A differential diagnosis of inherited endocrine tumors and their tumor counterparts

Sergio P. A. Toledo,[I] Delmar M. Lourenço Jr.,[I] Rodrigo A. Toledo[II]

[I]Faculdade de Medicina da Universidade de São Paulo, Endocrine Genetics Unit (LIM-25), Division of Endocrinology, São Paulo/SP, Brazil. [II]University of Texas, Health Science Center in San Antonio (UTHSCSA) – Medicine, San Antonio/Texas, USA.

Inherited endocrine tumors have been increasingly recognized in clinical practice, although some difficulties still exist in differentiating these conditions from their sporadic endocrine tumor counterparts. Here, we list the 12 main topics that could add helpful information and clues for performing an early differential diagnosis to distinguish between these conditions. The early diagnosis of patients with inherited endocrine tumors may be performed either clinically or by mutation analysis in at-risk individuals. Early detection usually has a large impact in tumor management, allowing preventive clinical or surgical therapy in most cases. Advice for the clinical and surgical management of inherited endocrine tumors is also discussed. In addition, recent clinical and genetic advances for 17 different forms of inherited endocrine tumors are briefly reviewed.

■ INTRODUCTION

Familial endocrine tumors have been of interest for many years (1). This subject likely attracted attention from researchers and clinicians because patients with inherited endocrine tumors (IETs) usually present rare tumor types, genealogies with several affected family members and strikingly common clinical and genetic features. The first report of pheochromocytoma (PHEO) was presented by Felix Frankel in 1888 and described a patient who had recently been characterized as having multiple endocrine neoplasia (MEN) type 2 (MEN2) (2). A familial predisposition to endocrine tumors was described in 1940, although the multiple endocrine adenoma entity was recognized a decade later by Wermer (3,4). More recently, updates on MENs have become available and recommend adequate procedures for the management of IET patients (5-10). However, IETs will likely remain a challenging subject of study involving topics such as the genetic diagnosis of asymptomatic cases, familial screening, detailed characterization of the phenotype, exome and transcriptome studies, preventive surgery, new therapeutic strategies, genetic counseling, and ethics (11,12). In addition, advanced techniques such as sophisticated in vitro functional studies, RNAi analysis, genomic micro- and macroarray assays, genome-wide association studies, exome analysis, copy number variations, whole genome sequencing, and in silico analysis may be available on a routine and personal basis in the near future (13). Therefore, genomics may have a long-standing impact on the clinical and surgical management of patients with IETs.

Despite substantial advances in the study of IETs, some difficulties still remain, specifically in the early recognition of IET conditions and in its differentiation from sporadic endocrine tumors (SETs) (Table 1). The distinction between both conditions is critical for decision making with respect to the affected index-case and their mutation-positive family members. Therefore, we will focus on the 12 typical clinical and genetic characteristics of IETs that may help clinicians to recognize IETs early and recommend preventive or early therapeutic interventions in this review. The IET characteristics mentioned below are intended to provide a practical clinical approach for the care of these patients.

1 – Age at diagnosis - IETs typically tend to develop in younger patients than their SET counterparts. Parathyroid hyperplasia/adenomas leading to primary hyperparathyroidism (HPT) associated with MEN type 1 (MEN1) are usually diagnosed by 20-35 years of age. In contrast, sporadic primary HPT is mostly recognized in patients older than 50 years of age (5,14-16). Medullary thyroid carcinoma (MTC) associated with MEN2 can be diagnosed at early ages (<5-10 yr old), mostly in family members who have been genetically screened for RET proto-oncogene mutations (17-19). In addition, the highly aggressive MTC associated with MEN2B caused by RET 918 codon mutations usually develop during the first year of life (20). Conversely, cases with sporadic MTC are usually diagnosed at later ages (>20-30 yr old) (21). Patients with inherited PHEO/paraganglioma who carry germline mutations in the SDHA, SDHB, SDHC, SDHD, RET, and MAX genes are

Table 1 - Main characteristics of inherited endocrine tumors and their sporadic endocrine tumor counterparts, and the differential management of these conditions.

Age at diagnosis	IETs low	SETs counterparts high
Associated tumors	+	-
Germline mutation	+	-
Inheritance	A.D.	-
Multicentric tumors	+	-
Bilateral tumors	+	-/rare
Pre-malignant stage	+	-
Aggressiveness	>	<
Specific tumor locations	+	+
Mixed tumors types	+	-/rare
Genetic heterogeneity	+	-
Clinical heterogeneity	+	-
Founder effect	+	-
Two-hit model of tumorigenesis	+	-
Early genetic diagnosis	+	-
Genetic counseling	+	-
Pre-symptomatic diagnosis	+	-

usually diagnosed at 20-30 years (22,23). Conversely, sporadic PHEOs are frequently diagnosed in the fifth decade of life (20). One exception for PHEO is found in cases with isolated familial PHEO caused by germline TMEM127 mutations and neurofibromatosis type 1 (NF1)-associated PHEO, which are usually diagnosed at 40-44 years (24,25). Pituitary tumors (PITs) associated with MEN1 syndrome, Carney syndrome (CS), and familial isolated pituitary adenoma (FIPA) are usually diagnosed in the second decade of life, although they may occur as early as 5 years of age (8,26). These data strongly contrast with sporadic PITs, which are usually diagnosed during the third and fourth decades. In addition, gigantism from excess growth hormone secretion is far more frequent in patients with FIPA and CS than in patients with sporadic somato-tropinomas (8,26,27). A general trend for diagnosis at early ages is also applied to several other types of IETs. In brief, IET cases harboring either germline-activating mutations in proto-oncogenes or inactivating mutations in tumor suppressor genes have a marked predisposition to develop tumors at early ages.

2 – Associated tumors - Many IETs are associated with syndromes in concert with several independent, primary tumors in a single patient, such as a patient with MEN1 and MEN2, von Hippel-Lindau (VHL), NF1, CS, or Li-Fraumeni complex (LFS) (5,27). As many as 20 different endocrine and non-endocrine tumors have been described in association with MEN1 syndrome, such as HPT, PITs, pancreatic-endocrine tumors (PETs), adrenal tumors, and skin neoplasias (5). Patients with VHL may have renal, cerebellar, and pancreatic tumors and PHEO (28). In patients with MEN2, MTC is found in almost all cases, whereas PHEO and HPT are also highly prevalent (17-19,20,22). Patients with CS usually present PITs leading to acromegaly/gigantism and primary pigmented nodular adrenocortical disease leading to Cushing's syndrome (29). In patients with LFS, the adrenocortical carcinoma (ACC) is frequently associated with breast and ovary neoplasias. Patients with more than one primary endocrine tumor are potential candidates for an IET and should be actively investigated for other primary neoplasias.

