THEMATIC REVIEW

65 YEARS OF THE DOUBLE HELIX

Genetics informs precision practice in the diagnosis and management of pheochromocytoma

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Abstract

Although the authors of the present review have contributed to genetic discoveries in the field of pheochromocytoma research, we can legitimately ask whether these advances have led to improvements in the diagnosis and management of patients with pheochromocytoma. The answer to this question is an emphatic *Yes*! In the field of molecular genetics, the well-established axiom that familial (genetic) pheochromocytoma represents 10% of all cases has been overturned, with >35% of cases now attributable to germline disease-causing mutations. Furthermore, genetic pheochromocytoma can now be grouped into five different clinical presentation types in the context of the ten known susceptibility genes for pheochromocytoma-associated syndromes. We now have the tools to diagnose patients with genetic pheochromocytoma, identify germline mutation carriers and to offer gene-informed medical management including enhanced surveillance and prevention. Clinically, we now treat an entire family of tumors of the paraganglia, with the exact phenotype varying by specific gene. In terms of detection and classification, simultaneous advances in biochemical detection and imaging localization have taken place, and the histopathology of the paraganglioma tumor family has been revised by immunohistochemical-genetic classification by gene-specific antibody immunohistochemistry. Treatment options have also been substantially enriched by the application of minimally invasive and adrenal-sparing surgery. Finally and most importantly, it is now widely recognized that patients with genetic pheochromocytoma/paraganglioma syndromes should be treated in specialized centers dedicated to the diagnosis, treatment and surveillance of this rare neoplasm.

Key Words

- brown adipose tissue
- white adipose tissue
- lipid metabolism
- oxidative stress

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Introduction

Over the last two decades, advances in the genetics of pheochromocytoma with the detection of germline (heritable) mutations in many new genes that predispose to this neoplasm and other extra-adrenal paraganglial tumors have led to improved molecular diagnosis, effective predictive testing of as yet unaffected relatives and informed gene-specific medical management.

A personal remembrance by Hartmut Neumann

I can remember well the publication in *Nature* in 1985 by Steven Reeders and coworkers (Oxford, UK) that located the gene encoding autosomal dominant polycystic kidney disease (ADPKD) on chromosome 16 using, then still novel, linkage analysis (Reeders *et al*. 1985). For a nephrologist with a central interest in the causes of disease, to me this was a first glimmer of modern medicine. The next day, in the morning meeting of all branches of the Department of Internal Medicine of the University of Freiburg, I raised my hand and gave a brief report of this exciting discovery. As these morning meetings were exclusively dedicated to newly admitted patients, such scientific news was never announced and my colleagues surely thought they had another 'addled' member.

I had joined the Department of Internal Medicine 2 years prior to that fateful morning, after a 5-year training program in pathology, with the goal of establishing an academic career. In my third week on staff, I was confronted with a patient with pheochromocytoma whose sister reported that her son had surgery for an adrenal pheochromocytoma at age 13 years and contralaterally at age 16 years and that she had herself undergone surgery for cerebellar hemangioblastoma the previous year. Something was clearly amiss in this family and by the next day I could say with confidence, 'You have Von Hippel–Lindau disease (VHL)'. I quickly wrote a case report detailing the family, which unfortunately later 'died' on the desk of an editor-in-chief of a German medical journal. In parallel, I made an appointment for a meeting with the entire VHL family in question, drew blood from affected and unaffected members of three generations and I went to the Institute of Human Genetics in order to persuade these colleagues to find the gene. Unfortunately, they failed to grasp the opportunity to create a new center for mapping the *VHL* gene. At that time only very few fully

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grasped the concept of mutations in genes associated with disease. It was also not yet known whether genes had a specific structure or how they could be found in an endless sea of DNA. Perhaps understandably, the Freiburg team was not prepared to take on the responsibility of clinical research in an entirely new field of human genetics. Therefore, alone and slightly frustrated, I nevertheless decided to take on this quest myself.

ADPKD was an important clinical challenge, since 20% of our patients on dialysis and numerous patients in the wards suffered from this disease. ADPKD was now a very attractive disease model because the cause was clear: inheritance. But what role could be played by clinical research? That was, and still is, the principal question. In other words: *Cui bono* – for whose benefit? In ADPKD, research programs pursued the use of ultrasonography to identify disease in relatives. However, it became immediately clear that in doing so asymptomatic ADPKD would be detected in young women and men. The dilemma that I now faced was that I clearly could not conceal the findings, but how could I answer their questions regarding preventative treatment options and hopes of avoiding the fate of mothers and fathers, which had dominated their family life? Inevitably, given the clinical options at the time, any answers I could provide would undoubtedly precipitate major psychological problems in young, mostly unmarried, women and men. With no good answers in sight and to avoid moral conflicts, I decided to refocus my activities in other directions.

However, in the first inherited pheochromocytoma syndrome that I came across, VHL, the situation was completely different. VHL is characterized by kidney cancer, pheochromocytoma and other neoplasias. Ambitious researchers could easily see the potential benefit for VHL families of early diagnosis in time for curative surgery for pheochromocytomas and other tumors. A lecture by Bruce Ponder from the University of Cambridge, UK at a symposium in Heidelberg also opened new avenues for research of another inherited pheochromocytoma-associated disorder and multiple endocrine neoplasia type 2 (MEN 2) (see review in this issue and MEN 2 anniversary issue). I subsequently visited his group in Cambridge, where I saw the memorable slogan: 'Fight Cancer on All Frontiers'. On my return to Freiburg, I collaborated with the Cambridge group, sending blood samples from patients and families with MEN 2. These mutual efforts resulted in joint publications in the genetics and management of pheochromocytoma, led by Charis Eng, then a postdoctoral fellow with Prof. Ponder (1992–1995) and myself. The mid-1980s saw the birth of the era of gene hunting, which included VHL and MEN 2. During this heady era of human molecular genetics, the heritable endocrine neoplasias and especially pheochromocytoma proved to be beneficiaries.

Terminology and clinical characteristics of tumors of the 'pheochromocytoma family'

There is, unfortunately, still little consistency and systematic use of terminology and abbreviations for the paraganglia family of tumors. The World Health Organization (WHO) classification reserves the term pheochromocytoma exclusively for tumors of the adrenal medulla (Lloyd *et al.* 2017). The word *pheochromocytoma* is of Greek origin, but its usage only dates back to 1912 (Pick 1912). The last syllables *cytoma* means growing cells or tumor, the middle syllables *chromo* refer to the former usage of a special chromate-containing stain and *pheo* refers to the classic brown appearance after exposure to chromate staining (Bausch *et al.* 2017*b*). In contrast, *paraganglioma* is a terminology of pathoanatomy, meaning a tumor of the paraganglia, which are formed by the aggregation of the cell nuclei of the widespread autonomic nervous system, of which the adrenal medulla is the largest. A strict separation of these terms in clinical use as suggested by specialists is sophisticated and best recognized in everyday use of general physician, surgeons, internists and also congress announcements where pheochromocytoma is still used for all such tumors including their symptoms.

