contraindicated in pregnant women. The committee recommends that ^{123}I-MIBG scintigraphy be performed by and results be assessed by experienced nuclear medicine physicians.

Recommendation

2.5 We suggest the use of ^{18}F-FDG PET/CT scanning in patients with metastatic disease. ^{18}F-FDG PET/CT is the preferred imaging modality over ^{123}I-MIBG scintigraphy in patients with known metastatic PPGLs. (2|⊕⊕⊕○)

2.5 Evidence

In the initial study of Shulkin et al (126), the overall sensitivity of ^{18}F-FDG PET was 76%, but it was higher in patients with metastatic (88%) than benign (58%) PPGLs. This study and several subsequent studies showed a superiority of ^{18}F-FDG PET compared with ^{131}I-MIBG scintigraphy for detection of metastatic PPGLs (119, 120, 127–131). Overall, the sensitivity of ^{18}F-FDG PET was shown to be between 74 and 100%, with the highest performance for metastatic, particularly *SDHB*-related, PPGLs (120, 122, 126, 128–130, 132–134).

2.5 Values and preferences

The committee recognizes that some studies indicated that ^{18}F-FDG PET is complementary with other functional imaging studies in some patients. It is also recognized that there are limited data regarding the use of various PET imaging modalities in patients with different genetic mutations.

2.5 Remarks

The use of PET imaging modalities is contraindicated in pregnant women. There are also several drugs that may profoundly decrease the uptake of PET radiopharmaceuticals by PPGL, but the data are limited, and further studies are needed.

3.0 Genetic Testing

Recommendation

3.1 We recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing. (1|⊕⊕⊕○)

3.1 Evidence

Since 1990, 14 different PPGL susceptibility genes have been reported: *NF1* (135), *RET* (136), *VHL* (137), *SDHD* (138), *SDHC* (139), *SDHB* (140), *EGLN1/PHD2* (141, 142), *KIF1β* (143), *SDH5/SDHAF2* (144), *IDH1* (145), *TMEM127* (146), *SDHA* (147), *MAX* (148), and *HIF2α* (149). The roles of *EGLN1/PHD2* (150, 151), *KIF1β*, and *IDH1* (152) have not been confirmed by other studies, suggesting that mutations in these genes are an infrequent cause of hereditary PPGLs. The role of somatic or germline mutations in *HIF2α*, reported in a few patients (149, 153–156), awaits validation in a larger series.

There are several reasons to consider genetic testing in all patients who present with PPGLs: 1) at least one-third

Table 8. Detected Germline Mutations in All PPGL Patients

First Author, Year (Ref.)	No. of Cases	Mutations										n	%
		SDHB	SDHD	SDHC	VHL	RET	NF1	SDHA	SDHAF2	TMEM127	MAX		
Lefebvre, 2012 (170)	269	21	12	6	ND	ND	ND	ND	0	5	ND	44	16.3
Amar, 2005 (165); Burnichon, 2009 (166)	721	99	131	16	25	16	13	ND	ND	ND	ND	300	41.6
Mannelli, 2009 (162)	501	24	47	4	48	27	11	ND	ND	ND	ND	161	32.1
Cascón, 2009 (163)	237	25	11	1	20	36	ND	ND	ND	ND	ND	93	39.2
Jafri, 2012 (167)	501	121	44	ND	19	ND	ND	ND	ND	ND	ND	184	36.7
Erlic, 2009 (168)	1149	73	28	2	120	80	43	ND	ND	ND	ND	346	30.1
Korpershoek, 2011 (169)	316	16	26	2	19	26	21	5	5	2	ND	122	38.6
Total n	3694	379	299	31	251	185	88	5	5	7		1250	33.8
Mutation rate		10.3	8.9	1.0 (31/3193)	7.3 (251/3425)	6.3 (185/2924)	3.3 (88/2687)						

ND, not determined.

of all patients with PPGLs have disease-causing germline mutations (157); 2) mutations of *SDHB* lead to metastatic disease in 40% or more of affected patients (23, 24); and 3) establishing a hereditary syndrome in the proband may result in earlier diagnosis and treatment of PPGLs and other syndromic manifestations in relatives (159–161).

In clinical practice, patients with PPGLs can present with features that indicate a high likelihood of a hereditary cause. Such features include a positive family history (based on family pedigree or identification of a PPGL-susceptibility gene mutation in a relative), syndromic features, and multifocal, bilateral, or metastatic disease (157, 162, 163). Many patients with PPGLs, however, do not have the above-mentioned features.

Following the initial report of Neumann et al (15), genotyping of the main PPGL susceptibility genes (*SDHB, SDHD, VHL, RET*) has been performed in eight studies, each comprising more than 200 patients and encompassing 3694 subjects harboring 1250 germline mutations (33.8%) (162, 163, 165–170) (Table 8). This high frequency justifies consideration of genetic testing in each patient with a PPGL. The highest frequencies of germline mutations are for *SDHB* (10.3%), *SDHD* (8.9%), *VHL* (7.3%), *RET* (6.3%), and *NF1* (3.3%). Germline mutation frequencies of less than 2% are found for *SDHC, SDHA, MAX,* and *TMEM127* (169, 171–173). No germline *SDHAF2* mutations were found in a series of 315 apparently sporadic PPGLs (174).