3 – Germline mutation and inheritance - The signature of inherited tumors is the presence of a germline mutation in the pertinent disease-causing gene. For instance, the presence of a RET germline mutation in cases with MTC, PHEO, or HPT define these tumors as having inherited transmission. The finding of an NF1 germline mutation confirms NF1 disease. A MEN1 germline mutation helps to confirm the diagnosis of MEN1 syndrome and establish that the condition is inherited. The same pattern occurs with other cancer genes, although cases with either de novo mutations or large gene deletions are exceptions to this general rule. Conversely, the absence of a germline tumor-causing mutation supports the diagnosis that the patient has a SET that is frequently a counterpart of the IET.

Almost all IETs are inherited by autosomal dominant transmission, which means that the patient's first-degree relatives have a 50% risk of carrying the mutated gene; consequently, they have inherited a predisposition to develop the specific tumor condition. Additionally, cases with an apparently SET may harbor a germline mutation, as is true of 1-7% of cases with sporadic MTC harboring a RET germline mutation (8,21). Therefore, apparently sporadic PHEOs should be analyzed for VHL, RET, and SDHx germline mutations (30). In sum, one should consider the pros and cons of genetic testing in apparently SET cases to rule out a possible "hidden" germline mutation and avoid missing an IET diagnosis (8,9,21).

4 – Sex ratio- Because IETs are inherited by autosomal dominant transmission, their sex ratio is mostly 1:1, although this value may vary within small genealogies. In contrast, the sex ratio is 1:3 for sporadic primary HPT caused by parathyroid adenoma, with a definite predominance of middle-aged females (5).

5 – Multicentric tumors - A typical observation in IETs is the occurrence of multicentric tumors, as observed in MEN2-related tumors (MTC, HPT, PHEO), MEN1-related tumors (PETs, HPT), VHL-related PHEO, and CS (5,15,16). Conversely, sporadic MTC, PHEO, HPT, PETs, and PITs are usually represented by a single tumor (31,32). Sporadic gastrinomas in particular are usually represented by a single duodenal or pancreatic tumor, whereas multiple duodenal gastrinomas are routinely documented in MEN1 patients (33-35). Thus, the pre-surgical diagnosis of the IET conditions is an important requirement for providing surgeons with proper data to plan a surgical approach. For instance, a partial pancreatectomy is usually advised in sporadic PETs to remove a single tumor, whereas the multiple tumors found in inherited PETs should be approached using a sub-total or even total pancreatectomy (8,33-35).

6 – Bilateral tumors - Patients with IETs have a high risk (up to 60%) of contralateral tumors, as verified in patients with PHEO-associated MEN2 or VHL or in isolated familial PHEOs caused by TMEM127, MAX, and SDHx mutations (8,17,23-25). In addition, primary pigmented nodular adrenocortical disease in CS is usually bilateral, but it is unilateral in its sporadic form (36,37). Furthermore, both thyroid lobes are affected in MTC/MEN2, and both adrenal glands are frequently affected in VHL and CS. Additionally, renal cell carcinoma in VHL is frequently bilateral, although contralateral tumors may not occur simultaneously. In addition, the development of bilateral tumors in patients with IETs is frequently nonsynchronous (8,17,22,38). Conversely, most sporadic PHEO and MTC occur unilaterally. Thus, a long-standing clinical follow-up should be

performed in IET patients to detect possible contralateral tumors.

7 - Pre-malignant stage - IETs frequently present a preneoplastic stage, as represented by a hyperplastic phase that precedes neoplasia. One typical example is C-cell hyperplasia in MEN2 that evolves to MTC and is frequently associated with increased levels of serum calcitonin (17,39). Notably, patients who are submitted to preventive total thyroidectomy (TTx) during this early, pre-malignant stage and present repeatedly undetectable values of calcitonin after 5-10 years of post-surgical follow-up can be considered biochemically cured (40). In addition, cases of PHEO/MEN2A and VHL-associated PHEOs present adrenomedullary hyperplasia that precedes the tumor.

8 – Aggressiveness - IETs have a marked tendency to be more aggressive than their SET counterparts. Accordingly, FIPA-associated PITs develop faster than sporadic PITs, and most are invasive macroadenomas at diagnosis (41,42). Furthermore, the PITs in MEN1 are far more aggressive than their sporadic counterparts (43). Additionally, early occurring MEN1-associated HPTs lead to early, severe bone and renal complications, whereas sporadic HPT usually has a milder presentation (44-46). Cervical lymph node metastases have been described before the age of 3 years in MEN2-related MTC patients with RET codon 918 mutations. In addition, in cases with a RET codon 634 mutation, a micro-MTC was reported in a 2-year-old child, and local cervical metastases were present in another 5-year-old child (46-47). Tumor aggressiveness may be associated with therapy resistance, as observed in MTC patients with RET codon 804 mutations that are resistant to therapy with tyrosine kinase inhibitors, whereas the high aggressiveness observed in IETs is less frequently observed in SETs (48). These data reinforce the need to perform early diagnosis in IET patients as a crucial tool in preventive surgical therapy or at least early treatment (48).

9 – Tumor location- IETs and their SET counterparts may occur in different locations. Sporadic gastrinomas are mostly located in the pancreas, whereas MEN1-related gastrinomas are mainly located in the duodenum (8,10,33-35). Furthermore, sporadic gastrinomas are usually represented by a single pancreatic tumor, whereas multiple primary pancreato-duodenal gastrinomas are routinely documented in >80% of MEN1 patients (33). The parathyroid adenoma of sporadic primary HPT is mostly located in a single gland, whereas in HPT/MEN1, all parathyroid glands are usually affected, and there is a high risk of developing HPT in the supernumerary and ectopic parathyroid glands (5,49).