A distinct group of these tumors is located in the neck and the skull base. They originate from the parasympathetic paraganglia, mainly the carotid body, but also from the tympanic, jugular, vagal or other paraganglia. All these tumors, for which the abbreviations HNPGL or HNP are used, are mostly asymptomatic due to a lack of catecholamine overproduction and are very rarely metastatic. Only single cases of catecholamine-producing HNPs, mainly of the carotid body, are reported (Niemann *et al.* 2003, Zeng *et al.* 2013, Elshafie *et al.* 2014). Of note, however, virtually all clinicians still use the term pheochromocytoma when speaking of a tumor with symptoms of catecholamine overproduction, including those located outside the adrenal glands (Neumann 2018).

The incidence of pheochromocytoma and HNP based on nearly 1500 patients who were diagnosed and histopathologically confirmed between 1995 and 2015 was 0.04–0.21 per 100,000 person-years (Berends *et al.* 2018). The incidence increased in the latter years of this study mainly by detection of the tumors in older age and a smaller tumor size at diagnosis.

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Pheochromocytoma is a rare and fascinating tumor, and there is virtually no patient who does not attract special interest. Besides being rare, interesting aspects include the broad spectrum of signs and symptoms, the frequently long delay before diagnosis, and the frequent young age of the patients. Paroxysms of headache, palpitations, tachycardia, profuse sweating and hypertension are the main signs and symptoms; but, the list of clinical presentations is long and also includes metabolic deterioration and psychiatric imbalance with depression or panic attacks (Neumann 2018). Due to the use of genetic testing and the widespread use of computed imaging, an increasing proportion of patients with pheochromocytoma are detected before the development of symptoms. About 10% of catecholamine-producing tumors are located outside the adrenals – mostly found in the vicinity of the adrenals and the organ of Zuckerkandl. Extra-adrenal tumors occur, though more rarely, also in the pelvis adjacent to the rectum, vagina or bladder; contractions of the bladder may indeed induce hypertensive crises. Tumors may also occur in the thorax, originating from the sympathetic chain or the mediastinal paraganglia (Turchini *et al.* 2018).

Pheochromocytomas have been found in patients in an age range of as young as age 4 to over 80 years of age, but the majority of tumors become symptomatic in mid-adulthood, during the 4th or 5th decades. Another feature observed in about 10% of patients is multifocal tumors, sometimes located in both adrenal glands, sometimes with both adrenal and extra-adrenal locations or with only extra-adrenal locations.

Metastatic pheochromocytomas are rare. About 10% of intra-adrenal tumors metastasize in comparison to almost 40% of extra-adrenal sympathetic PGLs (Lloyd *et al.* 2017). Tumor histology is a poor predictor of metastatic potential and no scoring system is unequivocally accepted. Current thinking is that all pheochromocytomas have some metastatic potential and the terms metastatic and non-metastatic pheochromocytoma are therefore preferred over the use of benign and malignant (Lloyd *et al.* 2017).

Pheochromocytoma-associated syndromes and hereditary pheochromocytoma

There are interesting patterns and variations in the leading features of the pheochromocytoma genetic syndromes. Prior to the advent of genetic testing, classic reports included (i) remarkable coincidences of several relatives with pheochromocytomas or (ii) patients where pheochromocytoma is but one component of the presentation, which includes other tumorous and non-tumorous manifestations or (iii) pheochromocytoma in one member of a given family and a completely different apparently coincident symptomatic tumor in a relative. DNA analyses were introduced during the late 1980s and remain the key determinant in a given patient as to whether a pheochromocytoma is genetic (i.e., heritable) or not. This became particularly evident in patients under 18 years of age demonstrating germline mutations of the *RET*, *VHL*, *NF1*, *SDHA*, *SDHB*, *SDHC* and *SDHD* genes in 80% of such patients; the most frequently mutated genes are *VHL* followed by *SDHB* and *SDHD* (Bausch *et al.* 2014). The major characteristics of the ten so far well-described syndromes are shown in Tables 1 and 2.

Multiple endocrine neoplasia type 2

DNA technology first linked genetic pheochromocytoma to the *RET* proto-oncogene (Mulligan *et al.* 1993). The gene is located on chromosome 10 (10q11.21) and contains 21 exons. Germline mutations in the *RET* proto-oncogene cause multiple endocrine neoplasia type 2

Table 1 Frequencies of clinical characteristics of pheochromocytomas/paragangliomas in patients with germline mutations in *MAX*, *NF1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *VHL* and *TMEM127*.

Mutated gene	Adrenal tumors	Head and neck tumors	Extra-adrenal retroperitoneal, pelvic or thoracic tumors	Multiple tumors	Family history in probands for components of the given syndrome
MAX	++++	(+)	+	++++	+++
NF1	++++	(+)	+	+++	++
RET	++++	(+)	(+)	++++	+++
SDHA	+++	+++	+++	+	+
SDHB	+++	+++	+++	++	++
SDHC	+	++++	(+)	++	++
SDHD	++	++++	++	++++	+++
VHL	++++	(+)	++	++++	+++
TMEM127	++++	+	(+)	+++	+

Frequency definitions: ++++=>50%; +++=25–50%; ++=11–24%; +=1–10%; (+)=<1%.

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Table 2 Key characteristics of 10 pheochromocytoma-associated syndromes.

Gene	Syndrome	Principle tumors	Other rare tumors	Prevalence of pheochromocytoma/HNP	Age at Dx mean (range)	Penetrance (%/by age)	Penetrance for pheochromocytoma/ HNP in non-probands (%/by age)	Metastatic pheochromocytoma (%)	Transmission
VHL	VHL	Retinal and CNS hemangioblastomas, RCC, pheochromocytoma, pancreatic NET	Endolymphatic Sac tumor	10–20%/rare	30 (5–58)	87%/50 year	Not reported	4	AD
NF1	NF1	Cutaneous NF, malignant peripheral nerve sheath tumor	Breast cancer	0.1–5.7%/rare	41* (14–67)	50%/42 year 78%/50y	Not reported	7	AD
RET	MEN2	MTC, pheochromocytoma HPT		47%/Rare	37 (12–89)	43%/50 year	Not reported	0.4	AD
SDHA	PGL5	Pheochromocytoma/HNP	PitAd, GIST, RCC	65%⁺/35%⁺	28* (8–76)	75%/50 year	13%/40 year	9	AD
SDHB	PGL4	Pheochromocytoma/HNP	PitAd, GIST, RCC	53%⁺/43%⁺	34* (7–68)	40%/70 year	22%/60 year	30	AD
SDHC	PGL3	Pheochromocytoma/HNP	PitAd, GIST	12%/92%⁺	29 (15–40)	81%/50 year	Not reported	0	AD
SDHD	PGL1	Pheochromocytoma/HNP	PitAd, GIST, RCC	20%⁺/93%⁺	36 (5–96)	75%/40 year	43%/60 year	5	AD (mi)
SDHAF2	PGL2	HNP		0/100%⁺		88%/45 year	Not reported	Not reported	AD (mi)
MAX	No name	Pheochromocytoma/HNP	RCC	100%⁺/0	36* (13–80)	88%/50 year	22%/40 year	2	AD
TMEM127	No name	Pheochromocytoma/HNP		78%⁺/22%⁺	47* (16–76)	67%/50 year	33%/40 year	10	AD

*Median; ⁺percent of all paraganglial tumors.
AD, autosomal dominant; CNS, central nervous system; Dx, diagnosis; GIST, gastrointestinal stromal tumor; HNP, head and neck paraganglioma; HPT, hyperparathyroidism; MEN2, multiple endocrine neoplasia type 2; mi, maternal imprinting; MTC, medullary thyroid carcinoma; NET, neuroendocrine tumor; NF, neurofibromas; NF1, neurofibromatosis type 1; PGL, paraganglioma syndrome; PitAd, pituitary adenoma; RCC, renal cell carcinoma; VHL, von Hippel–Lindau disease.

