REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Pheochromocytoma and Paraganglioma

Hartmut P.H. Neumann, M.D., William F. Young, Jr., M.D., and Charis Eng, M.D., Ph.D.

From the Section for Preventive Medicine, Medical Center–University of Freiburg, Faculty of Medicine, Albert-Ludwigs-University, Freiburg, Germany (H.P.H.N.); the Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine, Mayo Clinic, Rochester, MN (W.F.Y.); and the Genomic Medicine Institute, Lerner Research Institute, and Taussig Cancer Institute, Cleveland Clinic, Cleveland (C.E.). Address reprint requests to Dr. Neumann at the Section for Preventive Medicine, Faculty of Medicine, Albert-Ludwigs-University, 79104 Freiburg, Germany, or at hartmut.neumann@uniklinikum-freiburg.de.

This article was updated on August 8, 2019, at NEJM.org.

N Engl J Med 2019;381:552-65.
DOI: 10.1056/NEJMra1806651


Pheochromocytoma fascinates and, at times, confounds clinicians. The symptoms due to hypersecretion of catecholamines can mimic more than 30 medical disorders.[1] This rare tumor can be lethal if left undiagnosed. Thus, rapid recognition is vital. Yet selecting a good approach to biochemical testing and selecting imaging studies for purposes of localization can be confusing and complex. Although surgical resection is the treatment of choice, the preparation for and timing of surgery are uncertain; furthermore, selection of the appropriate operative technique for a given tumor may be controversial. Finally, recent progress in understanding the genetic basis for these tumors and how to manage a specific case according to the gene involved adds to the complexity. Here, we highlight recent advances in the diagnosis and management of this rare neoplasm.

## History, Terminology, and Histologic Features

Max Schottelius (1849–1919), a pathologist in Freiburg, Germany, was the first person to describe the histopathological features of pheochromocytoma; in 2017, Schottelius was finally profiled.[2] He provided the histologic description of bilateral adrenal tumors in an 18-year-old woman who died in 1886 after a long history of panic attacks, tachycardia, and sweating.[3] This report was translated into English and published in the series "Classics in Oncology" in 1984.[4] In 2007, we reported that this patient was the first described to have multiple endocrine neoplasia type 2 (MEN-2); descendants of her brother were found to carry a rearranged during transfection (*RET*) mutation.[5] The adrenal tumors in this patient were described by Schottelius as chromaffin tumors on the basis of staining with Müller's solution. The term pheochromocytoma dates back to 1912, when it was used by the German pathologist Ludwig Pick.[6]

In the 2017 World Health Organization (WHO) classification, pheochromocytoma is an adrenal tumor, and paraganglioma is an extraadrenal tumor; since the two tumor types cannot be differentiated on the basis of histologic findings (Fig. 1), anatomical location is used to distinguish between them.[7,8] Tumor growth shows the so-called zellballen pattern, consisting of well-developed tumor cells showing nested growth, with an intervening stromal component of fibrovascular tissue and peripheral sustentacular cells. Immunohistochemical examination shows chief cells stained with chromogranin and sustentacular cells stained with S100.[8]

## Clinical Presentation and Diagnosis

The incidence of pheochromocytoma and paraganglioma is about 0.6 cases per 100,000 person-years.[9] A broad spectrum of potential presenting symptoms includes the classic triad of headaches, palpitations, and profuse sweating.[10] Symp-

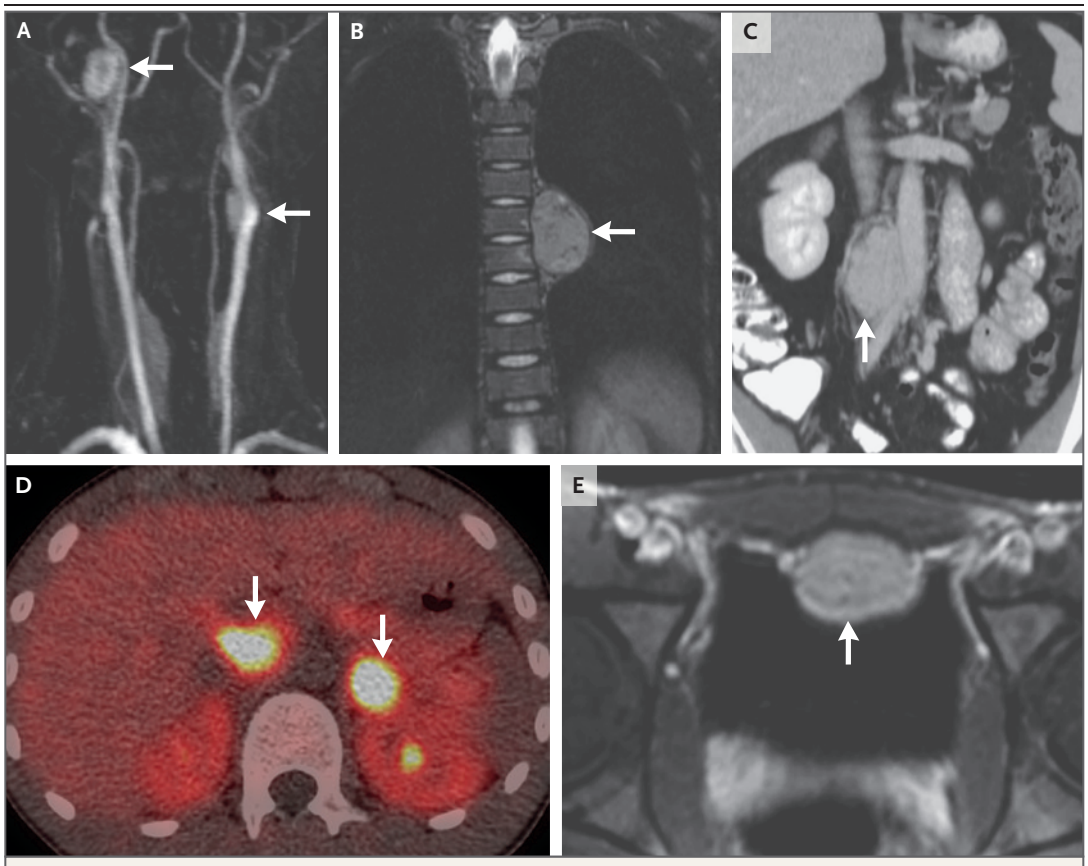



**Figure 1. Anatomical Location of Pheochromocytoma and Paraganglioma.**

Panel A shows a tumor in the right carotid body (arrows), seen in the frontal view on magnetic resonance imaging (MRI) with gadolinium contrast medium. Panel B shows a thoracic paravertebral paraganglioma on the left side (arrow), seen in the frontal view on MRI with gadolinium contrast medium. Panel C shows a retroperitoneal paraganglioma (arrow) in the frontal view on MRI with gadolinium contrast medium. Panel D shows a left adrenal pheochromocytoma and a right retroperitoneal paraganglioma (arrows) in the axial plane on $^{18}$F-labeled L-dihydroxyphenylalanine–positron-emission tomography–computed tomography ($^{18}$F-L-DOPA–PET–CT). Panel E shows a paravesicular pelvic paraganglioma on the anterior wall (arrow) in the axial plane on MRI with gadolinium contrast medium.

toms of anxiety and panic attacks are common in the general population, and identifying the rare patient with pheochromocytoma or paraganglioma is a challenge for clinicians. However, with the widespread use of cross-sectional imaging, the incidental discovery of an adrenal mass is becoming common.[11] In addition, asymptomatic cases of pheochromocytoma and paraganglioma are increasingly being discovered on the basis of family and germline-mutation testing.