These data are crucial for the surgeons who are planning the appropriate surgical approach for IET cases. The first surgical option for sporadic HPT is to remove the single parathyroid adenoma (adenomectomy), whereas total parathyroidectomy (PTx) followed by a parathyroid implant in the forearm or sub-total PTx is used for HPT/MEN1 cases (49-52). In addition, sporadic insulinoma is frequently treated with surgery by single pancreatic nodule removal, whereas cases with insulinoma/MEN1 are usually submitted to sub-total pancreatectomy (83,117). For gastrinoma in MEN1, subtotal or total duodenopancreatectomy or subtotal pancreatectomy associated with duodenotomy is applied, and partial pancreatectomy is usually the surgical choice in sporadic gastrinoma (33,34,51,52).

10 – Mixed tumor types - Mixed tumor types occurring in a single endocrine gland are frequent in IETs and rare in their SET counterparts. Different types of secretory PITs associated with either MEN1 or FIPA have been simultaneously reported in the same patient and in a single family. Thus, mixed tumors secreting GH and prolactin are frequently found in FIPA and MEN1 (8,15). In contrast, sporadic PITs are less frequently mixed (53). Furthermore, different secretory cell tumors may occur in PETs/MEN1, mainly with gastrin and insulin (8,10).

11 – Genetic heterogeneity - Similar clinical features observed in IET patients may be caused by different genes. As an example, germline CDKN1B/p27 mutations have been reported in MEN1-like patients who present no germline MEN1, and this condition is called MEN4, whereas the rat equivalent disease is named MENX (54). In addition, inherited PHEO/paragangliomas may occur in the context of MEN2, VHL, and isolated familial PHEO. In these cases, several mutations may be present in genes such as SDHA, SDHB, SDHC, SDHD, RET, VHL, TMEM127, and MAX (23-25). In addition, approximately 80% of CS cases are caused by a PRKAR1A mutation at chromosome 17, although a second putative gene in chromosome 2p was reported though not fully characterized to date (55). Patients with the two genetic origins present similar phenotypes (10).

Thus, for IET cases with superimposed phenotypes that could be related to different genes, rational approaches should be applied in genetic testing, as performed in recent cases with isolated familial PHEO/paraganglioma (56).

12 – Clinical heterogeneity - IET patients harboring the same specific type of germline mutation and belonging to a single family may present a high degree of clinical variability, as typically occurs in MEN1 (57,58). MEN1 patients may present up to 20 different tumor types, and no consistent genotype-phenotype correlation has been reported so far (5). Concordantly, in a very large MEN1 family (>20 affected cases) of Italian origin, we observed a high prevalence of PITs and PETs, but no genuine genotype-phenotype correlation (44,45). This challenging finding may be caused by tissue-specific modulating factors, such as epigenetic events (hypermethylation), a second MEN1 mutation, RNAi or even mutations in another gene. Although there is a high rate of genotype-phenotype correlation in conditions like MEN2 and VHL, a large range of clinical heterogeneity may still be observed (20,22,30,59). Thus, depending on the specific IET, substantial phenotypic diversity and variable penetrance may be observed in patients harboring the same type of mutation. Overall, a periodic screening should be performed for all tumor types that are potentially involved in IETs to try to provide early diagnosis. Alternatively, genetic testing can exclude germline mutations, avoiding long-standing periodic screening in the latter cases.

Some additional comments on IETs are needed.

1 – Founder effect - Familial cancer clustering has been one of the main avenues toward improving cancer etiology and is an indicator of heritable gene involvement (60). A founding VHL mutation was reported in a large conglomerate of PHEO patients living in the Black Forest of Germany (30). In addition, founding mutations have been reported in six very large MEN1 families (>20 affected cases) (44). One of these families originally came from Veneto, Italy to Brazil in 1889. More than 50 affected family

members currently harbor the same specific MEN1 mutation in exon 2 and are living in São Paulo State, Brazil (44,45). Moreover, we identified a large MEN2 familial cluster from the northeast area of Brazil, including more than 45 affected MEN2 cases carrying a RET Cys620Arg mutation (20,40,61). In Germany, MEN2 families could be traced back to the early 20th century, and a few of them have been traced to the 19th century (62). In addition, a common founding arg337-to-his (R337H) P53 germline mutation in exon 10 was reported in cases with LFS from southern Brazil (63). Recently, a high penetrance founding mutation was reported in 287 affected cases from Trentino, Italy with paraganglioma associated with a low prevalence of PHEO. A common ancestor was identified from the 14th-15th centuries (64). Additionally, a large FIPA genealogy from northern Finland could be traced back to the 18th century (41). Similarly, a founding couple could be traced in a FIPA family from Ireland to the 18th century (65). In summary, very large IET genealogies frequently carry a founding mutation and constitute an excellent opportunity to expand our knowledge of inherited cancer conditions. Further topics for investigating familial cancer clustering are intra-familial phenotype variations, possible superimposing consanguineous marriages, and the occurrence of homozygous mutations.

2 – Two-hit model of tumorigenesis - As mentioned, most IET conditions are caused by tumor suppressor genes such as VHL, p27, MEN1, PRKAR1A, SDHs, and TMEM127, and the two-hit model mutation proposed by Alfred Knudson has been appropriately applied to these conditions. This model is based on the presence of two sequential mutations. The first is a germline mutation inherited from a parent; by itself, it is not sufficient to start tumor development, although it leads to IET genetic predisposition. The second event is a somatic mutation that occurs at random in the same gene, within a specific tissue (endocrine gland). This latter event results in biallelic gene inactivation and a loss of heterozygosity (LOH) that will lead to the onset of tumor development (66). Conversely, there are rare reports that suggest that LOH in tumors is caused by proto-oncogenes, although these data require validation (67). Thus, the presence of LOH in a tumor supports the possibility that it is inherited, most likely through tumor suppressor genes.

Management

Similar genetic and clinical approaches are frequently applied to the management of most IETs.