A mutation rate of 11.6% was revealed from a systematic review of the literature featuring an analysis that included only patients who fulfilled at least three of four criteria: 1) a negative family history of PPGL; 2) absence of syndromic features; 3) absence of bilateral disease; and 4) absence of metastatic disease (Brito, J. P., N. Asi, C. Undavalli, L. Prokop, V. M. Montori, and N. H. Murad, submitted for publication).

3.1 Values and preferences

The committee's recommendation that genetic testing should be considered in each patient does not imply that genetic testing should be done in each patient. In particular, in view of the financial costs, genetic testing has limited incremental value in patients with unilateral pheochromocytoma and no syndromic or malignant features and no positive family history. The importance of the diagnosis of an inherited disease for at-risk families must be balanced against any negative impacts and financial costs of genetic testing. The costs of genetic testing will probably decrease with adoption of next-generation sequencing methods. This may shift the balance in favor of more widespread genetic testing than currently practiced according to the variable country insurance-specific limitations of health care coverage.

Recommendation

3.2 We recommend the use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations. (1|⊕⊕⊕○)

3.2 Evidence

The committee proposes a decisional algorithm for sequential genetic testing, with selection of genes to be tested prioritized according to a syndromic or metastatic presentation (Figure 1). Considerations of young age at PPGL presentation, positive family history, and presentation of multifocal PPGLs or bilateral adrenal tumors are also recommended for prioritizing patients for testing. Thereafter, considerations of tumor location and catecholamine biochemical phenotype may further guide selection of genes for testing when justified.

A positive family history or syndromic presentation in patients with PPGLs not only indicates a high priority for genetic testing, but also may direct targeted germline mutation testing. Six different familial autosomal dominant diseases can be suspected clinically: neurofibromatosis
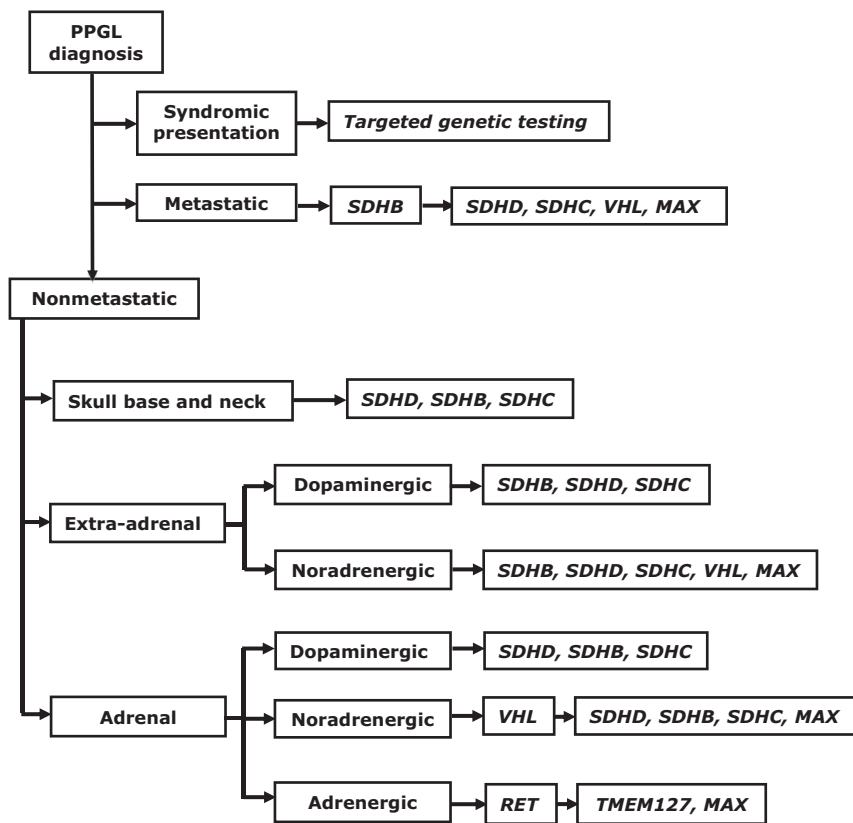
Figure 1. Decisional algorithm for genetic testing in patients with a proven PPGL. Dopaminergic, noradrenergic, and adrenergic phenotypes are defined as significant productions of respective 3-methoxytyramine, normetanephrine, and metanephrine relative to combined production of all three metabolites.

static PPGLs (23). In a later review, Pasini and Stratakis (184) documented a prevalence of 36% of *SDHB* mutations in malignant PPGLs. Moreover, this higher risk was observed in a pediatric series (185). Furthermore, a meta-analysis of 12 studies showed that the pooled risk of malignant PPGL for *SDHB*-mutation carriers in incidence and prevalence studies was 17% and 13%, respectively (186). The above evidence justifies *SDHB* genetic testing in patients with metastatic PPGLs (Figure 1).