The approach to making a diagnosis may differ from center to center, but a consensus approach is shown in Table 1. The diagnosis of pheochromocytoma or paraganglioma requires both proof of excessive release of catecholamines and anatomical documentation of the tumor. An increase in plasma fractionated metanephrines (metanephrine and normetanephrine) has a mean sensitivity of 97% and a specificity of 93% across 15 studies.[12] In contrast, measurement of fractionated catecholamines (epinephrine, norepinephrine, and dopamine) is less sensitive, but clearly elevated values (>2 times the upper limit of the normal range) are also diagnostic.[13,14] However, mild elevations in the levels of fractionated metanephrines and catecholamines in plasma and urine are common in persons who do not have pheochromocytoma. Medications (e.g., tricyclic antidepressants, antipsychotic agents, serotonin-reuptake or norepinephrine-

**Table 1. Approach to Pheochromocytoma and Associated Syndromes According to the Clinical Scenario.***

| Clinical Scenario | Initial Biochemical Testing and Imaging | Follow-up Biochemical Testing and Imaging |
|---|---|---|
| Signs and symptoms on presentation (e.g., resistant hypertension or paroxysms of hypertension, palpitations, perspiration, headaches, and markedly elevated metanephrines or catecholamines) | Perform abdominal contrast-enhanced CT or MRI; if abdominal imaging is negative, consider MRI of skull base, neck, chest, and pelvis | Measure metanephrines postoperatively and then annually; if bilateral pheochromocytomas were removed with cortical-sparing surgery, document normal glucocorticoid secretory function with cosyntropin-stimulation test |
| Incidentally discovered adrenal or retroperitoneal mass with attenuation >10 Hounsfield units on unenhanced CT | If levels of metanephrines are clearly elevated, perform contrast-enhanced CT or MRI; if mass is >10 cm in diameter or is extraadrenal, search for additional paragangliomas or metastatic disease with $^{123}$I-MIBG scintigraphy, $^{68}$Ga-DOTATATE–PET–CT, or $^{18}$F-FDG–PET–CT | If a pheochromocytoma or paraganglioma was resected, measure metanephrines postoperatively and then annually |
| Patient identified as carrier of disease-causing mutation | | |
| *RET* mutation | Measure metanephrines and perform abdominal MRI; measure serum calcitonin and calcium; seek endocrine surgery consultation if thyroid gland not previously resected | Measure serum calcitonin, metanephrines, and serum calcium annually |
| *VHL* mutation | Measure metanephrines; perform MRI of the brain, spinal cord, and abdomen; perform ophthalmoscopy | Measure metanephrines yearly; perform MRI of the brain, spinal cord, and abdomen; perform ophthalmoscopy; if no tumor found, monitor every 2 or 3 years |
| *SDHA*, *SDHB*, or *SDHD* mutation | Perform MRI of skull base and neck, thorax, retroperitoneum, and pelvis; alternatively, perform $^{68}$Ga-DOTATATE–PET–CT; also measure metanephrines | Measure metanephrines yearly; if a pheochromocytoma or paraganglioma was removed, perform MRI of the surgical region annually for yr 1–3; for body areas that had no tumors, perform MRI every 3 yr |
| *SDHC* or *SDHAF2* mutation | Measure metanephrines; perform MRI of skull base and neck or $^{68}$Ga-DOTATATE–PET–CT | If a paraganglioma or pheochromocytoma was removed, perform MRI of the surgical region annually for yr 1–3; for body areas that had no tumors, perform MRI every 3 to 5 yr |
| *MAX* or *TMEM127* mutation | Measure metanephrines; perform MRI of the abdomen or $^{68}$Ga-DOTATATE–PET–CT | Measure metanephrines yearly; if a pheochromocytoma or paraganglioma was removed, perform MRI of the surgical region annually for yr 1–3; perform MRI of the abdomen every 3 yr |
| Neurofibromatosis type 1 | Measure metanephrines | If hypertension or clinical symptoms develop, measure metanephrines |

* The term metanephrines refers to metanephrine and normetanephrine. CT denotes computed tomography, $^{18}$F-FDG $^{18}$F-fluorodeoxyglucose, $^{68}$Ga-DOTATATE $^{68}$Ga-labeled 1,4,7,10-tetraazacyclododecane–1,4,7,10-tetraacetic acid–octreotate, $^{123}$I-MIBG $^{123}$I-labeled metaiodobenzylguanidine, MRI magnetic resonance imaging, and PET positron-emission tomography.

reuptake inhibitors, and levodopa) could cause elevations in endogenous catecholamines, and clinical circumstances (e.g., acute illness) could lead to false positive test results. To effectively screen for catecholamine-secreting tumors, tricyclic antidepressants and other psychoactive agents should be tapered and discontinued at least 2 weeks before any hormonal assessments are performed.

For medical imaging of pheochromocytoma or paraganglioma (Table 1), three scenarios must be considered: first, typical symptoms combined with clearly elevated metanephrine or catecholamine levels; second, incidental detection of an adrenal or retroperitoneal mass; and third, a germline mutation in a susceptibility gene on molecular genetic testing and the associated syndrome. In scenario 1, the tumor has to be localized by means of either contrast-enhanced computed tomography (CT) or T2-weighted magnetic resonance imaging (MRI). Standard imaging includes the entire retroperitoneum,

since nearly all extraadrenal, catecholamine-secreting tumors are located in the retroperitoneum rather than in the pelvis or thorax. In scenario 2, CT without contrast material is important, because when CT attenuation is 10 Hounsfield units or less, a lipid-rich mass is present, which rules out the diagnosis of pheochromocytoma or paraganglioma, and biochemical testing is not needed.[15] For masses with CT attenuation of more than 10 Hounsfield units, biochemical testing must be performed. When biochemical testing is abnormal, cross-sectional imaging with contrast-enhanced CT or MRI is indicated. For scenario 3, see the discussion below on the care of asymptomatic germline mutation carriers and relatives.

Once a pheochromocytoma or paraganglioma has been identified, the need for additional total-body imaging is questionable.[16] Functional imaging (e.g., scintigraphy with $^{123}$I-labeled metaiodobenzylguanidine [MIBG] or positron-emission tomography [PET]–CT with $^{68}$Ga-labeled 1,4,7,10-tetraazacyclododecane–1,4,7,10-tetraacetic acid–octreotate [DOTATATE] or $^{18}$F-labeled L-dihydroxyphenylalanine [L-DOPA]) is very effective in localizing pheochromocytomas and paragangliomas (Fig. 1).[17] Furthermore, the results of $^{68}$Ga-DOTATATE–PET–CT correlate with biochemical measurements.[18] The main indication for functional imaging is the search for metastatic disease or identification of multiple chromaffin tumors.

In contrast, head-and-neck paragangliomas are usually manifested as painless, slowly growing masses, mainly as carotid-body tumors and vagal paragangliomas, or with conductive hearing loss and pulsatile tinnitus caused by jugulotympanic paragangliomas. Lower-cranial-nerve deficits are frequently seen in patients with advanced head-and-neck paragangliomas. Catecholamine hypersecretion is rarely found in such patients.[19,20]

## TREATMENT

Surgical resection of pheochromocytoma or paraganglioma is the cornerstone of therapy. Most of these tumors are resected on the basis of biochemical and CT or MRI documentation. The major questions concern the timing of surgery and the surgical approach.