1 - Pre-symptomatic diagnosis may be performed in IETs, leading to a recommendation of preventive surgical treatment for specific cases (8,9). Conversely, pre-symptomatic diagnosis and preventive treatment is not applied to the SET counterparts. After screening at-risk family members from the index-case, mutation-positive carriers should be invited for an interview at the hospital. In cases such as RET mutation-positive carriers, preventive TTx should then be recommended, as internationally established (8,9,62,68). RET mutation carriers should be submitted to preventive TTx during the first year of age (cases with RET mutations in codons 883 or 918), by the age of 3 years (codon 634), 5 years (codons 620, 618, 609, and others) or 5-10 years (codon 804 and others) (8,9,17,62). Concordantly, we successfully performed preventive TTx in 15 young cases in a single extended 620-codon mutation-positive MEN2 family (20,40,61). Some of these cases have been followed for up

to 10 years, and their calcitonin levels have remained undetectable, indicating that a ''biochemical cure'' was achieved (20,40,61). Preventive TTx has been successfully performed in MEN2 children from several Latin American countries, including Argentina, Chile, and Brazil (69-71). Preventive subtotal or total thymectomy should be performed in all MEN1 cases during PTx as recommended for HPT/MEN1 because the thymic carcinoid is a fast-evolving malignant tumor that is a frequent cause of death in MEN1 cases (8,10). Thus, preventive surgery may have a relevant and impressive impact in the management and outcome of many forms of IETs, as typically documented in MEN2-associated MTC.

2 – Curative surgery may still be achieved in some older IET cases in which preventive surgery is not applicable, but relatively early diagnosis could still be performed. For instance, curative TTx has been successfully performed at the early developmental stages of MTC in patients up to 12 years of age, who belonged to a MEN2 family with a RET Cys620Arg mutation (61). Similarly, MEN2A cases need to be searched annually for PHEO, and a curative adrenalectomy is usually considered as soon as the adrenal tumor is detected by CT or MRI, if the patients are symptomatic (8). Most patients with HPT/MEN1 will benefit from PTx performed as soon as there is a consensual indication for surgery, including the presence of osteoporosis, renal calculi, hypercalcemia, and an age below 50 years (46,103,104,111,115,116,149-154). Notably, a short-term bone mineral density improvement after total PTx followed by parathyroid auto-transplant in the forearm has been verified in our MEN1 cases (49,50). Interestingly, the impact of MEN1 mutations in the management of MEN1 cases was initially considered to be low (31). However, accumulating data presently indicate that the early genetic diagnosis of MEN1 germline mutations may have a substantial impact on the clinical and surgical management of MEN1 patients. For instance, preventive thymectomy and PTx in young, select MEN1-associated HPT cases may prevent the development of highly malignant thymic carcinoids and secondary complications of HPT, such as osteoporosis and renal calculi (10,15). Additionally, non-functioning PETs (NF-PETs) associated with MEN1 may occur at ages as early as 10, and adequate early surgical intervention should be considered in these cases (10). Furthermore, early detection and therapy in cases with GH-secreting tumor in patients with MEN1, FIPA, and CS may prevent the development of gigantism and further PIT expansion (8,29,37).

Taken together, these examples illustrate that early diagnosis and treatment in IET patients have strong clinical impacts and may ultimately lead to a better quality of life and decrease morbidity and mortality (15,72). To achieve these two beneficial goals, the genetic mutation analysis and the clinical periodic screening in affected index-cases and at-risk family members from IET genealogies should begin at early ages (8-10).

3 - Genetic counseling should be offered to IET cases and their at-risk relatives and may provide crucial information for couples, although a psychological burden must be avoided (11). Individuals who are at risk for developing hereditary cancers should be offered surveillance to improve their prognosis. Advisers should consider several options, with respect to psychological distress and the quality of life in individuals who are under surveillance for hereditary cancers. Notably, high-risk individuals with an

inherited predisposition for multiple tumors may be associated with increased distress and a lower quality of life. Common factors associated with poor psychological outcomes include a personal history of cancer, female gender, a first degree relative with cancer, negative illness perceptions, and coping style. The use of a simple screening tool to identify distressed individuals is recommended (73).

Several types of IETs have been increasingly recognized by clinical and genetic means over recent decades. Here, we briefly summarize the main IETs and some recent topics and issues related to these conditions.

von Hippel-Lindau syndrome

VHL disease is a complex inherited condition caused by germline mutations in the VHL tumor suppressor gene located on chromosome 3p. More than 300 VHL genealogies with VHL mutations and double VHL mutations have been reported (http://www.umd.be/VHL/W_VHL; 74). VHL is a rare autosomal dominant syndrome (1/36,000 live births) with high penetrance that predisposes a patient to the development of a panel of highly vascularized benign and malignant tumors, such as angiomas and hemangioblastomas, particularly in areas that are rich in blood vessels such as the retina, cerebellum, and spine. Renal cell carcinoma (RCC), PHEO, PETs (~10%), and visceral cysts (renal, pancreatic, and epididymal) are also prevalent (75). VHL is classified as type 1 (without PHEO), type 2A (with PHEO), 2B (PHEO and RCC), and 2C (isolated PHEO, without hemangioblastoma or RCC). PHEO in VHL is usually diagnosed by 30 years of age, the risk of malignancy is 5%, and it secretes high levels of normetanephrine (>112 pg/mL). Young PHEO patients are frequently associated with either VHL or MEN2A and less often with MEN2B, NF1, and paraganglioma (SDH-B), sustained hypertension with infrequent hypertensive peaks, bilateral tumors, and malignancy (76). Classic and non-classic VHL phenotypes have been reportedly associated with VHL mutations. The vast majority of PETs in VHL are malignant NF-PETs located in the pancreas. PETs in VHL are relatively frequent (10-17%). Most are non-functioning, asymptomatic, single pancreatic tumors; they are malignant in up to 50% of cases and metastasize in up to 27% of cases. Further, they are the third highest cause of death in relation to VHL (77). Therefore, these tumors must be routinely scrutinized during follow-ups. Head and neck paragangliomas (HNPs) may be found in patients with VHL (78). HNPs can occur in the sporadic or familial form, and the latter is mostly associated with germline mutations in SDHB, SDHC, or SDHD (SDHx). Non-SDHx HNP might occur in patients with VHL, MEN2, and NF1. Therefore, molecular genetic testing for VHL or RET mutations in HNP patients should be recommended if personal and/or family history shows evidence for one of these syndromes. VHL-related tumors may present as apparently sporadic but harboring a VHL mutation, so a routine search for VHL-related tumors and VHL mutations should be considered in these cases. In addition, large germline VHL deletions, including that of the HSPC300 gene, predisposes patients to RCC in VHL, and biallelic somatic inactivation of the VHL gene may lead to sporadic RCC (28). Thus, RCC should be actively searched in VHL cases because it has become the most common cause of death (77). Conversely, VHL disease is the main cause of inherited RCC. In addition, marked intra-familial phenotype variation may be observed and can