In the absence of a syndromic, familial, or metastatic presentation, selection of genes for testing may be guided by tumor location and biochemical phenotype (Figure 1) but prioritized according to age or presentation of multiple tumors. Lower age at PPGL presentation among patients with germline mutations than those without mutations is well established (15, 162, 163, 165, 168, 185, 187). Although there is no agreement upon age cutoff for genetic testing, the likelihood of a mutation in patients with nonsyndromic PPGLs younger than 45 years is 5-fold higher than in patients older than 45 years (168). Prevalence of germline mutations among children with PPGLs is particularly high (185, 188–191), justifying mutation screening in all such cases.

Prevalence of germline mutations is also high among patients with bilateral or multifocal PPGLs (162, 163, 165, 166, 168, 192). *SDHB* mutations result mainly in extra-adrenal tumors (182). In a large study of patients with nonsyndromic PPGLs (168), the prevalence of germline mutations associated with multiple PPGLs was 5-fold higher than for solitary PPGLs (54 vs 11.5%). In the same study, an extra-adrenal tumor location was shown to carry a 4-fold higher risk of a germline mutation than an adrenal location, with mutations confined to *SDHx* genes. This high risk associated with extra-adrenal tumors has been confirmed by numerous studies (159, 162, 163, 166, 193), justifying the recommendation for screening of *SDHx* gene mutations in affected patients.

As reviewed by Pasini and Stratakis (184), *SDHx*-related genotype-phenotype correlations have been assessed by several studies based on international registries. Mul-

type 1 (NF1), multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau (VHL) syndrome (see Table 3), renal cell carcinoma with *SDHB* mutation (176), Carney triad (paragangliomas, gastric stromal tumors, pulmonary chondromas), and Carney-Stratakis syndrome (paragangliomas and gastric stromal sarcomas) (177). The MEN2 and VHL syndromes are usually characterized by distinct clinical stigmata that directs targeted testing of *RET* and *VHL* genes. Detection of mutations in the *NF1* gene is complex, and although testing is available in specialized laboratories (178), the diagnosis of NF1 can be invariably established by clinical findings alone (179). Nevertheless, some patients with NF1 and an apparently sporadic PPGL presentation have been reported, all with mild features of the disease (180, 181); these findings illustrate the importance of careful clinical investigation of possible clinical stigmata of an underlying mutation in all patients with PPGL.

Since 2003, several studies have reported that the identification of a germline *SDHB* mutation is an important risk factor for malignancy for patients affected by PPGLs (165, 182) and of poor prognosis for patients affected by metastatic PPGLs (24). Conversely, pathogenic *SDHB* mutations were reported in 30% of patients with meta-

tiple skull base and neck tumors or a family history of PPGL in the paternal branch suggests an *SDHD*-related PPGL (159, 166, 192). In contrast, *SDHB*-related PPGLs are often diagnosed as a single extra-adrenal tumor without any family history. *SDHC* mutation carriers are rare but may develop all the stigmata of the disease. Mutations of *SDHA* and *SDHAF2* were described in only a few patients. Negative *SDHB* immunohistochemistry in tumoral tissue suggests the presence of a mutation in one of the *SDHx* genes (194). Hormonally functional *SDHx*-related PPGLs are best detected by measurements of normetanephrine and methoxytyramine (195). Increases in methoxytyramine are particularly prevalent in patients with PPGLs due to *SDHx* mutations, justifying targeted testing of these mutations associated with this biochemical presentation (Figure 1).

For nonsyndromic tumors with adrenal locations, mutations are far less common than for tumors at extra-adrenal locations and encompass all established tumor susceptibility genes. When justified by young age at presentation or bilaterality, mutation testing should follow the decisional algorithm (Figure 1).

Hereditary PPGL due to *TMEM127* or *MAX* mutations are infrequent, typically diagnosed later in life, and preferentially adrenal in location; patients frequently have a positive family history (Table 8). *TMEM127*-related PPGLs typically produce epinephrine, whereas the biochemical phenotype of *MAX*-related tumors is intermediate between adrenergic and noradrenergic (173).

In the absence of more common germline mutations, rare cases such as *SDHA* germline mutations may be considered. For example, consider *SDHA* in patients with skull base and neck or thoracic-abdominal-pelvic paraganglioma associated with negative *SDHB* and *SDHA* immunohistochemistry on tumoral tissue.

3.2 Values and preferences

In recommending a sequential algorithm with selective testing prioritized according to risk of mutations, the committee has considered the systematic review, indicating that the current level of evidence does not support indiscriminate genetic testing of PPGL susceptibility genes. It is also recognized that the recommended selective approach to genetic testing will likely be made obsolete by development of next-generation sequencing methods allowing rapid and low-cost analysis of all PPGL susceptibility genes. Interpretations of pathogenicity, particularly associated with the greater number of variants of unknown significance (VUSs) generated by this technology, will nevertheless also increasingly require accurate knowledge of the genotype-

phenotype relationships that provide the basis for the current sequential algorithm.