Combined $\alpha$- and $\beta$-adrenergic blockade is standard treatment for patients with pheochromocytoma in order to control blood pressure and prevent intraoperative hypertensive crises.[21] Adrenergic blockade is typically accomplished with either a nonselective or a selective $\alpha$-adrenergic receptor antagonist (e.g., nonselective $\alpha$-adrenergic blockade with phenoxybenzamine, started at a dose of 10 mg by mouth two times a day and increased to up to 30 mg three times a day with adjustment for low-normal blood pressure for age; or selective $\alpha_1$-adrenergic blockade with doxazosin, started at a dose of 1 mg by mouth daily and increased to up to 10 mg twice daily as needed to achieve target blood-pressure levels), usually started at least 7 days before surgery.[1,22] Adrenergic blockade should be accompanied by a high-sodium diet (e.g., 5000 mg per day) and generous fluid intake (e.g., 2.5 liters per day).[1]

The $\beta$-adrenergic antagonist (e.g., oral administration of extended-release metoprolol at a starting dose of 25 mg by mouth once daily and increased to up to 100 mg twice daily as needed for a target average heart rate of 80 beats per minute) should be administered to control tachycardia after $\alpha$-adrenergic blockade has been effective in normalizing blood pressure, because with $\beta$-adrenergic blockade alone, severe hypertension or cardiopulmonary decompensation may occur as a result of unopposed $\alpha$-adrenergic stimulation.[22] However, postoperative sustained hypotension can be a complication of preoperative adrenergic blockade. In 2017, the concept of adrenergic blockade–free management was explored. A prospective study involving 110 patients who received preoperative treatment with $\alpha$-adrenergic blockade and 166 patients who did not revealed no relevant differences regarding maximal intraoperative systolic pressure, hypertensive episodes, or major complications.[23] In a patient who has not had adverse effects in association with long-term, episodic blood-pressure spikes without $\alpha$-adrenergic blockade, it seems unlikely that decompensation would occur in the few days before surgery, and nitroprusside-guided blood-pressure control during anesthesia may be justifiable. This opens the avenue for operation without further delay. There is no consensus in support of this approach, not even among us, and the 2014 pheochromocytoma guidelines issued by the Endocrine Society, as well as many experts, continue to recommend preoperative adrenergic blockade for all patients.[22]

Until 1996, the surgical approach for pheochromocytoma was open laparotomy and removal of the entire adrenal gland with the tumor.[24] On the basis of anecdotal evidence from many centers in the United States, Europe, and Asia, this procedure is still frequently performed. In 1996, Gagner and colleagues removed a pheochromocytoma endoscopically.[25] Over the subsequent decades, endoscopic technology with transabdominal or retroperitoneal access replaced the open surgical approach and became standard practice because of the shorter operative time, fewer intraoperative and postoperative complications, and shorter hospital stay.[26] Although it has been shown that pheochromocytomas with a diameter of 5 cm or more can be safely removed endoscopically,[27] their safe removal is still a matter of debate and should be considered on an individual basis according to tumor characteristics and surgical expertise. For bilateral adrenal pheochromocytoma, the concept of organ-sparing surgery was introduced in 1999 to avoid a postoperative requirement for glucocorticoid and mineralocorticoid replacement.[28] Approximately one third of one adrenal gland is sufficient for normal glucocorticoid and mineralocorticoid secretion.[29] Much like retroperitoneal tumors, tumors in unusual locations such as pelvic paravesicular and thoracic paravertebral regions have been removed with the use of minimally invasive surgery[30] (see the video, available with the full text of this article at NEJM.org; and the illustrative case in the Supplementary Appendix, available at NEJM.org).

*A video showing endoscopic removal of a thoracic paraganglioma is available at NEJM.org*

For a patient with a head-and-neck paraganglioma, finding the best treatment option often represents a challenge, and an individualized interdisciplinary approach is essential. Treatment options include surgery, stereotactic radiosurgery, external radiation therapy, and a wait-and-scan strategy. Determining the exact location and presence of tumor extension, as well as staging before any kind of treatment, is essential. Carotid-body tumors are most frequently classified with the use of the Shamblin classification, whereas the Fisch classification is used for jugulotympanic paragangliomas, both of which guide surgical management.[31,32] Surgical resection is the only potentially curative treatment option. With advanced cervical paragangliomas (Shamblin class III) and jugular paragangliomas (Fisch class C and D), lower-cranial-nerve deficits are frequently seen after surgery. Patients with these advanced tumors may have less treatment-related morbidity with the nonsurgical treatment options.

## SUSCEPTIBILITY GENES

The *RET* proto-oncogene was identified in 1993 as a risk factor for pheochromocytoma. Since then, at least 18 additional susceptibility genes have been reported.[33] In parallel with these investigations, gene-specific clinical data have been studied to guide clinical management strategies. Here, we delineate the most extensively studied clinical phenotypes (e.g., tumor location, number of tumors, and patient age at tumor manifestation) of the 10 currently clinically relevant syndromes (Table 2) that have been identified: MEN-2, caused by germline mutations of the *RET* proto-oncogene[34]; von Hippel–Lindau disease, caused by mutations in the *VHL* tumor-suppressor gene[35]; neurofibromatosis type 1, caused by mutations in the *NF1* tumor-suppressor gene[36]; paraganglioma syndromes 1 through 5, caused by mutations of the succinate dehydrogenase genes *SDHD* (syndrome 1),[37] *SDHAF2* (syndrome 2),[38] *SDHC* (syndrome 3),[39] *SDHB* (syndrome 4),[40] and *SDHA* (syndrome 5)[41]; and the hereditary pheochromocytoma syndromes caused by mutations in the genes encoding transmembrane protein 127 (*TMEM127*)[42] and MYC-associated factor X (*MAX*).[43] Other susceptibility genes, which have not yet undergone rigorous genotype–clinical outcome evaluation, include *EGLN1* (*PHD2*), *EGLN2* (*PHD1*), *KIF1B*, *IDH1*, *HIF2A*, *MDH2*, *FH*, *SLC25A11*, and *DNMT3A*.[44-53] Various publicly available gene-variation databases that are relevant to pheochromocytoma or paraganglioma susceptibility genes (e.g., LOVD-based *SDHx* variant database [www.LOVD.nl]) may be useful for clinicians and researchers.[54]

## PHEOCHROMOCYTOMA-ASSOCIATED SYNDROMES

The clinical features of pheochromocytoma-associated syndromes (Table 2) have been known for more than 100 years, starting with neurofibromatosis 1, von Hippel–Lindau disease, and MEN-2. With the identification of susceptibility genes containing various germline mutations, these and additional syndromes have been defined and differentiated. Unilateral or bilateral pheochro-

**Table 2. Characteristics of Pheochromocytoma-Associated Syndromes.***

| Gene | Syndrome | Nonchromaffin Tumors | Transmission | Adrenal Tumors | Head and Neck Tumors | Extraadrenal Tumors† | Multiple Tumors | Metastatic Tumors‡ | Family History§ |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *frequency (percent)* | | | | | |
| *VHL* | VHL | Retinal and CNS hemangioblastomas, RCC, pancreatic neuroendocrine tumor, ELST | Autosomal dominant | >50 | <1 | 10–24 | >50 | 1–9 | 25–50 |
| *NF1* | NF1 | Cutaneous neurofibromas, malignant peripheral-nerve-sheath tumor, breast cancer | Autosomal dominant | >50 | <1 | 1–9 | 25–50 | 1–9 | 10–24 |
| *RET* | MEN-2 | Medullary thyroid carcinoma, hyperparathyroidism | Autosomal dominant | >50 | <1 | <1 | >50 | <1 | 25–50 |
| *SDHA* | PGL5 | Rarely also pituitary adenoma, GIST, RCC | Autosomal dominant | 25–50 | 25–50 | 25–50 | 1–9 | 1–9 | 1–9 |
| *SDHB* | PGL4 | Rarely also pituitary adenoma, GIST, RCC | Autosomal dominant | 25–50 | 25–50 | 25–50 | 10–24 | 25–50 | 10–24 |
| *SDHC* | PGL3 | Rarely also pituitary adenoma, GIST | Autosomal dominant | 1–9 | >50 | <1 | 10–24 | Not reported | 10–24 |
| *SDHD* | PGL1 | Rarely also pituitary adenoma, GIST, RCC | Autosomal dominant, maternal imprinting | 10–24 | >50 | 10–24 | >50 | 1–9 | 25–50 |
| *SDHAF2* | PGL2 | | Autosomal dominant, maternal imprinting | 1–9 | >50 | Not reported | >50 | Not reported | >50 |
| *MAX* | No name | Rarely also RCC | Autosomal dominant | >50 | <1 | 1–9 | >50 | 1–9 | 25–50 |
| *TMEM127* | No name | | Autosomal dominant | >50 | 1–9 | <1 | 25–50 | 10–24 | 1–9 |