reflect established genotype-phenotype correlations for PHEO and RCC risks (28). VHL testing is indicated for VHL cases and VHL-similar phenotypes, for all cases with apparently sporadic PHEO because a high prevalence of VHL germline mutations has been reported in these patients, and for familial PHEO cases. Currently, the surgical approach to VHL-associated PETs has utilized laparoscopic organ-sparing resection (79). Furthermore, robot-assisted laparoscopic partial adrenalectomy has been used recently in the surgical treatment of PHEO/VHL to try to preserve the adrenal cortex and avoid adrenal insufficiency (80). Recently, VHL cases with PETs were shown to be significantly associated with blood group ''O,'' which may be useful in selecting VHL cases who are at higher PET risk (81). Clinical screening for PHEO in VHL should start at early ages by measuring plasma normetanephrine, mainly in families at high risk (28). PHEO in patients with VHL should be actively sought in at-risk family members because it may mimic stress conditions, and it is frequently subclinical (82). Anti-angiogenic drugs have been tested in patients with advanced RCC/VHL and are also potentially useful for VHL-associated PETs and malignant PHEOs. Moreover, new targets for novel potential medical treatments in VHL have been found (28). Recently, long-term disease control with sunitinib has been reported in a patient with metastatic PETs associated with VHL disease (83).

Carney complex

CS is an autosomal dominant MEN syndrome that affects the adrenal, pituitary, and thyroid glands and the gonads. PITs leading to GH hypersecretion and gigantism/acromegaly are usually observed. Papillary and follicular thyroid tumors, large-cell calcifying Sertoli cell tumors and adrenal carcinoma have also been described (84). Furthermore, benign primary pigmented nodular adrenocortical disease leading to Cushing's syndrome is frequently reported in CS. Because CS shares abnormalities with Peutz-Jeghers syndrome, a differential diagnosis is needed, and restricted clinical criteria should be applied (36). CS involves at least four endocrine glands, and a differential diagnosis with MEN1, MEN2 and MEN4 should be performed to allow for the adequate management of these patients. PITs in CS may occur in early life and present rapid growth (29,37). Several non-endocrine tumors are typically associated, such as heart myxomas; skin and breast, cutaneous and neural myxomatous tumors; psammomatous melanotic schwannomas; and virilizing ovarian stromal tumors. Additionally, lentigines in the face, lips, eyelids, conjunctiva and oral mucosa are often observed in CS (85,86). CS is caused by germline PRKAR1A mutations, which is located at 17q13, and two-thirds of affected cases present a heterozygous germline PRKAR1A mutation. More than 120 PRKAR1A mutations have been reported so far (27,85). A second putative disease-causing mutation was reported on chromosome 2p and may explain patients with no mutation in PRKAR1A, although this gene was has not been fully characterized to date (29,37,55). The second locus at chromosome 2p16, to which most (but not all) of the remaining affected families are mapped, is also involved in the molecular pathogenesis of CS tumors, as demonstrated by multiple genetic changes at this locus, including LOH and copy number gain (36). Despite the genetic heterogeneity of the disease, clinical analysis has not detected any corresponding phenotypic differences between patients with and without PRKAR1A

mutations (36). Recently, it was shown that the differential roles of PKA catalytic subunits might mediate the CS phenotype (87,88).

In 2012, ACC was first reported in association with CS in a large Azorean family harboring the S147G PRKAR1A mutation (88). A second CS patient with ACC presented a germline heterozygous PRKAR1A mutation that created a premature stop codon in exon 2 (p.Lys32Argfs*12), and a cortisol/androgen-secreting 8.5-cm tumor was detected. ACC was confirmed, and there were pigmented micronodules typical of PPNAD in the adrenal gland adjacent to the ACC (89). In two cases, the unilateral ACC co-secreted androgen and cortisol, whereas benign secreting tumors caused cortisol excess only. The large size of ACCs and the occurrence of metastasis demonstrate its malignant nature. Thus, doctors and patients should be aware of this rare, devastating event in association with CS (90). Moreover, cardiac myxoma, which is a genetic source of multiple strokes in CS, has been successfully removed (91).

Neurofibromatosis type 1

This syndrome is a tumor inherited condition that presents PHEO/paragangliomas in 5% of cases and in up to 13% of autopsies. NF1 is usually diagnosed at early ages in response to the presence of neurofibromas, café-au-lait skin spots, skinfold freckling, iris Lisch nodules, optic pathway gliomas, and bone dysplasia. Malignant peripheral nerve sheath tumors, other gliomas, gastrointestinal stromal tumors, gastric carcinoids, juvenile myelomonocytic leukemia, glomus tumors, and astrocytomas may also be present (92-94). NF1 has almost 100% penetrance by the age of 5 years and is relatively frequent, affecting 1 of 3,500 individuals worldwide, and it is caused by the inactivation of the NF1 tumor suppressor gene that encodes neurofibromin protein. NF1 is a large gene and has one of the highest known mutation rates in man, and up to 50% of NF1 cases have de novo mutations that may give rise to a mosaic phenotype. Inactivating NF1 mutations lead to decreased cellular neurofibromin levels that may predispose patients to neoplasias (29). In 216 NF1 cases with PHEO/paraganglioma, 96% had PHEO, and 6% had paragangliomas, all of which originated from the sympathetic system. Additionally, 9% of the PHEOs were malignant, and the mean age at diagnosis was 42 years. A high degree of inter- and intra-familial phenotype variation was also noted (29). Screening for the NF1 gene in apparently sporadic NF1 cases has been recommended (30). PETs may occur in up to 5% of NF1 cases, are usually <1.0 cm and must be actively observed (77). The NIH clinical diagnostic criteria for NF1 is based on the finding of two or more of the following features: six or more café-au-lait macules with diameters >5 mm in prepubertal patients and >15 mm in postpubertal patients; two or more neurofibromas of any type or one plexiform neurofibroma; axillary or inguinal freckling; optic glioma; two or more Lisch nodules in the iris; a distinctive osseous lesion, such as sphenoid wing dysplasia or pseudarthrosis; or a first-degree relative diagnosed with NF1 (95). Mild clinical forms of NF1 presenting only two typical features may be missed, and genetic testing is currently offered by only a few centers, mostly because of the large size of the NF1 gene (60 exons). The origin of bone lesions and osteopenia/osteoporosis associated with NF1 has recently been investigated. NF1 germline mutations lead to altered neurofibromin production and unrepressed

RAS, which acts on the osteoblasts/osteoclasts, leading to bone mineral loss and eventually to osteopenia/osteoporosis (96). In addition, mice lacking Nf1 in osteochondroprogenitor cells display skeletal dysplasia similar to patients with NF1 (97). In sum, there is a relatively high prevalence of NF1 in human populations, and a routine search for PHEO/paraganglioma and PETs should be performed in all cases.