(MEN 2). The components of MEN 2 include medullary thyroid carcinoma (MTC) and pheochromocytoma. The prevalence is estimated to be approximately 1/40,000. Clinical subtypes are MEN 2A with hyperparathyroidism and MEN 2B with cutaneous and skeletal anomalies. Mutations in only a few codons in the *RET* proto-oncogene, mainly located in exons 10, 11, 13, 14 and 16, predispose to MEN 2 (Eng *et al*. 1995, 1996, Gimm *et al*. 1997). The largest known population-based registry, with 1210 patients with MEN 2, was published in 2014 (Castinetti *et al*. 2014). Pheochromocytoma was detected in 563 (47%) patients: 54% developed symptomatic pheochromocytoma after a prior diagnosis of MTC; in 30% pheochromocytoma was detected at the same time as MTC and in 16% pheochromocytoma was diagnosed before MTC. Overall, 388 (69%) of the 563 patients had symptomatic pheochromocytoma. Bilateral adrenal pheochromocytomas were identified in 61% (Fig. 1); 50% of these patients had unilateral pheochromocytoma by age 44 years and bilateral by age 61 years. Extra-adrenal pheochromocytoma occurred in only 1% of patients, all of which were located close to the adrenal glands. Only two patients (0.4%) had metastatic pheochromocytomas. The germline *RET* mutations were all of the missense type and were mainly located in exons 10 (10%), 11 (85%) and 16 (5%) of *RET*. Few other large cohorts have been reported over the last 5 years. Mucha *et al*. reported that the penetrance and age at diagnosis of pheochromocytoma were correlated with medullary thyroid carcinoma aggressiveness, and both correlated with *RET* mutation position: for instance, the penetrance was estimated at 47% in *RET* exon 11 vs 30% in exon 10 carriers (Mucha *et al*. 2017). Castinetti *et al*. showed that even in *RET* codon 634 mutation (the most highly penetrant) carriers, the penetrance could be highly variable depending on the geographical area of the patient's origin, suggesting the roles of yet-unknown modifiers (Castinetti *et al*. 2017), while Siqueira *et al*. showed that *RET* polymorphisms had a modifying effect on the age at pheochromocytoma diagnosis (Siqueira *et al*. 2014). Of note, despite the fact that pheochromocytoma can be quite frequent in *RET* mutation carriers, Thosani *et al*. emphasized the lack of increased mortality in *RET* mutation carriers regularly screened for pheochromocytoma (Thosani *et al*. 2013).

Figure 1
Axial image from an abdominal CT scan showing bilateral adrenal pheochromocytomas (arrows) in a 42-year-old patient with MEN 2. Following bilateral adrenalectomy, the patient has surgically induced Addison's disease.

Von Hippel–Lindau disease

VHL is characterized by tumors in more than 6 organs and include retinal hemangioblastomas (von Hippel disease) and hemangioblastomas of the central nervous system (CNS), mainly in the cerebellum (Lindau disease); renal clear cell cancer (RCC); pheochromocytoma; pancreatic neuroendocrine tumors; endolymphatic sac tumors of the inner ear and cysts and cystadenomas of the pancreas, epididymis and broad ligament (Lonser *et al*. 2003). The *VHL* gene is located on chromosome 3 (3p25-26) and contains 3 exons (Latif *et al*. 1993). The germline mutations are distributed over the whole *VHL* gene, although hot spots are found at codons 167 and 161. A broad spectrum of mutations has been observed, including missense, nonsense, intra-exonic insertions and deletions, splice site and large deletions and rearrangements (Zbar *et al*. 1996). Missense mutations are the most frequent cause of VHL-associated with pheochromocytoma. VHL was especially interesting from the RCC perspective and the fact that the most frequently observed sporadic form of RCC shows somatic mutations of the *VHL* gene, thus uncovering the etiology and pathogenesis (Gnarra *et al*. 1994).

A recent country-wide study from Denmark showed a prevalence of VHL of 1/46,900, a birth incidence of 1/27,300 and a penetrance of 87% at age 60 years; of note, 20% mutation carriers were asymptomatic at age 60 years (Binderup *et al*. 2017*a*). Estimated life expectancies of VHL patients born in 2000 are 67 years for males and 60 for females; CNS hemangioblastoma was the dominate cause of death (Binderup *et al*. 2017*b*). In the Freiburg-VHL-Registry that includes 265 VHL patients with pheochromocytomas, the tumor was symptomatic in 77% of the patients, and the most frequent

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pheochromocytoma was the dominating or even only manifestation of (Bender *et al.* 2001). Extra-adrenal and multiple, often bilateral, adrenal pheochromocytomas are not infrequent in VHL (Table 1) (Bausch *et al.* 2014, Aufforth *et al.* 2015), but thoracic paraganglial tumors and HNPs are very rare (Fig. 2). Overall, 51% of the patients had more than one paraganglial tumor, and 87% of these patients had their tumor detected by age 50 years. Only 4% of the patients had metastatic pheochromocytomas (Table 1). Of note, 55% of the patients had exclusively paraganglial tumors. Calculated optimal surveillance intervals for pheochromocytomas in VHL are about 4 years but shorter for other VHL-associated tumors (Kruizinga *et al.* 2014) and clinical investigations for VHL-associated pheochromocytomas are recommended to be initiated at an age of 5 years (Aufforth *et al.* 2015).

Neurofibromatosis type 1

The two largest reported series for neurofibromatosis type 1 (NF 1)-associated pheochromocytoma are the Freiburg International NF 1 pheochromocytoma study and the Mayo Clinic pheochromocytoma and PGL registry (Bausch *et al.* 2006, Gruber *et al.* 2017). Only 2% of patients in the Freiburg study, and 1.2% of patients in the Mayo Clinic registry, have symptomatic paraganglial tumors and NF 1. Other NF 1 patient registries report pheochromocytomas in 0.1–5.7% of NF 1 patients (Gutmann *et al.* 1997, Gruber *et al.* 2017). Thus, NF 1-related pheochromocytomas are relatively uncommon.