* For multiple endocrine neoplasia type 2 (MEN-2), von Hippel–Lindau disease (VHL), and neurofibromatosis type 1 (NF1), the frequencies of the characteristics shown are for patients with chromaffin tumors, since such tumors do not develop in all patients with these syndromes. CNS denotes central nervous system, ELST endolymphatic-sac tumor of inner ear, GIST gastrointestinal stromal tumor, HPT hyperparathyroidism, PGL paraganglioma syndrome (PGL1 through PGL5 denote paraganglioma syndromes 1 through 5), and RCC renal-cell carcinoma.
† These tumors consist of retroperitoneal, pelvic, and thoracic tumors.
‡ These tumors consist of metastatic pheochromocytoma and paraganglioma.
§ Shown is the frequency of a family history of components of the given syndrome.

mocytomas develop in up to 50% of patients with these syndromes.[55,56] Once the pathogenic *RET* mutation is identified in a patient with pheochromocytoma, clinicians must be aware that virtually all mutation carriers will have medullary thyroid carcinoma, whereas 20% of patients with MEN-2A, but not MEN-2B, will have hyperparathyroidism. It would be rare for a patient with MEN-2B (characterized chiefly by the *RET* p.M918T mutation) to first present with pheochromocytoma, since the typical components are manifested relatively early, even in infancy, such as early-onset medullary thyroid carcinoma; ganglioneuromas typically involving the tongue, lips, and eyelids; skeletal deformities (e.g., kyphoscoliosis and marfanoid habitus); joint laxity; and intestinal ganglioneuromatosis.[56]

By contrast, in patients with von Hippel–Lindau disease, especially type 2, pheochromocytomas and paragangliomas are common, may be part of the patient's initial presentation, even in early infancy, and are often associated with mutations in codons 98, 161, and 167.[33,57,58] Missense *VHL* mutations predict von Hippel–Lindau disease type 2. Truncating *VHL* mutations are often associated with renal-cell carcinoma and in rare cases are associated with pheochromocytoma (von Hippel–Lindau disease type 1). Other features of von Hippel–Lindau disease include retinal and central nervous system (CNS) hemangioblastomas and pancreatic neuroendocrine tumors.[59]

Neurofibromatosis 1 is characterized by neurofibromas, café au lait spots, axillary freckling, iris hamartomas (Lisch nodules), bony abnormalities, CNS gliomas, macrocephaly, and cognitive deficits, but pheochromocytomas and paragangliomas are present in only 1 to 3% of affected persons.[60-62] Patients with mutations of *SDHx*, *TMEM127*, or *MAX* generally have only pheochromocytomas and paragangliomas. A minority of *SDHx* mutation carriers have had gastrointestinal stromal tumors (GISTs), renal-cell carcinomas, or pituitary adenomas.[63-69] The autosomal dominant Carney–Stratakis syndrome is characterized by the association of pheochromocytoma, paraganglioma, or both with GISTs, and the so-called 3PAs syndrome (pheochromocytoma, paraganglioma, and pituitary adenoma) is associated with *SDHx* mutations.[70,71]

The concept of genetic predisposition may be confusing to patients and their families. Inheritance is autosomal dominant for pheochromocytoma-predisposing germline mutations. This means that offspring of a carrier have a 50% likelihood of inheriting the parent's mutation. However, *SDHD* and *SDHAF2* are maternally imprinted (the gene is not expressed from the maternal allele). This means that inheriting a mutation from the mother only rarely results in tumor development,[72] which explains why one or more generations appear to be skipped.

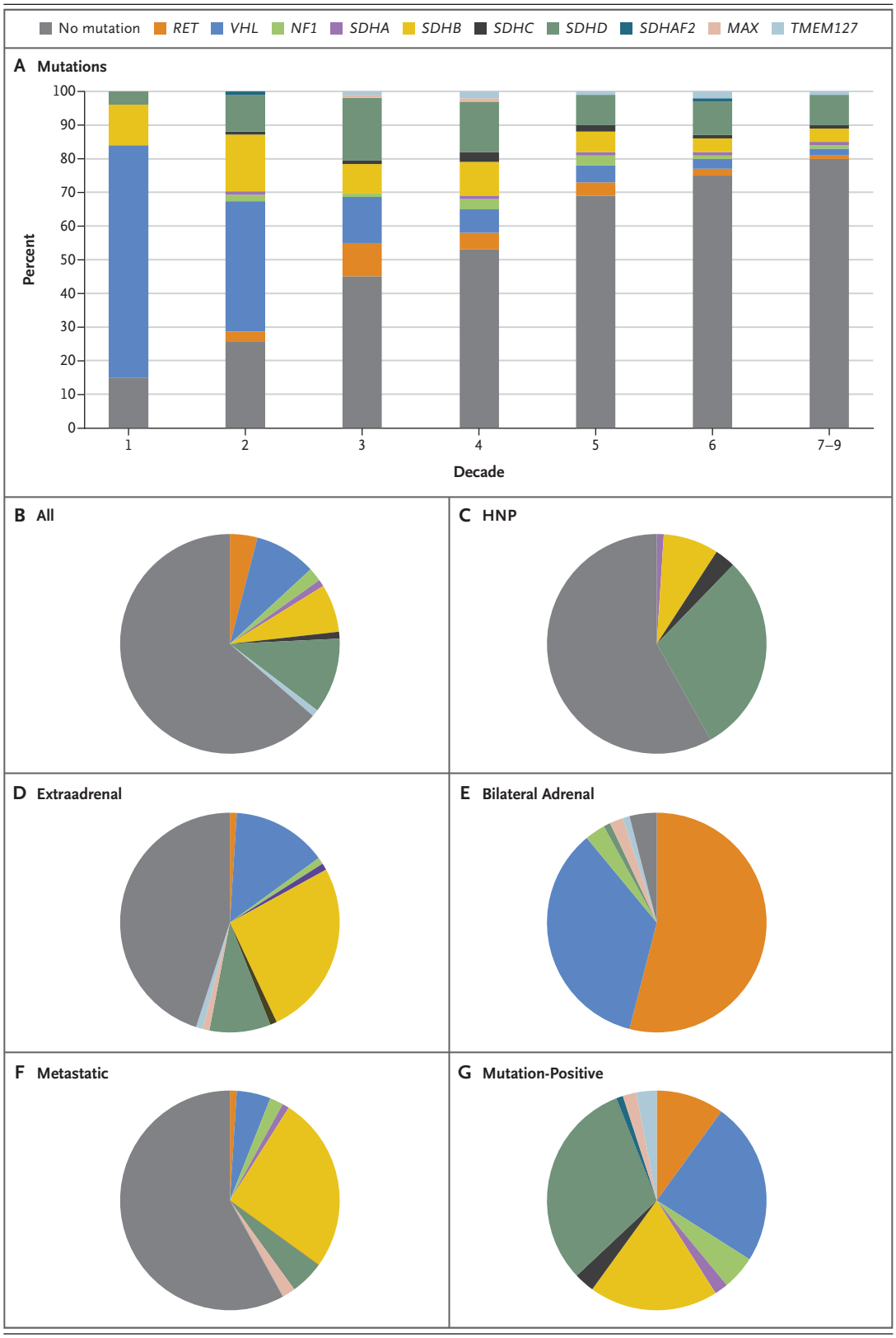
**Figure 2 (facing page). Frequencies of Gene Mutations in Patients with Pheochromocytoma or Paraganglioma.**

Data are from the joint Freiburg, Germany, and Padua, Italy, registries, which contain information about more than 3300 patients with chromaffin tumors.[7,55,61,73,74] Panel A shows the relative percentages of germline mutations among all mutation carriers, according to decade of age at presentation. In Panels B through G, the relative percentages of patients with mutations in various genes and patients without mutations are shown in pie charts. The overall percentages of mutation carriers are shown in Panel B; the percentages for head-and-neck paragangliomas (HNP), extraadrenal tumors, bilateral adrenal tumors, and metastatic tumors are shown in Panels C through F, respectively. In Panel G, the pie chart for mutation-positive tumors shows the relative frequencies of mutations in susceptibility genes among mutation carriers. Proportions of less than 1% are not shown.