Tuberous sclerosis

This is a multisystem disorder characterized by multiple hamartomas in the brain, skin, heart, kidneys, and lung. Epilepsy, learning difficulties, behavioral problems, and autism are also frequent. Renal angiomyolipomas are common and can ultimately lead to renal failure, although renal cysts and RCCs may also be found. Cardiac rhabdomyomas, lung lymphangioleiomyomatosis, melanotic macules, facial angiofibromas, and patches of connective tissue nevi have been frequently reported. TSC presents a wide clinical spectrum, and some patients may have minimal symptoms with no neurologic disability (98,99). TSC type 1 (TSC1) is caused by a mutation in TSC1 located at 9q.34 (hamartin), and TSC type 2 (TSC2) is caused by mutations in TSC2 located at 16p.13 (tuberin). Overall, 20% of affected cases have TSC1, and the remaining 80% present TSC2, which is usually more severe. A definitive diagnosis of the TSC complex may require two or more distinct lesion types, rather than multiple lesions of the same type in the same organ system. A clinical diagnosis is not usually difficult to perform, although a few cases may not fulfill the criteria. Couples with more than one child with a TSC complex, no extended family history, and no clinical features of a TSC complex are likely to have germline mosaicism for TSC. Germline mosaicism, which is fortunately rare, will not be suspected based on either diagnostic criteria or molecular testing until a couple has multiple affected children. Families with one affected child may include a small (1-2%) possibility of recurrence, even for parents who present no evidence of a TSC complex after a thorough diagnostic evaluation (95). In addition, angiomyolipomas are benign mesenchymal tumors originating from the kidney and adrenal glands and have been frequently reported in TSC. PETs in TSC and are usually small (<1.0 cm) and malignant (77). At present, the therapeutic approach to TCS is based on mTOR inhibitors (100). Because PETs in TSC are usually small and malignant, patients should be routinely screened for them by endoscopic ultrasound.

Li-Fraumeni syndrome

This condition is rare, characterized by multiple endocrine and non-endocrine tumors, and has a high penetrance (101). The usual criteria for identifying LFS cases and performing genetic testing are based on the following: 1) a patient with sarcoma or a first- or second-degree relative affected before 46 years of age; 2) an index-case with multiple primary tumors, two out of three tumors, with the first occurring before 36 years regardless of family history; and 3) an index-case with ACC regardless of the onset age or family history (101). An estimated 50% of LFS cases will develop tumors before 30 years of age, and most (>90%) will present a LFS-related tumor at 70 years of age. Up to 70% of typical LFS cases harbor a germline mutation in the P53 tumor suppressor gene, although many LFS cases are

caused by de novo mutations, and copy number variations are exceedingly high (101). Data from the IARC TP53 database showed that cases with P53 mutations are prone to present rhabdomyosarcomas at early ages (<5 yr), whereas other types of sarcomas occur at any age (102). More than 300 P53 germline mutations have been reported in association with the LFS phenotype. Because ACC may also occur in Beckwith-Wiedemann syndrome, MEN1, familial adenomatous polyposis coli (FAP), and NF1, a careful differential diagnosis should be performed (103). Cases with ACC/LFS were thought to be associated with P53 missense mutations located in the loops that oppose the protein-DNA contact surface. Interestingly, the incidence of pediatric ACC in southern Brazil is 10 to 15 times higher than the worldwide prevalence (104,105). Most cases (78-97%) exhibit a founding P53 arg337-his (R337H) germline mutation in exon 10 (106). The present data indicate that these patients have an increased risk of developing several LFS-related tumors and are an intrinsic part of LFS (107,108). In southern Brazilian populations, the allele frequency is very high (0.0015), leading to several hundred thousand carrier subjects. This prevalence may explain the high frequency of ACC, colorectal cancer, and other types of cancers in children and adults living in this geographic area. The ACC penetrance in these cases was evaluated at 10%, so IET patients associated with non-endocrine tumors from southern Brazil are particularly prone to P53 germline mutations and LFS-related tumors.

Cowden syndrome

This rare condition is characterized by multiple hamartomas in several organs and a high risk of breast and thyroid carcinomas, although asymptomatic and undiagnosed cases may occur. The penetrance is 100% by the age of 40 years, and the phenotype includes skin lesions such as lipomas, fibromas, hemangiomas, trichilemmomas, acral keratosis, and typical oral/plantar lesions. Follicular thyroid carcinoma (3-10% of cases), early breast cancer (25-50%), and macrocephaly (20-40%) are also found, and the specific criteria for a Cowden syndrome diagnosis are usually based on clinical manifestations (109). Furthermore, familial follicular cell-derived thyroid carcinoma may be associated with several inherited conditions, as in Cowden syndrome. This condition is caused by PTEN germline mutations that occur in 80% of cases, and there is an exon 5 hotspot (110). A germline epigenetic regulation of the Killin gene has been shown in cases with both Cowden syndrome and Cowden syndrome-like phenotypes. Finally, cases of breast carcinoma associated with thyroid follicular carcinoma may have Cowden syndrome, and the diagnosis should be supported by other phenotypic features and genetic testing.