Of the patients with NF 1 and pheochromocytoma in the Freiburg and Mayo registries, respectively, all except one patient had adrenal tumors. Bilateral adrenal tumors were present in 25% and 17%, respectively. Extra-adrenal paraganglial tumors were detected in only 2 patients from both registries. Metastatic pheochromocytomas were found in 7% of the patients in the two databases. In the Freiburg registry, 50% of the NF 1 patients with pheochromocytoma had such tumors by age 42 years and 78% by age 50 years. In the Mayo registry, the median age at pheochromocytoma diagnosis was 41 years (range, 14–67), although 4 patients were aged 21 years or younger.

In the Freiburg registry, all patients had multiple cutaneous neurofibromas, and other observed tumors included breast cancer, lung cancer and medullary thyroid cancer, each in one different individual. Only 27% of the patients had a family history for NF 1 and in only one case was a pheochromocytoma known in a relative. The detected mutations were missense mutations in 16%, nonsense mutations in 22%, frameshift mutations in 32%, splice site in 20% and large deletions/rearrangements in 10% of patients, but without detection of NF 1 mutations in apparently sporadic pheochromocytomas (Bausch *et al.* 2006, 2007). However, more recently, a case with sporadic pheochromocytoma and a *NF1* germline mutation has shown that 'dogmas' may have exceptions (Gieldon *et al.* 2018).

Paraganglioma syndromes type 1–5

The PGL syndromes (PGLs) were characterized over the decade from 2000 to 2010 (Baysal *et al.* 2000, Niemann & Muller 2000, Astuti *et al.* 2001, Hao *et al.* 2009, Bayley *et al.* 2010, Burnichon *et al.* 2010). All five syndromes are associated with mutations that affect genes encoding subunits of the enzyme succinate dehydrogenase (SDH). The term *PGL syndromes* was introduced when the first detected susceptibility gene (*SDHD*, PGL1) was found in families with head and neck PGLs (HNPs) (Baysal *et al.* 2000). Another family with exclusively HNPs was described by van Baars *et al.* in 1982, but the gene *SDHAF2* was not identified until 2010 and is now referred to as PGL2 (van Baars *et al.* 1982, Bayley *et al.* 2010). The PGL3 syndrome is caused by mutations of *SDHC*, PGL4 by mutations in *SDHB* and PGL5 by mutations in *SDHA*. Studies of patients with paraganglial tumors at other locations revealed that retroperitoneal, pelvic and thoracic paraganglial tumors also showed germline mutations of any of the SDH genes (*SDHx*). Germline mutations in one of the SDH genes, especially the *SDHD* and *SDHB* gene, are found in 8–10% of hereditary pheochromocytoma and HNP (Neumann *et al.* 2002, Curras-Freixes *et al.* 2015).

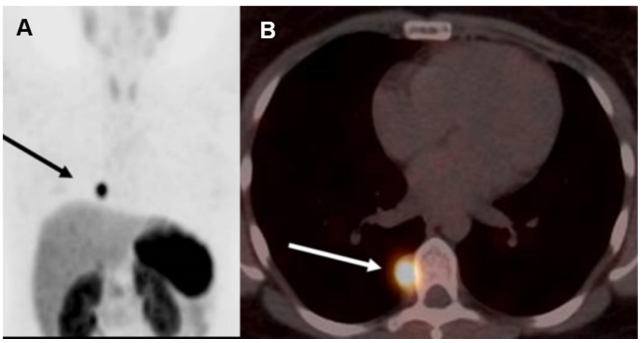

Figure 2
Imaging studies showing a thoracic paravertebral pheochromocytoma (arrows) in a 25-year-old woman with VHL. (A) Coronal maximum-intensity projection of [^{68}Ga] DOTATATE–PET/CT. (B) Axial fused image. The paravertebral tumor was removed by endoscopic surgery.

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PGL1–PGL5 are transmitted autosomal dominantly, but in PGL1 and PGL2 tumors (although fewer families have been described with PGL2 vs PGL1) virtually never occur in mutation carriers who inherited the mutation from their mothers (maternal imprinting). The key information is presented in Table 2.

Paraganglioma syndrome type 1 (*SDHD*)

The *SDHD* gene is located on chromosome 11 (11q23) and contains 4 exons. Germline mutations are broadly distributed across the *SDHD* gene. So far, only one founder mutation has been described: p.Asp92Tyr (Hensen *et al.* 2012). So far, 148 disease-causing mutations associated with PGL syndrome type 1 have been described in the literature. A broad spectrum of mutations is observed: 25% missense, 14% nonsense, 41% small insertions and/or deletions, 7% variants affecting splicing and 13% large deletions and rearrangements (https://databases.lovd.nl/shared/genes/SDHD). Family pedigrees show that patients who inherit the mutation from their mothers almost never develop pheochromocytomas or HNPs (Taschner *et al.* 2001, Neumann & Erlic 2008, Burnichon *et al.* 2017). HNPs and multifocal tumors characterize PGL1. Pheochromocytoma are less frequently observed (Neumann *et al.* 2004, Schiavi *et al.* 2005, Benn *et al.* 2006, Ricketts *et al.* 2010). The life-time penetrance is high with manifestation of the disease in 75% of the mutation carriers at age 40 years (Benn *et al.* 2006). Recent data for non-probands showed a penetrance of 43% at age 60 years (Andrews *et al.* 2018).

In the Freiburg International Registry and the French study (Burnichon *et al.* 2009, Neumann 2018), a total of 284 subjects were included. HNPs were present in 93% of the patients and extra-adrenal or thoracic tumors in 20%. Multiple tumors were detected in 68% of the patients, and metastatic disease in 5% of the patients. The range of age at diagnosis was 5–96, mean 36 years. A single paraganglial tumor without a family history was observed in about 30% of mutation carriers. Tumors outside the paraganglia are rare in PGL1. These include RCC (Casey *et al.* 2017*b*), pituitary adenomas (Ricketts *et al.* 2010, Xekouki & Stratakis 2012, Evenepoel *et al.* 2015, Xekouki *et al.* 2015) and gastrointestinal stromal tumors (GISTs) (Pasini *et al.* 2008, Miettinen & Lasota 2013).

Paraganglioma syndrome type 2 (*SDHAF2*)

PGL2 is caused by germline mutations of the *SDHAF2* gene (Hao *et al.* 2009), which is located on chromosome 11 (11q13) and contains 4 exons. Similarly to *SDHD* and unlike other SDH genes, patients who inherit the mutation from their mothers do not develop pheochromocytomas or HNPs. Only 37 patients have been described, which include 34 from the same large Dutch pedigree (Hensen & Bayley 2011). A separate but unrelated Spanish family has also been identified (Bayley *et al.* 2010, Kunst *et al.* 2011, Casey *et al.* 2014, Curras-Freixes *et al.* 2015, Bausch *et al.* 2017*a*). So far, only five mutations have been reported in the literature (https://databases.lovd.nl/shared/genes/SDHAF2). All patients with bona fide pathogenic mutations show HNPs, typically multiple carotid body tumors. Three patients with unilateral adrenal pheochromocytoma have been described, but all carried relatively common SNPs that are unlikely to be related to disease. But of note, clinical characteristics and the mode of inheritance are based on only a very limited number of index cases and families.