## CLINICAL HALLMARKS OF HEREDITARY PHEOCHROMOCYTOMA AND PARAGANGLIOMA

In addition to family history, classic hallmarks of hereditary pheochromocytoma and paraganglioma include an early age at onset, extraadrenal and multiple primary tumors, and associated nonparaganglial tumors (Table 2 and Fig. 2). The age at diagnosis is about 15 years younger for syndromic pheochromocytomas and paragangliomas than for sporadic cases, with von Hippel–Lindau disease diagnosed at the earliest age.[74] Paraganglioma occurring in an unusual location, such as the organ of Zuckerkandl, thorax, or urinary bladder, should suggest the possibility that the patient has a syndrome associated with the tumor.

Anatomical locations of pheochromocytomas and paragangliomas differ widely among the syndromes (Table 2). Adrenal pheochromocytomas occur almost exclusively in patients with



germline mutations in *RET*. In contrast, in patients with mutations in *VHL*, *NF1*, *MAX*, and *TMEM127*, pheochromocytomas are common, but retroperitoneal paragangliomas are also observed. Patients with *SDHx* mutations frequently have head-and-neck paragangliomas, but pheochromocytomas and retroperitoneal paragangliomas are seen mainly in carriers of *SDHD*, *SDHB*, and *SDHA* mutations. The rare thoracic paragangliomas are associated mostly with mutations in *SDHB*, *SDHD*, or *VHL*. Multiple primary tumors often occur in patients with germline mutations in *RET*, *VHL*, *SDHD*, or *MAX*.

## METASTATIC PHEOCHROMOCYTOMA

The diagnosis of malignant pheochromocytoma is problematic. Pathologists have correlated histologic features such as growth patterns, mitoses, and atypia of cells and nuclei with malignant biologic features in pheochromocytomas and paragangliomas, and these findings form the basis for scoring systems (e.g., Pheochromocytoma of the Adrenal Gland Scaled Score [PASS] and Grading System for Adrenal Pheochromocytoma and Paraganglioma [GAPP]).[75,76] However, it remains difficult to predict the clinical behavior of individual tumors, and no single risk-stratification scheme is endorsed or in widespread use.[77,78] Only metastases are the proof for a malignant pheochromocytoma or paraganglioma, and the updated WHO classification of endocrine tumors has replaced the term "malignant pheochromocytoma" with "metastatic pheochromocytoma."[8] Metastases are located where chromaffin tissue is normally not found (e.g., lymph nodes, lung, liver, and bones), and frequently, metastases are not confirmed histologically but are instead documented on nuclear imaging.[79] When pheochromocytoma is the primary tumor, the typical metastatic sites are bones and lymph nodes, whereas when paraganglioma is the primary tumor, hepatic metastases are more common.[80] As a cautionary note, recurrent and metastatic disease may occur after intraoperative rupture of the tumor capsule, a complication that can lead to incurable tumor spread.[81,82]

Treatment options for metastatic pheochromocytoma include surgical resection, use of targeted radiolabeled carriers (e.g., $^{131}$I-MIBG or $^{90}$Y-DOTATATE and $^{177}$Lu-DOTATATE), thermal ablation, chemotherapy, and external irradiation. Surgical resection of as much tumor tissue as possible should be the initial approach.[83] Most patients with metastatic pheochromocytoma or paraganglioma have sporadic tumors, whereas among patients with heritable pheochromocytoma in whom metastatic disease develops, tumors caused by *SDHB* mutations account for up to 43% of cases, followed by *VHL*, *SDHD*, and *NF1* mutations.[84] Overall survival and disease-specific survival are surprisingly favorable, at 25 years and 34 years, respectively.[80]

## MAJOR NEEDS OF AFFECTED PATIENTS

The key concerns from the patient's perspective include early diagnosis, the effect of germline mutation on treatment, best surgical option, postoperative care guided by genetic features, and appropriate care and surveillance of relatives. Early diagnosis in patients with sporadic pheochromocytomas or paragangliomas relies on keen clinicians who recognize signs and symptoms of catecholamine-secreting tumors. Once the diagnosis is established, it is important to consider when genetic testing in the context of genetic counseling should be performed, since all patients with pheochromocytoma or paraganglioma should undergo genetic analysis. After detection of the mutation, the specific gene guides the tailoring of imaging studies and subsequent medical management (Table 1). For example, imaging studies are performed for medullary thyroid carcinoma if *RET* is mutated; for hemangioblastomas of the eyes and CNS and for tumors of the ears, kidneys, and pancreas if *VHL* is mutated; and for other chromaffin tumors or the rare kidney cancers, pituitary adenomas, or GISTs if *SDHx*, *MAX*, or *TMEM127* is mutated. An important question is whether screening for mutations should be performed before a pheochromocytoma is resected. Bilateral adrenal tumors can occur metachronously, with intervals of more than a decade, especially in patients with *RET* germline mutations.[55] Thus, operative planning for preservation of sufficient adrenal cortex will be guided by the results of gene testing.

Favorable surgical outcomes include complete tumor resection, no permanent complications,

limited postoperative pain, good cosmetic results, and a short hospital stay. Minimally invasive surgery performed by expert surgeons is key in achieving these goals.

An organized, long-term postoperative care program is essential for patients with germline mutations and should be in the hands of endocrinologists. The goals of such programs (Table 1) include surveillance and early detection of pheochromocytomas and paragangliomas and surveillance for and management of associated nonchromaffin tumors such as medullary thyroid carcinoma and primary hyperparathyroidism in patients with MEN-2; hemangioblastomas of the retina, cerebellum, and spine, along with renal-cell carcinomas and pancreatic neuroendocrine tumors, in patients with von Hippel–Lindau disease; peripheral-nerve-sheath tumors and breast cancer in patients with neurofibromatosis 1; and GISTs, renal-cell carcinomas, and pituitary tumors in patients with *SDHx* and *MAX* mutations.

## TESTING OF RELATIVES AND ASYMPTOMATIC GERMLINE-MUTATION CARRIERS

All first-degree relatives of a mutation carrier should be offered predictive (or cascade) testing in the context of genetic counseling. Testing of relatives results in a 50% likelihood of identifying mutation carriers, who are typically asymptomatic. These asymptomatic mutation carriers should be offered clinical surveillance and management specific to the gene (Table 1).[22] The age at onset and gene-specific, age-related penetrance guide management to look for pheochromocytoma, paraganglioma, and nonchromaffin tumors in order to identify these neoplasms at an early stage, when they are resectable.

It is important that both patients and clinicians understand the concept of disease penetrance. Some studies provide penetrance figures that include all mutation carriers of a given gene, whereas others provide only data subsets for the clinical type of a syndrome such as MEN-2A and MEN-2B, for asymptomatic carriers, or for specific gene mutations. Common features of all susceptibility genes for pheochromocytoma or paraganglioma are age dependency and incomplete penetrance; thus, disease does not develop in all carriers of gene mutations. For example, the mean penetrance of pheochromocytoma or paraganglioma in *RET* mutation carriers is 50% by the age of 44 years, whereas for carriers of mutations that increase susceptibility to von Hippel–Lindau disease type 2, the mean penetrance is 50% at the age of 52 years.[55,57] *SDHA* mutation penetrance is 39% by the age of 40 years in probands, as compared with only 10% at the age of 70 years, with a lifetime disease penetrance of 1.7% in mutation carriers who are relatives of probands.[73,85,86] Unlike *SDHA* mutation penetrance, *SDHB* mutation penetrance is similar in probands and relatives, at 22% by the age of 60 years, which also reflects lifetime penetrance, whereas lifetime penetrance is 8% for *SDHC* and 43% for *SDHD* by the age of 60 years.[85,87] Penetrance estimations are pending for *MAX*, *TMEM127*, and *SDHAF2* and for the newer genes.