Recommendation

3.3 We suggest that patients with paraganglioma undergo testing of SDH mutations and that patients with metastatic disease undergo testing for *SDHB* mutations. (2|⊕⊕⊕○)

3.3. Evidence

See previous Section 3.2.

3.3 Values and preferences

See previous Section 3.2.

Recommendation

3.4 We recommend that genetic testing for PPGL be delivered within the framework of health care. Specifically, pretest and post-test counseling should be available. All tests for PPGL genetic testing should be performed by accredited laboratories. (Ungraded recommendation).

3.4 Evidence

In 2002, the Organization for Economic Cooperation and Development (OECD) produced guidelines for quality assurance in molecular genetic testing (196). The OECD guidelines encompassed the general principles and best practices for molecular genetic testing, the quality assurance systems and proficiency testing programs, the quality of result reporting, and the education and training standards for laboratory personnel. All molecular genetic testing services should be provided and practiced under a quality assurance framework by accredited laboratories. A required signed informed consent to test should be obtained according to national applicable standards (197). Pretest and post-test counseling should be available. Molecular genetic testing laboratories should have policies and procedures to document the analytical validity of all tests performed.

The European Molecular Genetics Quality Network provides external quality assessment schemes for VHL disease and MEN2 (see www.emqn.org). The application of these guidelines was recommended in the United States after the realization of a survey comparing data on the molecular genetic testing in laboratories in the United States with those in 18 others countries (198). Certification and accreditation, based on ISO 9001 and ISO 15189, respectively, are widely encouraged in human molecular genetic testing laboratories (199).

Patients with PPGLs benefit from genetic counseling before and after germline mutation testing in order to be informed about the different suspected inherited diseases

Table 9.   Presurgical Medical Preparation

Drug	Starting Time	Starting Dose	Final Dose[b]
Preparation 1			
Phenoxybenzamine	10–14 d before surgery	10 mg b.i.d.	1 mg/kg/d
or Doxazosine	10–14 d before surgery	2 mg/d	32 mg/d
Preparation 2			
Nifedipine[a]	As add-on to preparation 1 when needed	30 mg/d	60 mg/d
or Amlodipine[a]	As add-on to preparation 1 when needed	5 mg/d	10 mg/d
Preparation 3			
Propranolol	After at least 3–4 d of preparation 1	20 mg t.i.d.	40 mg t.i.d.
or Atenolol	After at least 3–4 d of preparation 1	25 mg/d	50 mg/d

Abbreviations: b.i.d., twice daily; t.i.d., three times daily.

[a] Add when blood pressure cannot be controlled by α-adrenoceptor blockade (preparation 1).

[b] Higher doses usually unnecessary.

and their diagnosis and treatment, the diagnostic performance of corresponding genetic testing, and the familial risk of transmission. Access to national/international specialized networks/referral centers and patient support groups should be facilitated.

Except for *NF1* and *SDHA*, all known PPGL susceptibility genes can be routinely sequenced, and large deletions can be searched for with commercial multiplex ligation-dependent probe amplification kits and/or by quantitative PCR procedures by specialized genetic laboratories (157). A misinterpretation of genetic testing or incorrect results can lead to deleterious consequences for the patient and his or her family (187). Every identified variant should be cautiously interpreted. The PPGL genetic test may be positive (when the identified mutation clearly disrupts gene function), negative (when no variation or a known nonfunctional polymorphism is found in DNA sequence), or uncertain (when a sequence VUS is detected). The prediction of the clinical impact of a VUS is based on variant classification systems using the clinical, biological, and familial context of the patient; the presence of the VUS in general and/or specific polymorphisms/mutations databases; in silico prediction tools; and functional tests, when available (200–202).

3.4 Values and preferences

In making this recommendation, the committee has adopted OECD recommendations in recognition of the importance of the quality of the methods applied for genetic testing and for associated genetic counseling.

3.4 Remarks

Several quality assurance index items for molecular genetic testing exist and should be applied for PPGL genetic testing, such as the use of negative and positive controls in analyses and the confirmation of a positive test result on a second aliquot of germline DNA. Accredited laboratories should analyze sequence VUSs with robust methods for interpretation. The interpretation of reporting should be adapted to the individual patient and clinical situation. Genetic test results should be reported back to qualified healthcare professionals to enable healthcare decision-making and to facilitate delivery of clear, well-informed interpretation of the consequences to the patient and family members, when appropriate.

4.0 Perioperative Medical Management

Recommendation

4.1 We recommend that all patients with a hormonally functional PPGL should undergo preoperative blockade to prevent perioperative cardiovascular complications. (**1/**⊕⊕○○) We suggest α-adrenergic receptor blockers as the first choice. (**2**|⊕⊕○○)

4.1 Evidence

Evidence from randomized controlled clinical studies regarding the comparable effectiveness of nonselective α- vs α1-selective adrenergic receptor blockers is unavailable (203, 204). However, retrospective studies support the use of α-adrenergic receptor blockers as the first-choice drug class to minimize perioperative complications (17, 101, 204–206, 209). Retrospective studies demonstrated that α1-selective adrenergic receptor blockers were associated with lower preoperative diastolic pressure, a lower intraoperative heart rate, better postoperative hemodynamic recovery (210), and fewer adverse effects such as reactive tachycardia and sustained postoperative hypotension than nonselective adrenergic blockers (211). Another study did not show any difference between selective and nonselective α-adrenergic receptor blockers (212).