Paraganglioma syndrome type 3 (*SDHC*)

PGL3 is caused by germline mutations of the *SDHC* gene, which is located on chromosome 1 (1q23.3) and contains 6 exons. A mutation hot spot at p.Arg133Ter has been described; otherwise, germline mutations are randomly distributed over the *SDHC* gene (Bourdeau *et al.* 2016). Thus far, 46 disease-causing mutations have been published: 39% missense, 13% nonsense, 15% small insertions and/or deletions, 11% variants affecting splicing and 22% large deletions and rearrangements (https://databases.lovd.nl/shared/genes/SDHC). Pooling of the clinical data from the Freiburg-International-Pheochromocytoma-Paraganglioma-Registry (Neumann 2018), the Ann Arbor study (Else *et al.* 2014) and the French study (Burnichon *et al.* 2009) together include 61 patients. HNPs were present in 92% of the patients, mostly carotid body tumors. Four percent of the patients had retroperitoneal tumors and 8% had thoracic tumors. Multiple paraganglial tumors were detected in 25% of the patients, but none had a metastatic tumor. Eighty-one percent of the patients had tumors by age 50 years. Of particular note, 87% of the patients showed HNPs exclusively. The majority of the patients had only a single tumor and no family history. Extra-paraganglial tumors in patients with *SDHC* germline mutations have been renal cell carcinoma in 4 cases (Malinoc *et al.* 2012, Ricketts *et al.* 2012, Gill *et al.* 2013, 2014) and GIST and pituitary adenoma in 1 case (Miettinen & Lasota 2013, De Sousa *et al.* 2017).

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Paraganglioma syndrome type 4 (*SDHB*)

PGL4 is caused by mutations of the *SDHB* gene, which is located on chromosome 1 (1p36.1-p35) and contains eight exons. Most germline mutations are randomly distributed over the *SDHB* gene; only two hot spots have been described: SDHBc.423+1G>A and the Dutch founder large deletion in exon 3 (Bayley *et al.* 2009, Niemeijer *et al.* 2017). To date, 226 disease-causing mutations associated with PGL 4 have been described in the literature: 40% missense, 8% nonsense, 28% small insertions and/or deletions, 11% variants affecting splicing and 13% large deletions/duplications (https://databases.lovd.nl/shared/genes/SDHB). In contrast to PGL1, PGL4 is associated with pheochromocytomas, extra-adrenal thoracic or abdominal and metastatic tumors (Neumann *et al.* 2004, Benn *et al.* 2006, Ricketts *et al.* 2010). The Freiburg International and the French Registries (Burnichon *et al.* 2009, Neumann 2018) include 287 patients with *SDHB* germline mutations. Of note, 53% had extra-adrenal retroperitoneal, pelvic and/or thoracic tumors and 43% had HNPs. Multiple tumors occurred in 13% and metastatic tumors in 30% of the patients (Fig. 3). Age range at diagnosis was 8–78 years. Family history was positive for paraganglial tumors in 19% of patients. The life-time penetrance is low with penetrance estimates of 20% by age 50 years and 40% by age 70 years (Jochmanova *et al.* 2017, Rijken *et al.* 2018). For genetic counseling, the penetrance of non-probands is of special interest and was reported as 22% by age 60 years (Andrews *et al.* 2018). Reported tumors outside the paraganglial system also included RCC (Vanharanta *et al.* 2004, Gill *et al.* 2014), GISTs (Miettinen & Lasota 2013) and pituitary adenomas (Xekouki *et al.* 2015) rarely.

Paraganglioma syndrome type 5 (*SDHA*)

PGL5 is caused by germline mutations of the *SDHA* gene, which is located on chromosome 5 (5p15.33) and contains 15 exons. Two *SDHA* studies appeared in 2017, one from Freiburg, Germany and one from Cambridge, UK with 29 and 24 patients, respectively (Bausch *et al.* 2017*a*, Casey *et al.* 2017*a*). Thirty different disease-causing mutations, randomly distributed over the gene, have been described including 77% missense, 10% nonsense, 10% small insertions and/or deletions and 3% variants affecting splicing. Tumor locations are adrenal in 24% and extra-adrenal retroperitoneal pheochromocytomas in 41% of patients. HNPs were present in 35% of the patients. Multiple paraganglial tumors were present in 11% of the patients, and 9% of the patients had a metastatic tumor. Age range at diagnosis was 12–66 years. Seventy-five percent of the patients had paraganglial tumors by age 50 years. Family history for a paraganglial tumor was positive in only 5% of the patients. Tumors observed outside the paraganglial system are rare and include RCC, GIST and pituitary adenoma (Miettinen & Lasota 2013,

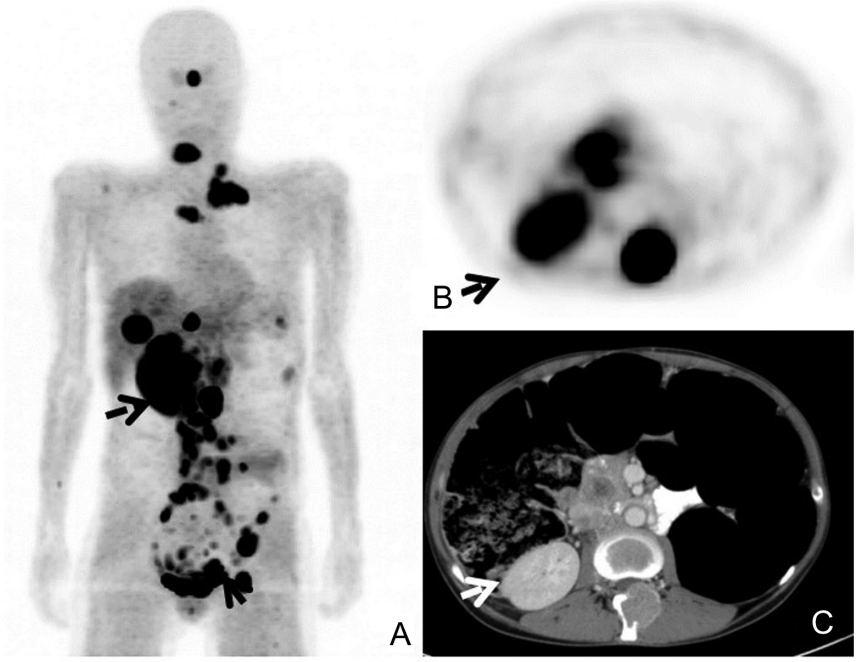

Figure 3
Metastatic pheochromocytoma in a 31-year-old woman with PGL4 (*SDHB* mutation). (A) Coronal maximum-intensity projection of [^{18}F]fluoro-dopa-PET shows extensive metastatic spread with the only noteworthy physiological tracer uptake in the urinary bladder (lower arrow), the pituitary gland and the remaining right kidney (upper arrow). (B) Axial PET image showing two foci of metastatic pheochromocytoma and the right kidney (arrow). (C) Axial CT image corresponding to the axial PET image shows diffuse retroperitoneal disease and the remaining right kidney (arrow).