Postoperatively, asymptomatic patients should undergo annual biochemical testing and cross-sectional digital imaging of the operated area annually for at least 3 years. The intervals for subsequent surveillance imaging remain open to debate, but at most specialized centers, imaging is performed every 2 to 3 years (Table 1). Special guidelines are available for postoperative surveillance of patients with asymptomatic extra-paraganglial tumors.[59,60,88]

## PREGNANCY IN PATIENTS WITH PHEOCHROMOCYTOMA OR PARAGANGLIOMA

Pheochromocytoma during pregnancy is regarded as one of the great challenges in medicine. Of paramount importance is interdisciplinary cooperation of obstetricians, endocrinologists, and surgeons. Pregnant patients have symptoms that are similar to those in patients who are not pregnant and may have had hypertension before becoming pregnant. The tumors can become symptomatic in any period of gestation. The diagnosis should be suspected clinically and confirmed biochemically. For imaging, ultrasonography and MRI without contrast material are recommended. Any nuclear medicine imaging is contraindicated. Pharmacologic treatment, mostly $\alpha$-adrenergic blockade, is a challenge, since uteroplacental circulation must be adequately preserved. Endoscopic removal of the tumor is the option of choice and has been repeatedly

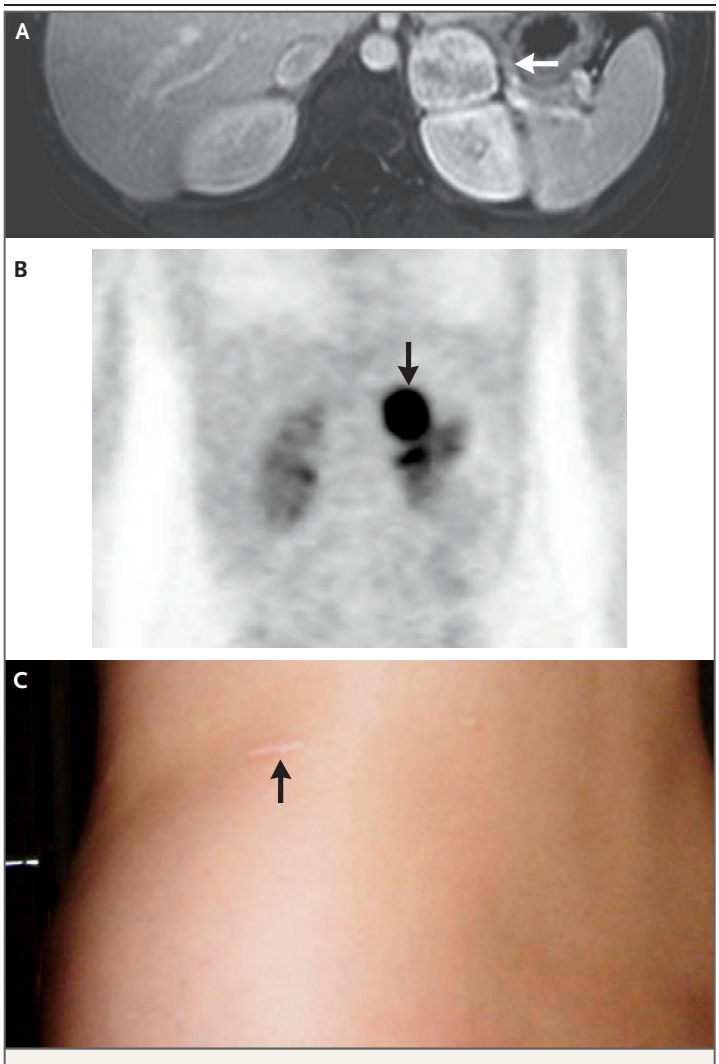



**Figure 3. Presymptomatic Resection of a Juxta-Adrenal Paraganglioma after Mutation Identification in an 18-Year-Old Woman.**

The patient's brother and father had pheochromocytoma. Genetic testing of the patient revealed germline mutation *VHL* c.298T→C. After the mutation was identified, the patient underwent VHL-informed MRI surveillance for von Hippel–Lindau disease, which revealed the juxta-adrenal paraganglioma. Five years later, the patient had an uneventful pregnancy and gave birth to a healthy child. In Panel A, MRI with gadolinium contrast medium (axial plane) shows the tumor (arrow). In Panel B, PET (frontal view) shows an $^{18}$F-L-DOPA–avid paraganglioma (arrow). Panel C shows the 1-cm scar (arrow) after endoscopy with single-incision access was used to remove the tumor.

performed with good outcomes for mother and child; the preferred timing is the second trimester of pregnancy.[89-91] An alternative approach is medical management during pregnancy and resection of the pheochromocytoma several weeks after delivery. Ideally, however, such tumors should be detected well before a pregnancy is planned. In this context, molecular genetics is an ideal tool. The proof of principle is shown in Figure 3, which presents the case of an 18-year-old woman who underwent resection of an asymptomatic paraganglioma after identification of a germline *VHL* mutation and had an uneventful pregnancy 5 years later.

## CONCLUSIONS

More than 130 years have passed since the first patient with documented pheochromocytoma was described. The evolution in diagnosis and treatment has been dramatic. The clinical presentation has evolved from classic symptoms of paroxysmal hypertension, palpitations, and headaches to the incidental discovery of an adrenal mass on cross-sectional imaging and detection of asymptomatic pheochromocytomas on the basis of germline-mutation testing. The biochemical methods for case detection have become more sensitive and specific. Effective tumor localization has been facilitated by advances in cross-sectional imaging with CT and MRI and in functional imaging with $^{123}$I-MIBG scintigraphy or $^{68}$Ga-DOTATATE-PET-CT. The development of minimally invasive surgical techniques has improved operative outcomes. Individualized treatment and tumor surveillance have been remarkably advanced on the basis of the identification of 19 genes in which germline mutations cause pheochromocytoma or paraganglioma.

These endocrine neoplasms are rare, and many clinicians will never encounter them. Nevertheless, it is important for clinicians to remain vigilant and to suspect, confirm, localize, and resect these tumors, because the associated symptoms and hypertension are curable with surgical removal. If the tumor is not diagnosed and removed, there is a risk of lethal paroxysm and cardiac disorders. These tumors have malignant potential, and early resection is the way to prevent metastatic disease.

The evidence to date shows that more than 40% of patients presenting with pheochromocytoma or paraganglioma, irrespective of age at onset and family history, carry germline mutations. Ideally, all persons presenting with these neoplasms should undergo gene-panel testing in the context of genetic counseling, so that pro-

spective gene-specific management can be initiated proactively. If a patient is found to carry a mutation, all first-degree relatives should be offered mutation-specific testing. Although gene-informed surveillance, with early detection and cure, is a triumph of gene-informed precision care, it would be much more desirable to provide a targeted preventive therapy in order to avoid the risks of cumulative radiation doses and contrast medium associated with current tumor-surveillance strategies.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Tobias Krauss, M.D., Juri Ruf, M.D., Stephan Meckel, M.D., and Martin Walz, M.D., for providing clinical, radiographic, and histologic images; and Giuseppe Opocher, M.D., Francesca Schiavi, Ph.D., and Birke Bausch, M.D., for providing genetic data presented graphically.

## REFERENCES

**1.** Young WFJ. Endocrine hypertension. In: Melmed S, Polonsky KS, Larsen PR, Kronenbreg HM. Williams textbook of endocrinology. 13th ed. Philadelphia: Elsevier, 2016:556-88.

**2.** Bausch B, Tischler AS, Schmid KW, Leijon H, Eng C, Neumann HPH. Max Schottelius: pioneer in pheochromocytoma. J Endocr Soc 2017;1:957-64.

**3.** Fränkel F. Ein Fall von doppelseitigem, völlig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis. Arch Pathol Anat Physiol Klin Med 1886;103:244-63.

**4.** Classics in oncology: a case of bilateral completely latent adrenal tumor and concurrent nephritis with changes in the circulatory system and retinitis: Felix Fränkel, 1886. CA Cancer J Clin 1984;34:93-106.