Familial adenomatous polyposis/Gardner syndrome

Familial follicular thyroid carcinoma may occur in association with familial adenomatous polyposis (FAP), which is characterized by a large number of intestinal polyps and is frequently associated with colon carcinoma (110). This latter condition is also named Gardner syndrome, and patients frequently present other associated neoplasias, such as desmoid tumors and other skin lesions. Thus, patients with FAP should be routinely screened for follicular thyroid carcinoma. The disease is caused by mutations in the APC gene (OMIM, Gardner syndrome).

Multiple endocrine neoplasia type 2

MEN2 is a dominant inherited tumor syndrome that comprises MTC, PHEO, and HPT, whereas congenital megacolon may occur less frequently. MEN2A refers to cases with at least two of the three main MEN2-related tumors. MEN2B refers to patients with very aggressive MTC; PHEO; an absence of HPT; the presence of marfanoid body habitus, mucosal neuromas, and intestinal ganglioneuromas; and an inability to cry tears. FMTC refers to MEN2 cases with isolated MTC. MEN2 is caused by RET germline mutations and has a strong genotype-phenotype correlation, as documented in the first comprehensive MEN2 study (6-9). This correlation has been confirmed by several other investigators (17-20,111,112). RET mutation analysis consistently has a large impact on the clinical management of MEN2 patients (20). Several key clinical investigations and review articles are currently available to provide proper data on the genetic, clinical, pathological, and molecular aspects of MEN2 (17,48,111,113). Thus, we will briefly review some recent advances and issues that may be associated with MEN2.

Recently, exome studies performed in sporadic and familial MTC patients documented a high prevalence of RET and RAS mutations and concluded that mutations in both genes are the main tumor drivers, although they are mutually exclusive (114,115). Additionally, second or even third RET mutations coexisting in MEN2 cases have been reported (116,117). Somatic RET codon M918T mutations have also been confirmed as a frequent event (~40%) in sporadic MTC and are usually related to a poor MTC outcome (118).

Importantly, the 2009 Guidelines on MTC reduced by two years (from 5 yr to 3-4 yr of age) the age at which the 2001 MEN Consensus recommended performing preventive TTx in RET 634 codon mutation carriers (8,9). Notably, the surgical approach should be completed with a dissection of all lymph nodes from the central compartment when nodules are >0.5 cm and calcitonin >40 pg/mL. This shift towards intervention at earlier ages was based on the finding of micro-MTC in a 2-year-old patient harboring a RET 634-mutation and another in a 5-year-old child with metastatic MTC (9,46,47).

There has been some debate regarding RET Y791F and Ser649Leu variants. So far, these two variants have been viewed as disease-causing mutations, and TTx has been recommended in patients carrying the RET Y791F and Ser649Leu variants (118,119). However, recent findings have challenged this concept (75,111). Recently, in vitro studies showed that transfected cells with the RET L790F variant had no capacity for malignant transformation (120). Moreover, authorized catalogs such as the ARUP Online Scientific Resource (www.arup.utah.edu/database/MEN2/MEN2_welcome.php) and others eliminated Y791F and Ser649Leu variants from the list of RET mutation-causing diseases (111). Although further studies might be needed to clarify this topic, it would be cautious not to recommend preventive TTx in these cases based only on the presence of RET Y791F, Ser649Leu, and L790F variants. In 2012, RET polymorphisms G691S, L769L, S836S, and S904S from genetic carriers and non-carriers were studied, and they had no significant impact on the MTC phenotype (121). In contrast, RET polymorphisms may influence the expression of RET V804M mutations. Others found that cumulative SNPs may lead to aggressive MTC phenotypes (122). In

addition, the SDHD G12S SNP may modulate the MEN2A phenotype (123). In contrast, RET polymorphisms may influence the expression of RET V804M mutations. However, larger sample sizes of control individuals and affected patients are needed to provide further conclusions on the clinical significance of these RET variants (121).

Moreover, double RET germline variants were initially reported in three cases with atypical MEN2B presenting both a Val804Met (GTG-to-ATG) mutation in exon 14 and a Ser904Cys (TCC-to-TGC) mutation in exon 15 (22,59,124). However, in vitro studies of these variants are required to determine whether these variants are really mutations or non-synonymous SNP (120). Furthermore, we recently described the double RET Cys634Tyr/Y791F variant in four unrelated families with early, aggressive PHEOs associated with MTCs presenting the usual outcome for RET 634 mutations (22). Based on in vitro studies, we interpreted the RET 791 variant as a modulating factor of the PHEO/MEN2A phenotype (22).

Overall, non-cysteine RET codon mutations have a lower transformation cell capacity than cysteine codon mutations (111). In addition, some ''weak'' non-cysteine RET mutations, such as mutations at codons 804 and 883, may occasionally lead to MTC disease only in the homozygous condition (125). In particular, RET codon 804 mutations may lead to a wide range of phenotypes, variable penetrance and diverse clinical outcomes (126). In addition, V804/E805K, V804M/Y806C, and V804M/S904C RET mutations can cause MEN2B disease (124).

RET genetic testing should be performed in all patients with PHEO, congenital megacolon, MEN2B-related features, and apparently sporadic MTC cases (8,22,127). Furthermore, specific RET haplotypes have been confirmed in the last few years to be involved in congenital megacolon associated with MEN2 (128,129). Recent data demonstrated that the two RET protein isoforms, namely RET9 and RET51, are important factors in the intracellular trafficking and maintenance of RET signaling (130). Interestingly, recent clinical approaches involving numerous RET mutation-positive MEN2 patients with specific exons or codon disturbances have been reported (61,131). These investigations provide new insights into mutation-specific risk profiles and have improved our understanding of genotype-phenotype correlations in MEN2 (114-116).

An active familial screening for MEN2 is crucial, and some MEN2 patients and at-risk family members from Holland have been followed since 1975 (132,133). In São Paulo, Brazil, we have been clinically screening MEN2 cases and their parents since 1990 and genetically screening since 2002 (59,134).

The association of MTC with papillary thyroid cancer has been increasingly recognized in many patients, although new data are needed on the possible molecular mechanisms underlying this finding (135).

Calcitonin is an excellent serum tumor marker for MTC, although its accuracy is not 100%. However, many other conditions may lead to increased calcitonin values (136,137). Accordingly, the MTC risk is 8%, 25%, and 100% in cases with calcitonin values reaching up to 50 pg/ml, 100 pg/ml, and above 100 pg/ml, respectively (137). Thus, one should use 100 pg/ml as the cutoff point to avoid false-positive calcitonin tests, MTC misdiagnosis, and unnecessary thyroidectomies, as had occurred until a few years ago (136).