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Oudijk *et al.* 2013, Ozluk *et al.* 2015, Yakirevich *et al.* 2015). About 85% of the patients had only one paraganglial tumor and a negative family history.

Hereditary pheochromocytoma syndrome associated with mutations in *MAX*

Germline mutations of the *MAX* gene (MYC-associated factor X) cause pheochromocytoma and HNPs (Comino-Mendez *et al.* 2011). *MAX* is located on chromosome 14 (14q23.3) and contains 5 exons. Thus far, 58 cases have been described with 29 different germline mutations (Comino-Mendez *et al.* 2011, Burnichon *et al.* 2012, Rattenberry *et al.* 2013, Bausch *et al.* 2017*a*). Mutations include missense in 38%, nonsense mutations in 46% and splice site or frameshift mutations in 16% of patients. Adrenal tumor locations dominate and HNPs are very rare, whereas multifocal tumors are frequent. Metastatic tumors are also rare. Age range at diagnosis is 13–80 years; 88% of the patients had paraganglial tumors by age 50 years. Patients with a single paraganglial tumor and a negative family history were found in 36% of the mutation carriers.

Hereditary pheochromocytoma syndrome associated with mutations in *TMEM127*

Germline mutations of the *TMEM127* gene (transmembrane protein 127) cause pheochromocytoma and HNP. *TMEM127* is located on chromosome 2 (2q11.2) and contains four exons. Thus far, 100 cases have been described showing 40 different germline mutations (Qin *et al.* 2010, Yao *et al.* 2010, Abermil *et al.* 2012, Rattenberry *et al.* 2013, Casey *et al.* 2014, Welander *et al.* 2014, Curras-Freixes *et al.* 2015, Toledo *et al.* 2015, Patocs *et al.* 2016, Bausch *et al.* 2017*a*). Mutation types included 18% missense, 10% nonsense, 46% splice site and 18% frameshift mutations. Seventy percent of the mutation carriers had adrenal tumors, 5% HNPs, 29% multifocal tumors and 3% metastatic tumors. Age range at diagnosis was 16–76 years; 67% of the patients had paraganglial tumors by age 50 years. Only one paraganglial tumor and a negative family history were found in only 39% of the mutation carriers. Tumors outside the paraganglia included RCC, malignant melanoma, colon cancer, pancreatic adenocarcinoma, acute myeloid leukemia and parathyroid adenoma, each in one patient (Hernandez *et al.* 2015, Bausch *et al.* 2017*a*).

Apparent hereditable pheochromocytoma syndrome associated with mutations in other susceptibility genes (*FH*, *PHD1* and *PHD2*, *MDH2*, *KIF1Bβ*, *HIF2alpha*)

There are reports of germline mutations in additional susceptibility genes such as *IDH* (isocitrate dehydrogenase), *HIF2A/EPAS1* (endothelial pas domain 1), *FH* (fumarate hydratase), *PHD1* and *PHD2* (prolyl hydroxylase domain proteins 1 and 2), *MDH2* (malate dehydrogenase 2) and *KIF1β* (kinesin family member 1β). However, few of these genes currently appear to account for a considerable proportion of pheochromocytomas. Reported cases remain in the single digits for these genes. An example is mutations in *FH*, which were found in only 5 patients (0.8%) with pheochromocytoma and HNP among 598 patients with disease-causing mutations (Letouze *et al.* 2013, Castro-Vega *et al.* 2014, Clark *et al.* 2014). For the *PHD1* and *PHD2* genes, one patient with *PHD1* and two patients with *PHD2* germline mutations have been identified (Welander *et al.* 2014, Yang *et al.* 2015). For the *MDH2* gene, a germline mutation was found in one patient with multiple malignant PGLs, and *KIF1Bβ* germline mutations have been described in only four patients with pheochromocytoma (Schlisio *et al.* 2008, Yeh *et al.* 2008, Welander *et al.* 2014, Cascon *et al.* 2015). In addition, there are syndromes in which pheochromocytoma has been observed, however infrequently. The main example is multiple endocrine neoplasia type 1.

Summary of genetics of pheochromocytoma

In 2014, it was concluded that about 50% of patients with pheochromocytoma carry germline mutations (Fishbein *et al.* 2017, Toledo *et al.* 2017). Others have reported even higher percentages. A closer look at the Freiburg International Pheochromocytoma-Paraganglioma-Registry suggests a figure of 35%. It is important to note that following the identification of the 'major' genes, which include *RET*, *VHL*, *SDHD*, *SDHB* and *SDHC*, progress in terms of explaining further patients has been marginal, probably because any newly identified gene mutation is drawn from a pool of patient registries in which known genes have already been tested. We recently found germline mutations in *SDHA*, *SDHAF2*, *MAX* and *TMEM127* in not more than 6% of such patients, representing 3% of all subjects (Bausch *et al.* 2017*a*). Furthermore, all patients in our registry with a positive family history have now been diagnosed with germline mutations.

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The large number of pheochromocytoma susceptibility genes is an ideal challenge for new sequencing technologies in order to identify germline mutations. First reports of application of whole exome or whole genome sequencing are promising (Comino-Mendez *et al.* 2011, Crona *et al.* 2013, Rattenberry *et al.* 2013, Welander *et al.* 2014). An international consortium has recommended next generation sequencing in the context of pheochromocytomas and HNPs (Toledo *et al.* 2017). Using these technologies is supposed not only to identify the mutations faster, but also to be less expensive. Larger studies will show whether we shall be confronted with limitations.

Has genetics changed the diagnosis and management of pheochromocytoma?

Answer 1: Diagnosis and management of head and neck paragangliomas (HNPs)

Up until the 2000, HNPs were considered to be rare lesions and were generally neglected by clinicians and scientists internationally. The identification of the *SDHD* gene changed this scenario (Baysal *et al.* 2000). National and international HNP registries showed that HNPs are a constant and important manifestation in not only germline mutation carriers of *SDHD*, but also of *SDHB*, *SDHC*, *SDHA* and *SDHAF2* (Fig. 4) (Neumann *et al.* 2004, Schiavi *et al.* 2005, Hao *et al.* 2009, Bausch *et al.* 2017*a*, Casey *et al.* 2017*a*). In parallel, patients initially presenting with abdominal tumors were diagnosed with HNPs as a co-manifestation. The genetics of pheochromocytoma emerged first to the scientific and soon after to the clinical otolaryngology community. At international meetings, the option of identification of germline mutation carriers and subsequent early diagnosis and treatment of HNPs is now discussed enthusiastically.