**5.** Neumann HPH, Vortmeyer A, Schmidt D, et al. Evidence of MEN-2 in the original description of classic pheochromocytoma. N Engl J Med 2007;357:1311-5.

**6.** Pick L. Das Ganglioma embryonale sympathicum (Sympathoma embryonale), eine typische bösartige Geschwulstform des sympathischen Nervensystems. Berlin Klin Wochenschr 1912;49:16-22.

**7.** Neumann HP. Pheochromocytoma. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's principles of internal medicine. 20th ed. New York: McGraw-Hill Education, 2018:2739-46.

**8.** Tischler AS, de Krijger RR, Gill AJ, et al. Phaechromocytoma: In: WHO classification of tumours of endocrine organs. 4th ed. Lyon, France: International Agency for Research on Cancer, 2017:183-90.

**9.** Berends AMA, Buitenwerf E, de Krijger RR, et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. Eur J Intern Med 2018;51:68-73.

**10.** Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005;366:665-75.

**11.** Gruber LM, Hartman RP, Thompson GB, et al. Pheochromocytoma characteristics and behavior differ depending on method of discovery. J Clin Endocrinol Metab 2019;104:1386-93.

**12.** Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287:1427-34.

**13.** Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003;88:553-8.

**14.** Neumann H, Berger DP, Sigmund G, et al. Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel–Lindau disease. N Engl J Med 1993;329:1531-8.

**15.** Canu L, Van Hemert JAW, Kerstens MN, et al. CT characteristics of pheochromocytoma: relevance for the evaluation of adrenal incidentaloma. J Clin Endocrinol Metab 2019;104:312-8.

**16.** van Berkel A, Pacak K, Lenders JW. Should every patient diagnosed with a phaeochromocytoma have a (1)(2)(3) I-MIBG scintigraphy? Clin Endocrinol (Oxf) 2014;81:329-33.

**17.** Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of $^{68}$Ga-DOTA-conjugated somatostatin receptor-targeting peptide PET in detection of pheochromocytoma and paraganglioma: a systematic review and metaanalysis. J Nucl Med 2019;60:369-76.

**18.** Amodru V, Guerin C, Delcourt S, et al. Quantitative $^{18}$F-DOPA PET/CT in pheochromocytoma: the relationship between tumor secretion and its biochemical phenotype. Eur J Nucl Med Mol Imaging 2018;45:278-82.

**19.** Erickson D, Kudva YC, Ebersold MJ, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. J Clin Endocrinol Metab 2001;86:5210-6.

**20.** Smith JD, Harvey RN, Darr OA, et al. Head and neck paragangliomas: a two-decade institutional experience and algorithm for management. Laryngoscope Investig Otolaryngol 2017;2:380-9.

**21.** Weingarten TN, Welch TL, Moore TL, et al. Preoperative levels of catecholamines and metanephrines and intraoperative hemodynamics of patients undergoing pheochromocytoma and paraganglioma resection. Urology 2017;100:131-8.

**22.** Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2014;99:1915-42.

**23.** Groeben H, Nottebaum BJ, Alesina PF, Traut A, Neumann HP, Walz MK. Perioperative $\alpha$-receptor blockade in phaeochromocytoma surgery: an observational case series. Br J Anaesth 2017;118:182-9.

**24.** Pheochromocytoma and paraganglioma treatment (PDQ): health professional version. Bethesda, MD: National Cancer Institute, 2010 (https://www.ncbi.nlm.nih.gov/books/NBK65873/).

**25.** Gagner M, Breton G, Pharand D, Pomp A. Is laparoscopic adrenalectomy indicated for pheochromocytomas? Surgery 1996;120:1076-9.

**26.** Walz MK, Alesina PF, Wenger FA, et al. Laparoscopic and retroperitoneoscopic treatment of pheochromocytomas and retroperitoneal paragangliomas: results of 161 tumors in 126 patients. World J Surg 2006;30:899-908.

**27.** Wang W, Li P, Wang Y, et al. Effectiveness and safety of laparoscopic adrenalectomy of large pheochromocytoma: a prospective, nonrandomized, controlled study. Am J Surg 2015;210:230-5.

**28.** Neumann HP, Bender BU, Reincke M, Eggstein S, Laubenberger J, Kirste G. Adrenal-sparing surgery for phaeochromocytoma. Br J Surg 1999;86:94-7.

**29.** Brauckhoff M, Gimm O, Thanh PN, et al. Critical size of residual adrenal tissue and recovery from impaired early postoperative adrenocortical function after subtotal bilateral adrenalectomy. Surgery 2003;134:1020-7.

**30.** Walz MK, Iova LD, Deimel J, et al. Minimally invasive surgery (MIS) in children and adolescents with pheochromocytomas and retroperitoneal paragangliomas: experiences in 42 patients. World J Surg 2018;42:1024-30.