Calcium channel blockers are the most often used add-on drug class to further improve blood pressure con-

trol in patients already treated with α-adrenergic receptor blockers (213–215) (Table 9); however, some studies have suggested that this drug class can be used as the first choice (216). Monotherapy with calcium channel blockers is not recommended unless patients have very mild preoperative hypertension or have severe orthostatic hypotension with α-adrenergic receptor blockers.

Preoperative coadministration of β-adrenergic receptor blockers is indicated to control tachycardia only after administration of α-adrenergic receptor blockers. Use of β-adrenergic receptor blockers in the absence of an α-adrenoceptor blocker is not recommended because of the potential for hypertensive crisis due to unopposed stimulation of α-adrenergic receptors. There is no evidence to support the preference of β1-selective adrenergic receptor blockers over nonselective β-adrenergic receptor blockers. Labetalol with its fixed but more potent β than α antagonistic activities (α:β of 1:5) should not be used as the initial therapy because it can result in paradoxical hypertension or even hypertensive crisis (217).

α-Methyl-paratyrosine (metyrosine) inhibits catecholamine synthesis and may be used in combination with α-adrenergic receptor blockers for a short period before surgery to further stabilize blood pressure to reduce blood loss and volume depletion during surgery (218, 219).

There has been one report that preoperative α1-adrenergic receptor blockade offers no benefit in maintaining intraoperative hemodynamics of normotensive PPGL patients (79). Nevertheless, it is the view of the committee that for such patients α-adrenergic receptor blockers and/or calcium channel blockers remain recommended to prevent unpredictable increases in blood pressure during surgery (124).

4.1 Values and preferences

Our recommendation to initiate adrenergic blockade before surgery places a higher value on the potential benefit of these drugs by preventing unpredictable instability in blood pressure during surgery and a relatively lower value on the potential for medication-related adverse effects.

Recommendation

4.2 We recommend preoperative medical treatment for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate. Treatment should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction preoperatively to prevent severe hypotension after tumor removal. (**1**|⊕⊕○○)

4.2 Evidence

Evidence from randomized, controlled studies is unavailable. Retrospective studies report that α-adrenergic receptor blockers should be started at least 7 days preoperatively to normalize blood pressure and reverse blood volume contraction (124, 158). Intravenous infusion of phenoxybenzamine for 5 hours per day for 3 days before surgery has been reported as one effective approach (164, 175).

Evidence from randomized, controlled studies that treatment should also include a high-sodium diet and fluid intake is not available (203). Retrospective studies report that initiation of a high-sodium diet a few days after the start of α-adrenergic receptor blockade reverses blood volume contraction, prevents orthostatic hypotension before surgery, and reduces the risk of significant hypotension after surgery (26, 209). Continuous administration of saline (1–2 L) is also helpful if started the evening before surgery. Treatment with α-adrenergic receptor blockers alone was shown to reverse blood volume contraction in only about 60% of patients (183). Caution is required for volume loading in patients with heart or renal failure.

There is no evidence from randomized controlled studies to determine the optimal target blood pressure. Based on retrospective studies and institutional experience, a target blood pressure of less than 130/80 mm Hg while seated and greater than 90 mm Hg systolic while standing seems reasonable, with a target heart rate of 60–70 bpm seated and 70–80 bpm standing (26, 209). These targets should be modified in each patient according to age and accompanying cardiovascular diseases (26, 216, 207). It should be noted that complete prevention of intraoperative hypertension and tachycardia cannot be achieved by any doses and combinations of antihypertensive and other drugs.

4.2 Values and preferences

The recommendation to use α-adrenergic receptor blockers at least 7 days preoperatively places a higher value on the potential benefit of preventing unpredictable instability in blood pressure during surgery and a relatively lower value on the potential for medication-related adverse effects. The recommendation for preoperative volume loading places a higher value on preventing severe and sustained hypotension after removal of the tumor and a lower value on the potential for adverse effects such as blood pressure increase.

Recommendation

4.3 We recommend monitoring blood pressure, heart rate, and blood glucose levels with adjustment of associ-

ated therapies in the immediate postoperative period. (**1**|⊕⊕○○)

4.3 Evidence

The major potential postoperative complications are hypertension, hypotension, and rebound hypoglycemia. Our recommendation that blood pressure, heart rate. and plasma glucose levels should be closely monitored for 24–48 hours is mainly based on retrospective studies and institutional experience (208, 209). Because of potential adrenal insufficiency, particular attention needs to be paid to patients who undergo: 1) bilateral adrenalectomy; 2) bilateral cortical-sparing adrenalectomy; or 3) unilateral cortical-sparing adrenalectomy of a sole remaining adrenal gland. There are numerous case reports of postsurgical hypoglycemia but no studies documenting its exact prevalence.