The main manifestations of carotid body tumors (CBTs) as well as jugular and tympanic PGLs must first be classified clinically, according to Shamblin for CBTs and to Fisch for jugulo-tympanic HNPs (Shamblin *et al.* 1971, Fisch & Mattox 1988). While complete surgical resection represents the only curative treatment option for HNPs, multiple studies have demonstrated that complication rates after surgery were very much dependent on location and stage of the tumor (Suarez *et al.* 2013, 2014, 2015). CBTs in Shamblin class I and II, as well as tympanic PGLs, can usually be completely resected with a very low risk of morbidity and without mortality (Suarez *et al.* 2013, 2015). Tumor recurrence in this group of patients is very low. On the other hand, in patients with class III CBTs, vagal paragangliomas and jugular PGLs, intraoperative damage to major vessels and inferior cranial nerves is frequently seen (Suarez *et al.* 2013, 2014, 2015). Recurrent tumor growth is another problem frequently detected after surgical resection of jugular PGLs (Suarez *et al.* 2013, 2015). Of note, HNPs, including those diagnosed using the new genetic tools, are nearly always non-metastatic, non-catecholamine secreting and slowly growing (Suarez *et al.* 2015). Thus, multiple asymptomatic HNPs are not infrequently detected in newly recognized patients with *SDHD* mutations (PGL1); it seems to be wiser to decide not to operate but only to observe these HNPs. An exception to this indolent course is seen in carriers of *SDHB* mutations; in the Freiburg-International-Pheochromocytoma-Paraganglioma-Registry, there are 82 cases with *SDHB* mutations and HNPs and, of these, 11 had metastatic paraganglial tumors, including 5 with HNP only and 6 subjects with an additional abdominal PGL. The discussion of whether surgery should be focused on CBTs Shamblin class I and II and tympanic HNPs is ongoing (Suarez *et al.* 2013, 2014, 2015). Stereotactic surgery and other forms of radiation therapy may be the treatment of choice for the majority of patients with jugular PGLs (Suarez *et al.* 2013, 2015). A wait-and-scan approach may be adequate for small asymptomatic HNPs and in patients with multiple HNPs. It is, however, important to emphasize that every patient with a HNP needs an individual therapeutic approach (Suarez *et al.* 2013, 2015). Important factors that have to be kept in mind include location; stage and size of the tumor; existing lower cranial nerve deficits and other clinical and psychologic impairments due to the tumor; age; general health condition of the patient; the presence of additional HNPs or other paraganglial tumors elsewhere in the body; genetic mutation with special emphasis on

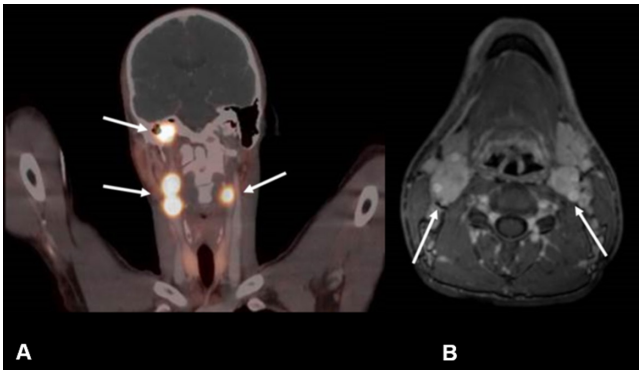

Figure 4
Multiple head and neck paragangliomas in a 24-year-old patient with PGL1 (*SDHD* mutation). (A) Coronal [^{68}Ga] DOTATATE–PET/CT image showing bilateral carotid body tumors (lower arrows) and a right jugular paraganglioma (upper arrow). (B) Axial image of contrast-enhanced MRI shows bilateral enhancing carotid body tumors (arrows).

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SDHB mutations and, last but not least, the preference of the patient.

Answer 2: Clinical diagnosis of pheochromocytomas

For each case of newly diagnosed pheochromocytoma, an interdisciplinary discussion raises the questions regarding which biochemical and imaging procedures are best and which ones are needed before surgery. Our interest in the genetics of pheochromocytoma inspired the only prospective investigation to study these questions, which was conducted in Freiburg (Neumann *et al.* 1993). All relevant methods available at that time were compared in a total of 42 newly diagnosed pheochromocytomas in 36 patients who all were later confirmed with mutations in *RET* or *VHL*. The primary findings showed very high diagnostic sensitivity for norepinephrine (86%) and high sensitivity for MRI (95%) (Neumann *et al.* 1993). Regarding biochemistry, subsequent studies demonstrated that 24-h urinary and also plasma normetanephrine is superior (but only marginally) to norepinephrine (Rao *et al.* 2017). We also learned that there are some differences regarding the proportion of metanephrine to normetanephrine excretion in carriers of mutations of different genes. Further, malignant pheochromocytoma can be associated with elevated methoxytyramine in the plasma (Peitzsch *et al.* 2013).

Regarding nuclear medicine imaging, we now recognize that [^{18}F]dihydroxyphenylalanine, ([^{18}F]fluoro-dopa), [^{18}F] Fluorodopamine and [^{68}Ga] DOTATATE PET CT/MRI are superior to 123- or 131-iodine-metaiodobenzylguanidine (MIBG) scintigraphy (Taieb *et al.* 2012, Rufini *et al.* 2013, Janssen *et al.* 2016).

For the key question of what is required before surgery, with advances in biochemistry and imaging, the answer that documentation of a clearly elevated fractionated catecholamine/metanephrine value combined with tumor localization by CT or MRI is sufficient, whereas nuclear-based imaging is optional.

Answer 3: Treatment options

Genetic predisposition to tumors results in specific gene-informed recommendations regarding treatment of diagnosed tumors and also includes considerations for prevention of potential tumor relapses or second tumors in the same organs. In terms of pheochromocytoma, curative treatment typically is adrenalectomy. However, as shown above, in genetic pheochromocytoma, bilateral adrenal tumors are frequent, and it needs to be emphasized that there may be a long interval until contralateral tumors become symptomatic and are detected. Thus, the adrenalectomy approach carries with it a high risk of surgically induced Addison's disease, and registry experiences indeed show that morbidity and mortality due to insufficient steroid replacement is more frequent than some would expect, because the deficiency was either not diagnosed or because patients were not compliant with their adrenal replacement program (Fig. 1). Adrenal-sparing surgery was introduced in Germany for genetic pheochromocytoma even before germline mutation testing became available. The arguments in favor of this approach include long intervals to ipsilateral relapses, low malignancy risk and feasibility of reoperation. The adrenal-sparing surgical approach is supported by recently reported experience for MEN 2-associated pheochromocytoma in a large study (Castinetti *et al.* 2014, 2016).

Progress in minimally invasive surgery technology and new genetic insights led in parallel to the concept of endoscopic adrenal-sparing treatment of genetic pheochromocytoma. Of note, endoscopic surgery is now also standard for extra-adrenal retroperitoneal pheochromocytoma and even a good option for pelvic and thoracic pheochromocytoma (Fig. 2) (Walz *et al.* 2006, 2018).