**31.** Fisch U, Mattox D. Microsurgery of the skull base. New York: Thieme, 1988.

**32.** Shamblin WR, ReMine WH, Sheps SG, Harrison EG Jr. Carotid body tumor (chemodectoma): clinicopathologic analysis of ninety cases. Am J Surg 1971;122:732-9.
**33.** Neumann HP, Young WF Jr, Krauss T, et al. 65 Years of the double helix: genetics informs precision practice in the diagnosis and management of pheochromocytoma. Endocr Relat Cancer 2018;25(8):T201-T219.
**34.** Mulligan LM, Kwok JB, Healey CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 1993;363:458-60.
**35.** Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science 1993;260:1317-20.
**36.** Bausch B, Borozdin W, Neumann HP. Clinical and genetic characteristics of patients with neurofibromatosis type 1 and pheochromocytoma. N Engl J Med 2006;354:2729-31.
**37.** Baysal BE, Ferrell RE, Willett-Brozick JE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science 2000;287:848-51.
**38.** Hao HX, Khalimonchuk O, Schraders M, et al. SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. Science 2009;325:1139-42.
**39.** Niemann S, Müller U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. Nat Genet 2000;26:268-70.
**40.** Astuti D, Latif F, Dallol A, et al. Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. Am J Hum Genet 2001;69:49-54.
**41.** Burnichon N, Brière JJ, Libé R, et al. SDHA is a tumor suppressor gene causing paraganglioma. Hum Mol Genet 2010;19:3011-20.
**42.** Qin Y, Yao L, King EE, et al. Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. Nat Genet 2010;42:229-33.
**43.** Comino-Méndez I, Gracia-Aznárez FJ, Schiavi F, et al. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. Nat Genet 2011;43:663-7.
**44.** Gaal J, Burnichon N, Korpershoek E, et al. Isocitrate dehydrogenase mutations are rare in pheochromocytomas and paragangliomas. J Clin Endocrinol Metab 2010;95:1274-8.
**45.** Yang C, Zhuang Z, Fliedner SM, et al. Germ-line PHD1 and PHD2 mutations detected in patients with pheochromocytoma/paraganglioma-polycythemia. J Mol Med (Berl) 2015;93:93-104.
**46.** Yeh IT, Lenci RE, Qin Y, et al. A germline mutation of the KIF1B beta gene on 1p36 in a family with neural and nonneural tumors. Hum Genet 2008;124:279-85.
**47.** Comino-Méndez I, de Cubas AA, Bernal C, et al. Tumoral EPAS1 (HIF2A) mutations explain sporadic pheochromocytoma and paraganglioma in the absence of erythrocytosis. Hum Mol Genet 2013;22:2169-76.
**48.** Taïeb D, Yang C, Delenne B, et al. First report of bilateral pheochromocytoma in the clinical spectrum of HIF2A-related polycythemia-paraganglioma syndrome. J Clin Endocrinol Metab 2013;98:E908-E913.
**49.** Toledo RA, Qin Y, Srikantan S, et al. In vivo and in vitro oncogenic effects of HIF2A mutations in pheochromocytomas and paragangliomas. Endocr Relat Cancer 2013;20:349-59.
**50.** Cascón A, Comino-Méndez I, Currás-Freixes M, et al. Whole-exome sequencing identifies MDH2 as a new familial paraganglioma gene. J Natl Cancer Inst 2015;107(5):djvo53.
**51.** Castro-Vega LJ, Buffet A, De Cubas AA, et al. Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. Hum Mol Genet 2014;23:2440-6.
**52.** Remacha L, Currás-Freixes M, Torres-Ruiz R, et al. Gain-of-function mutations in DNMT3A in patients with paraganglioma. Genet Med 2018;20:1644-51.
**53.** Buffet A, Morin A, Castro-Vega LJ, et al. Germline mutations in the mitochondrial 2-oxoglutarate/malate carrier *SLC25A11* gene confer a predisposition to metastatic paragangliomas. Cancer Res 2018;78:1914-22.
**54.** Bayley JP, Devilee P, Taschner PE. The SDH mutation database: an online resource for succinate dehydrogenase sequence variants involved in pheochromocytoma, paraganglioma and mitochondrial complex II deficiency. BMC Med Genet 2005;6:39.
**55.** Castinetti F, Qi XP, Walz MK, et al. Outcomes of adrenal-sparing surgery or total adrenalectomy in phaeochromocytoma associated with multiple endocrine neoplasia type 2: an international retrospective population-based study. Lancet Oncol 2014;15:648-55.
**56.** Castinetti F, Waguespack SG, Machens A, et al. Natural history, treatment, and long-term follow up of patients with multiple endocrine neoplasia type 2B: an international, multicentre, retrospective study. Lancet Diabetes Endocrinol 2019;7:213-20.
**57.** Bender BU, Eng C, Olschewski M, et al. VHL c.505 T>C mutation confers a high age related penetrance but no increased overall mortality. J Med Genet 2001;38:508-14.
**58.** Neumann HP, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. Lancet 1991;337:1052-4.
**59.** Lonser RR, Glenn GM, Walther M, et al. Von Hippel-Lindau disease. Lancet 2003;361:2059-67.
**60.** Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997;278:51-7.
**61.** Bausch B, Borozdin W, Mautner VF, et al. Germline NF1 mutational spectra and loss-of-heterozygosity analyses in patients with pheochromocytoma and neurofibromatosis type 1. J Clin Endocrinol Metab 2007;92:2784-92.
**62.** Gruber LM, Erickson D, Babovic-Vuksanovic D, Thompson GB, Young WF Jr, Bancos I. Pheochromocytoma and paraganglioma in patients with neurofibromatosis type 1. Clin Endocrinol (Oxf) 2017;86:141-9.
**63.** Mannelli M, Canu L, Ercolino T, et al. Diagnosis of endocrine disease: SDHx mutations: beyond pheochromocytomas and paragangliomas. Eur J Endocrinol 2018;178:R11-R17.
**64.** Ozluk Y, Taheri D, Matoso A, et al. Renal carcinoma associated with a novel succinate dehydrogenase A mutation: a case report and review of literature of a rare subtype of renal carcinoma. Hum Pathol 2015;46:1951-5.
**65.** Malinoc A, Sullivan M, Wiech T, et al. Biallelic inactivation of the SDHC gene in renal carcinoma associated with paraganglioma syndrome type 3. Endocr Relat Cancer 2012;19:283-90.
**66.** Vanharanta S, Buchta M, McWhinney SR, et al. Early-onset renal cell carcinoma as a novel extraparaganglial component of SDHB-associated heritable paraganglioma. Am J Hum Genet 2004;74:153-9.
**67.** Hernandez KG, Ezzat S, Morel CF, et al. Familial pheochromocytoma and renal cell carcinoma syndrome: TMEM127 as a novel candidate gene for the association. Virchows Arch 2015;466:727-32.
**68.** Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. J Urol 2003;170:2163-72.
**69.** Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol 2012;188:2063-71.
**70.** Settas N, Faucz FR, Stratakis CA. Succinate dehydrogenase (SDH) deficiency, Carney triad and the epigenome. Mol Cell Endocrinol 2018;469:107-11.
**71.** Xekouki P, Brennand A, Whitelaw B, Pacak K, Stratakis CA. The 3PAs: an update on the association of pheochromocytomas, paragangliomas, and pituitary tumors. Horm Metab Res 2018 October 1 (Epub ahead of print).
**72.** Bayley JP, Oldenburg RA, Nuk J, et al. Paraganglioma and pheochromocytoma upon maternal transmission of SDHD mutations. BMC Med Genet 2014;15:111.
**73.** Bausch B, Schiavi F, Ni Y, et al. Clini-

cal characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. JAMA Oncol 2017;3:1204-12.
**74.** Neumann HPH, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med 2002;346:1459-66.
**75.** Kimura N, Takayanagi R, Takizawa N, et al. Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2014; 21:405-14.
**76.** Thompson LD. Pheochromocytoma of the Adrenal gland Scaled Score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol 2002;26:551-66.
**77.** Turchini J, Cheung VKY, Tischler AS, De Krijger RR, Gill AJ. Pathology and genetics of phaeochromocytoma and paraganglioma. Histopathology 2018;72:97-105.
**78.** Stenman A, Zedenius J, Juhlin CC. Over-diagnosis of potential malignant behavior in MEN 2A-associated pheochromocytomas using the PASS and GAPP algorithms. Langenbecks Arch Surg 2018; 403:785-90.
**79.** Timmers HJ, Chen CC, Carrasquillo JA, et al. Comparison of 18F-fluoro-l-DOPA, 18F-fluoro-deoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 2009;94:4757-67.
**80.** Hamidi O, Young WF Jr, Iñiguez-Ariza NM, et al. Malignant pheochromocytoma and paraganglioma: 272 patients over 55 years. J Clin Endocrinol Metab 2017;102: 3296-305.
**81.** Rafat C, Zinzindohoue F, Hernigou A, et al. Peritoneal implantation of pheochromocytoma following tumor capsule rupture during surgery. J Clin Endocrinol Metab 2014;99:E2681-E2685.
**82.** Thosani S, Ayala-Ramirez M, Palmer L, et al. The characterization of pheochromocytoma and its impact on overall survival in multiple endocrine neoplasia type 2. J Clin Endocrinol Metab 2013;98:E1813-E1819.
**83.** Strajina V, Dy BM, Farley DR, et al. Surgical treatment of malignant pheochromocytoma and paraganglioma: retrospective case series. Ann Surg Oncol 2017;24: 1546-50.
**84.** Amar L, Baudin E, Burnichon N, et al. Succinate dehydrogenase B gene mutations predict survival in patients with malignant pheochromocytomas or paragangliomas. J Clin Endocrinol Metab 2007;92: 3822-8.
**85.** Benn DE, Zhu Y, Andrews KA, et al. Bayesian approach to determining penetrance of pathogenic SDH variants. J Med Genet 2018;55:729-34.
**86.** van der Tuin K, Mensenkamp AR, Tops CMJ, et al. Clinical aspects of SDHA-related pheochromocytoma and paraganglioma: a nationwide study. J Clin Endocrinol Metab 2018;103:438-45.
**87.** Andrews KA, Ascher DB, Pires DEV, et al. Tumour risks and genotype-phenotype correlations associated with germline variants in succinate dehydrogenase subunit genes *SDHB*, *SDHC* and *SDHD*. J Med Genet 2018;55:384-94.
**88.** Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.
**89.** Donatini G, Kraimps JL, Caillard C, et al. Pheochromocytoma diagnosed during pregnancy: lessons learned from a series of ten patients. Surg Endosc 2018;32: 3890-900.
**90.** Quartermaine G, Lambert K, Rees K, et al. Hormone-secreting adrenal tumours cause severe hypertension and high rates of poor pregnancy outcome; a UK Obstetric Surveillance System study with case control comparisons. BJOG 2018;125:719-27.
**91.** van der Weerd K, van Noord C, Loeve M, et al. Endocrinology in pregnancy: pheochromocytoma in pregnancy: case series and review of literature. Eur J Endocrinol 2017;177:R49-R58.