4.3 Values and preferences

The committee's recommendation places a high value on preventing blood pressure and heart rate instability and postoperative hypoglycemia.

Recommendation

4.4 We suggest measuring plasma or urine levels of metanephrines on follow-up to diagnose persistent disease. We suggest lifelong annual biochemical testing to assess for recurrent or metastatic disease. (**2**|⊕⊕○○)

4.4 Evidence

Evidence from randomized, controlled studies is unavailable. These recommendations depend on personal and institutional experiences. Several studies reported high rates of recurrence or metastatic disease after surgical resection (17, 22, 220, 221).

4.4 Values and preferences

Our recommendation to measure plasma or urine metanephrines annually after surgery places a higher value in detecting tumor recurrence or metastasis and a lower value in avoiding the incremental expenses of the biochemical testing.

4.4 Remarks

To document successful tumor removal, biochemical testing should be performed upon recovery of the patient from surgery (eg, 2–4 wk after surgery).

5.0 Surgery

Recommendation

5.1 We recommend minimally invasive adrenalectomy (eg, laparoscopic) for most adrenal pheochromocytomas.

(**1**|⊕⊕○○) We recommend open resection for large (eg, >6 cm) or invasive pheochromocytomas to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence. (**1**|⊕○○○) We suggest open resection for paragangliomas, but laparoscopic resection can be performed for small, noninvasive paragangliomas in surgically favorable locations. (**2**|⊕○○○)

5.1 Evidence

There are no prospective randomized studies comparing laparoscopic with open adrenalectomy for pheochromocytomas. Several large single-institution series (some with historical controls) show laparoscopic adrenalectomy to be associated with less pain, less blood loss, fewer hospital days, and less surgical morbidity than open adrenalectomy (222, 223). There are no data regarding any difference in recurrence rate after open vs laparoscopic adrenalectomy. Mortality rate is about 1%, and the conversion rate and transfusion rate are about 5% (rate of conversion to open resection is influenced by tumor size and surgeon experience). Because pheochromocytomas are rare, a prospective randomized study comparing open with laparoscopic resection is unlikely.

The two most common laparoscopic approaches are the lateral transabdominal/transperitoneal (Gagner) approach and the posterior retroperitoneal (Walz) approach. The former allows intra-abdominal evaluation and has more space for dissecting larger tumors (222, 224). The latter may be preferable for patients who had prior abdominal operation or those requiring bilateral adrenalectomy (225, 226). Paragangliomas are more likely to be malignant and are frequently found in areas difficult for laparoscopic resection; thus, paragangliomas are more likely than pheochromocytomas to require open resection, but some can be safely resected laparoscopically by experienced surgeons (227).

5.1 Values and preferences

Patients prefer less pain, earlier recoveries, and shorter hospitalizations, which are possible with laparoscopic surgery.

5.1 Remarks

Safe laparoscopic adrenalectomy requires surgeons with skills and experience in advanced laparoscopic surgery and centers with appropriate expertise in the preoperative and postoperative management of pheochromocytoma, including anesthesia, endocrinology, and intensive care (228). Laparoscopic adrenalectomy can be performed transperitoneally or retroperitoneally depending on the surgeon's preference and expertise (222, 225).

Seeding and recurrence of tumors in the adrenal bed or throughout the abdominal cavity can occur if pheochromocytomas are fractured during dissection (229), mandating precise and gentle dissection. Specimen bags used for tumor retrieval should not tear. The operation should be converted to open resection if the laparoscopic approach is difficult. Hand assistance or robot assistance may be helpful in patients with large tumors that are difficult to resect (230) and are used per the surgeon's discretion.

Recommendation

5.2 We suggest partial adrenalectomy for selected patients, such as those with hereditary pheochromocytoma, with small tumors who have already undergone a contralateral complete adrenalectomy to spare adrenal cortex to prevent permanent hypocortisolism. (2|⊕○○○)

5.2 Evidence

Partial adrenalectomy is safe, with no increased surgical risks over complete adrenalectomy (231). Use of energy devices such as ultrasonic shears and bipolar sealers lowers the risk of bleeding from the cut edges of the adrenal gland. Selective removal of medullary tissue leaving only cortical tissue is attempted, but usually some medullary tissue remains, which can cause tumor recurrence.

For patients with prior contralateral adrenalectomies, a successful partial adrenalectomy preserving sufficient adrenal cortex can prevent postoperative adrenal insufficiency and requirements for glucocorticoid and mineralocorticoid replacement (232–234). About 90% of patients can remain steroid independent (235, 236). Larger tumors result in smaller remnants and a lower chance for steroid independence. Partial adrenalectomy increases the risk for tumor recurrence from the remnant. Estimated recurrence rates are 10–15% over 10 years for VHL patients (233, 235). The cumulative recurrence rate for MEN2 patients after adrenal-sparing surgery at 5 and 10 years is 38.5%, including ipsilateral and contralateral gland recurrence (237). In a recent series of 96 patients with hereditary bilateral pheochromocytomas, predominantly MEN2 and VHL, the 3-year recurrence rate in the remnant adrenal was 7%, and steroid independence was 78% (238). The risk of surgical complications when resecting a recurrent tumor in a previously dissected area may be higher than for primary resections; open adrenalectomy may be needed for reoperation.