Progress in genetics for pheochromocytoma resulted in an enhanced referral of such patients to special treatment centers and a reconsideration of the accepted dogmas, for example the concept of alpha-adrenergic blockade for preoperative treatment of pheochromocytoma patients has been standard for several decades (Lenders *et al.* 2014). Alpha-adrenergic blockade cannot reliably prevent intraoperative hypertensive episodes, and despite alpha-adrenergic blockade, many reports of intraoperative blood pressure increases above 200 mmHg have been reported. Furthermore, and of special note, patients under alpha-adrenergic blockade may develop significantly more perioperative hypotensive episodes. Moreover, the time needed for titration of the alpha-adrenergic blockade prior to surgery delays surgery and the final cure. The center in Essen recently reported 182 surgical procedures for pheochromocytoma completed without alpha-adrenergic blockade and free of any complications (Groeben *et al.* 2017). This new strategy of preoperative treatment continues to be under discussion.

In parallel to the advances in genetics, therapy of metastatic pheochromocytoma was strengthened by the introduction of radionuclide therapy, in which the coupling of the noradrenaline analogue MIBG to the cytotoxic beta-emitter iodine-131 allowed specific irradiation of neuroectodermal tumor tissue (Giammarile *et al.* 2008, Carrasquillo *et al.* 2016, Kong *et al.* 2017).

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Answer 4: Histopathology

The genetics of pheochromocytoma has also affected histopathology. The pathologist may play an expanded role in detection of apparently sporadic tumors with an occult hereditary basis. Furthermore, as all pheochromocytomas are now thought to have some metastatic potential, the classic binary approach to classification as either benign or malignant is being replaced by risk stratification. In keeping with this new thinking, the 2017 WHO classification replaces the terms benign and malignant with *non-metastatic* and *metastatic*, thereby avoiding confusion that historically resulted from competing definitions of malignancy (Tischler 2008, Lloyd *et al.* 2017). Although no formal histologic grading system for pheochromocytomas and PGLs is currently endorsed or universally applied, two systems, Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) and Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP), with overlapping histological parameters have been proposed (Thompson 2002, Kimura *et al.* 2014*a*). Categories of adverse features associated with metastatic tumors in both systems include invasion (vascular, capsular, periadrenal), necrosis, proliferative activity and diffuse growth or small cell size (Tischler & deKrijger 2015). However, so far, there is no consensus on histological criteria for risk stratification in pathology reports. Currently, the chief risk factor for metastasis is the presence of a *SDHB* mutation.

Insight into the genetic basis of pheochromocytomas and HNPs has led to the development of new immunohistochemical tools for pathologists, who in turn can now use immunohistochemistry as a guide for genetic testing or, if necessary, as a surrogate test (Fig. 5). Immunoreactivity for *SDHB* is lost in all tumors that are SDH deficient (Dahia *et al.* 2005, van Nederveen *et al.* 2009). *SDHA*-deficient tumors are negative for *SDHA* (Papathomas *et al.* 2015, Korpershoek *et al.* 2016). *MAX* antibodies are now also available and often show loss of staining in tumors with mutations of the *MAX* gene (Korpershoek *et al.* 2016). In order for a case to be interpreted as negative for any of these markers, positive staining in endothelial cells must be seen as an internal control (Fig. 5E) (Kimura *et al.* 2014*b*).

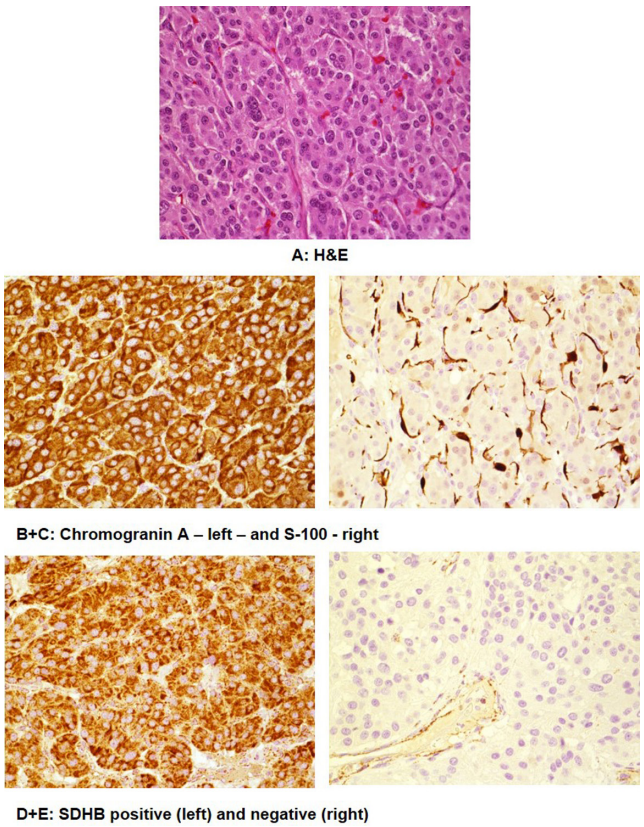

Figure 5
Histopathology and immunohistochemistry of pheochromocytoma. (A) H&E staining showing typical prominent uniform cell nests (Zellballen). (B) Diffuse immunohistochemical staining for chromogranin A. (C) Immunohistochemical stain for S-100 showing typical distribution of sustentacular cells. (D) Positive *SDHB* immunohistochemical staining. (E) Negative *SDHB* immunohistochemical staining.

Answer 5: Referral centers and long-term care

Patients with hereditary tumors need regular long-term care. Centers for rare diseases have been developed in large (usually university) hospitals. For hereditary pheochromocytomas, one center for around 20 million inhabitants seems to be sufficient. The investigations and reinvestigations by biochemistry and imaging procedures for these mostly young and working patients should be consolidated to one day and the test results and the options for treatment should be explained whenever possible the same day or by phone later. In particular, patients need psychological support when wait-and-scan policies are suggested or a rare finding of metastases has to be discussed. In this context, information on pheochromocytoma and pheochromocytoma-associated syndromes prepared especially for patients and their relatives by us in 15 languages have been well accepted (www.prevention-medicine.com).

The referral centers should provide patients with information on specific risk profiles, including risks for offspring and risks associated with *SDHD*/*SDHAF2* maternal inheritance. A major hurdle is the costs, since insurance may not cover all aspects of the suggested programs, in

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particular, MRI and nuclear medicine imaging, especially in the case of non-approved PET tracers.

Food for future thought

The optimal surveillance strategy for families with a hereditary endocrine tumor syndrome is an ongoing point of discussion within multidisciplinary teams. The discussion is a balance between defining the age at which to start surveillance and surveillance intervals based on the calculation of the risk of developing a tumor (for instance, a risk of <5% for missing a new manifestation) on the one hand (Kruizinga *et al*. 2014, Eijkelenkamp *et al*. 2017). On the other hand, surveillance recommendations may rest on the experience within a family with one exceptional family member – in all cases a child – who developed the tumor at a young age, leading to early and intensive surveillance. Another aspect is the lack of data regarding the behavior of a specific mutation within a family, or between individual to individual, as other biological characteristics or exposures may determine the behavior of a specific germline mutation. The above mentioned aspects are essential for the interpretation and application of international guidelines and make the counseling and support of these families a dedicated task.

Declaration of interest
The authors declare that there is no relevant conflict of interest.

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