5.2 Values and preferences

Some surgeons advocate partial adrenalectomy even for initial pheochromocytoma in patients who are at high risk for subsequent contralateral adrenalectomy for pheochromocytoma. The decision to perform partial adrenalectomy depends on the relative value placed on two competing problems. Complete bilateral adrenalectomy results in hypocortisolism, with lifelong steroid dependence and the need to adjust steroid doses during physiological and pathological stress. Partial adrenalectomy inevitably leaves some adrenal medullary tissues with risk for recurrent pheochromocytoma. The resulting potential for reoperations (likely to be more difficult, with higher conversion and complication rates) must be balanced against the risks associated with chronically treated adrenal cortical insufficiency. Unfortunately, the group of patients who would benefit from partial adrenalectomy is exactly the same group who are at higher risk for recurrent pheochromocytoma from the remnant.

5.2 Remarks

Partial adrenalectomy for smaller tumors, those in the periphery, and those away from the main adrenal vein is more likely to result in sufficient functioning of adrenal cortex. Usually one-third (if central vein is preserved) to one-half of one adrenal gland is needed to preserve cortical function and avoid hypocortisolism, although as little as 15% of an adrenal gland has been found to be sufficient (239).

6.0 Personalized Management

Recommendation

6.1 In recognition of the distinct genotype-phenotype presentations of hereditary PPGLs, we recommend a personalized approach to patient management (ie, biochemical testing, imaging, surgery, and follow-up). (Ungraded recommendation).

6.1 Evidence

Accumulating evidence shows that hereditary PPGLs are characterized by distinct clinical presentations and differences in biological behavior and mode of transmission that reflect underlying mutations (159, 195, 240–253).

Mutations of *RET* and *NF1* genes are almost always associated with adrenal tumors that produce normetanephrine and metanephrine (28, 195). In contrast, tumors due to mutations of *VHL* and *SDHx* genes lack significant production of metanephrine (195). Additional increases in methoxytyramine, the metabolite of dopamine, characterize 70% of tumors in patients with mutations of *SDHx* genes (195). Biochemical screening and interpretation of test results in these hereditary conditions can therefore benefit from a personalized approach that considers genotype-biochemical phenotype relationships.
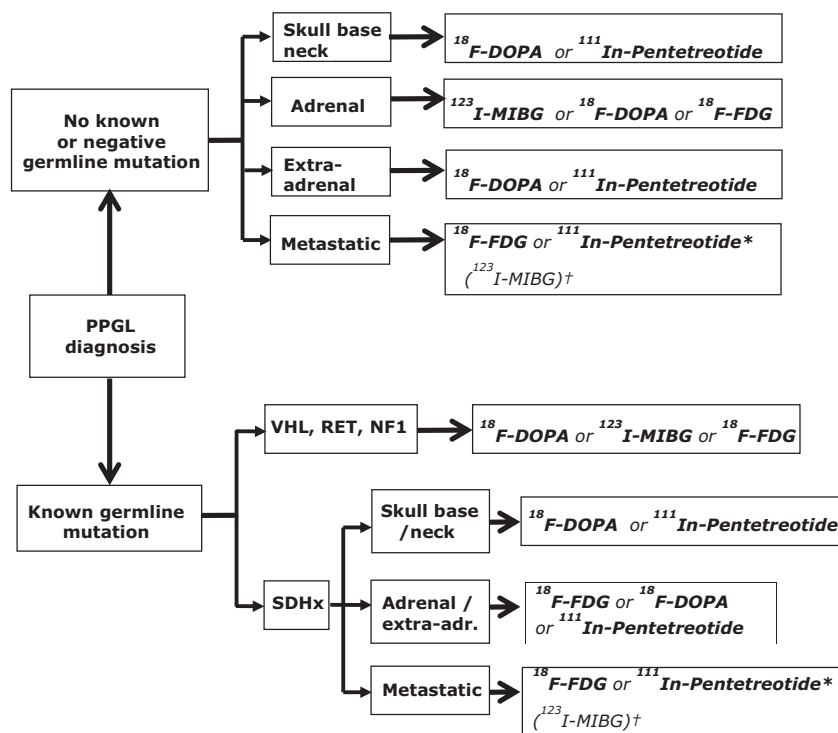
Figure 2. Decisional algorithm for functional imaging in patients with proven PPGL. *, When treatment with radiolabeled somatostatin analogs is considered. †, When treatment with ^{131}I-MIBG is considered.

$SDHx$ genes should involve appropriate strategies for localizing extra-adrenal tumors.

Recent studies support the existence of a genotype-specific imaging approach in the localization of PPGLs (134). ^{18}F-FDOPA PET is superior to CT/MRI or any other functional imaging modalities for detection of $SDHx$- and non-$SDHx$-related primary skull base and neck paragangliomas (117, 257). ^{18}F-fluorodopamine PET is overall the most sensitive method in the evaluation of primary (except head and neck) PPGLs (112, 122), but it has limited availability. ^{111}In-diethylene triamine pentaacetic acid-pentetreotide scintigraphy (Octreoscan) has been found to be a very good imaging method for the detection of PPGLs in $SDHx$ mutation carriers, although inferior to anatomical imaging (182).

The surgical approach should also be personalized according not only to tumor size and location but also to any underlying mutation; adrenal cortical-sparing surgery is a consideration for bilateral adrenal disease, whereas patients at risk for malignancy due to $SDHB$ mutations should be considered for approaches that minimize the possibility of recurrent or metastatic disease (237, 258).

Finally, all mutation carriers should receive consideration for annual biochemical surveillance for PPGLs. The nature of this surveillance should, however, take into account the particular gene affected according to the genotype-phenotype relationships described above, as well as considerations of penetrance and potential severity of disease. For example, because the penetrance of PPGLs in NF1 is low, screening for these tumors need not be considered unless indicated by signs or symptoms. At the other end of the spectrum, the high morbidity associated with undiagnosed PPGLs in patients with $SDHB$ mutations mandates closer attention; in addition to biochemical testing, periodic imaging with MRI should be considered to detect biochemically silent tumors. To avoid ionizing radiation, CT and nuclear medicine imaging modalities should be reserved to further characterize detected tumors.

Whereas VHL-associated tumors occur principally at adrenal locations, tumors due to mutations of $SDHx$ genes occur mainly at extra-adrenal locations and include skull base and neck paragangliomas with some differences depending on the particular SDH subunit affected (166, 241, 245, 249). Patients with mutations of the $SDHB$ gene deserve special attention because they have a high risk of malignant disease that reflects both the typically large sizes and extra-adrenal location of associated tumors (165, 182, 241, 254). Large tumor size and extra-adrenal location are both independent risk factors for malignant PPGLs that should be considered as part of the personalized management of any patient with PPGL (254, 255). An increase in plasma methoxytyramine is also a common feature of patients with metastatic PPGLs and is a promising new biomarker to identify such patients (254, 256).

In addition to a personalized approach to biochemical testing and test interpretation, the above observations dictate a need for personalized approaches to tumor localization. This need is further strengthened by additional findings that the underlying mutation and associated biological behavior impact the choice of functional imaging modality (134, 182, 252) (Figure 2).

Although localization in patients with RET and $NF1$ mutations or any patient with increased plasma or urine concentrations of metanephrine should primarily focus on the adrenals, localization in patients with mutations of

6.1 Values and preferences

The committee recognizes that currently there are no studies firmly establishing that a personalized approach provides im-

proved outcome. Nevertheless, it seems highly likely that such approaches will benefit patients, but they must also be considered according to cost; as covered below, a related point to any cost-benefit analysis is that such personalized approaches can only be feasible via specialist referral centers with appropriate multidisciplinary expertise.

Recommendation

6.2 We recommend that patients with PPGLs should be evaluated and treated by multidisciplinary teams at centers with appropriate expertise to ensure a favorable outcome. In particular, patients should be referred to such centers should there be pregnancy, metastatic disease, or issues concerning the complexity or difficulty in biochemical diagnosis; localization; performance, and interpretation of genetic testing; preoperative preparation; surgical treatment; and follow-up. (Ungraded recommendation)

6.2 Evidence

There are no trials that demonstrate that the outcome of patients who are diagnosed and treated for PPGLs in high-volume centers by high-volume surgeons/multidisciplinary teams is superior to the outcome of patients managed in a low-volume hospital with no dedicated expert team of different medical disciplines. However, several cross-sectional studies showed that high-volume centers had lower postsurgical morbidity with shorter hospital stay than low-volume centers (259–262). Some studies found higher rates of complications and conversions to laparotomy in low-volume nonreferral centers than in high-volume centers (262). These studies, however, did not focus on patients with pheochromocytoma.

The above differences are not unexpected because they have also been shown for other complex interventions such as vascular surgery (263). The strong inverse relation between case volume and postsurgical mortality for esophageal cancer surgery was based on the hospital setting in which these complex interventions were performed (264).

6.2 Values and preferences

PPGL is a very rare disorder with fewer than five patients presenting per year, even in some larger medical centers. The clinical presentation and course of PPGL are widely variable and can be part of a multisystem syndrome with many different organs affected. Most physicians are therefore unlikely to build sufficient specific experience to deal with this disorder. For a correct diagnosis, clinicians need to have appropriate experience in interpreting clinical and laboratory results, including results of genetic testing. Other physicians such

as radiologists and nuclear medicine specialists also play a crucial role for a reliable and accurate interpretation of imaging test results. Specialists such as cardiologists, anesthesiologists, and intensive care physicians must be involved in proper patient-tailored treatment. Therefore, the committee believes that a multidisciplinary team, experienced in dealing with these patients, offers the best outcomes.

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