The first main clinical manifestation of MTC is a single or multinodular thyroid disease, and most European authors recommend routine measurements of serum calcitonin in thyroid nodules (137). This procedure has several advantages for the diagnosis of MTC. First, cases with false-positive calcitonin tests can be ruled out, and most patients will have calcitonin values <100 pg/ml. Second, calcitonin measurements are more sensitive than cytology when searching for MTC, unless calcitonin immunocytochemistry is routinely applied. Third, 0.5-1% of the thyroid nodules may harbor MTC, and these cases could otherwise be missed. Fourth, the adequate recognition of MTC in thyroid nodules allows the surgeon to perform TTx associated with a central compartment lymphadenectomy, instead of other approaches. Fifth, the MTC outcome is favorably affected by MTC diagnosis at early stages (137).

Several reports have documented a predominance of specific RET mutation types in restricted geographic areas. For instance, a high frequency of the RET codon 804 mutation was documented in Italian MEN2 cases, and RET V804M occurred at high frequencies (59%) in 67 MEN2 cases from Sardinia and surrounding islands (138). Uncommon RET exon 8 mutations have been described mostly in Brazil and Greece, so routine RET exon 8 analysis should be performed, mostly in specific geographic areas of Brazil and Greece (139,140).

Interestingly, the cortical-sparing adrenalectomy has been recommended in cases with bilateral adrenal PHEOs, such as in patients with MEN2 (79,80). This approach has been performed to avoid secondary life-threatening corticoadrenal insufficiency, as noted in the early surgical approaches, and the retroperitoneoscopic adrenalectomy is considered the ideal approach for adrenal glands (141). Cortical-sparing adrenalectomies in patients with bilateral PHEO offer a postoperative corticoid-free course, although this approach must be balanced against the risk of local recurrence (79). In addition, robot-assisted posterior retroperitoneoscopic adrenalectomy has been recently applied. In cases with bilateral total adrenalectomy, the control of adrenal insufficiency may present actual risks. Therefore, cortical-sparing adrenalectomy should be welcomed by all endocrine surgeons, even when considering a 10-20% risk of local recurrence over the long run. So far, this surgical approach has been restricted to only a few centers.

The RET protein has been considered as a potential therapeutic target in sporadic and hereditary MTC cases with local and distant metastasis (48). Currently, treatment with tyrosine kinase inhibitors should be offered to metastatic MTC patients, and several drugs have been tested, such as sunitinib and vandetanib (142).

Multiple endocrine neoplasia type 1

MEN1 is a highly complex inherited tumor syndrome associated with at least 20 different types of tumors. The three main MEN1-associated neoplasias are HPTs (90-100%), PITs (10-60%), and PETs (60-70%), although cutaneous (30-85%) and adrenal tumors (20-40%) are also frequently found (5,10,57,58). In patients with PETs/MEN1, the NF-PETs (up to 50%), gastrinomas (40%), and insulinomas (10%) are the most frequent tumors (10,58). MEN1 is caused by germline mutations in the MEN1 tumor suppressor gene, and more than 1,300 germline and somatic mutations have been described so far. MEN1 mutation analysis is useful for confirming a clinical diagnosis,

allowing the genetic screening of at-risk family members and proper genetic counseling (11). MEN1 screening is usually offered to all at-risk relatives, allowing early diagnosis and treatment. Several review articles on MEN1 are available (5,8,10,48,57,58,143). Thus, we will focus on current advances and specific issues relating to MEN1.

As noted, the genetic screening of asymptomatic MEN1 mutation carriers was considered to have a low impact on the clinical management of MEN1 until a few years ago (8). Recent data demonstrated that MEN1 screening has a substantial impact on the management of MEN1 (15,16,33,48-50,58,72,144). Thus, this procedure allows us to rule out MEN1 non-mutation carriers and MEN1 phenocopies from annual clinical screening. PTx will benefit most HPT/MEN1 cases, and preventive thymectomy will prevent the development of highly malignant and relatively frequent (up to 2.6%) thymic carcinoid (8). Early treatment of GH-secreting MEN1-associated PITs may prevent the development of gigantism. Early diagnosis and treatment in gastrinoma/MEN1 cases may lead to long survival and a good quality of life, and malignant NF-PETs/MEN1 may be submitted to early curative/preventive surgery (8,15,16,29,33-35,48-50,58). A prospective study involving MEN1 mutant gene carriers showed that periodic follow-ups allowed for early diagnosis and treatment because MEN1-related tumors were recognized up to 10 years before clinical disease (144). Additionally, genetic testing decreased the mortality and morbidity of MEN1 patients, as shown in a study that included 258 MEN1-mutation positive carriers (145). Furthermore, death rates and morbidity in cases with malignant gastrinomas/MEN1 have decreased significantly after medical treatment with omeprazole or similar drugs (58).

Importantly, MEN1 screening should be offered to all first-degree family members who are at risk (50%) of carrying a MEN1 germline mutation, and clinical screening for MEN1-associated tumors should start at the ages recommended by the 2012 MEN1 Clinical Practice Guidelines (10). Another important topic is the ethics involved in MEN1 testing (12).

A recent meta-analysis verified that the prevalence of PITs in MEN1 varies from 10% to 60%. PIT appearing as the first clinical manifestation of MEN1 may occur in up to 10% of cases; in these cases, syndrome recognition may be substantially delayed (146). PIT in MEN1 may occur in childhood, have rapid growth and development, be highly aggressive, and exhibit often invasive behavior, and most of these tumors are secreting macroadenomas at diagnosis. Prolactinoma is prevalent (80%), and the majority of the remaining cases are GH-secreting tumors, although non-functioning PITs (17%) may occur (20,43,146,147). The majority of MEN1/prolactinomas are benign, although rare cases may present with metastasis [297]. The normalization of pituitary hypersecretion is much less frequent in MEN1/PIT patients than in their SET counterparts. In addition, PIT cancer patients may need to be treated with temozolomide (146,148). A transcriptome tumor profile for a 5-year-old boy with prolactinoma/MEN1 from 2000 disclosed new genes that may lead to early PIT disease (149). Based on this specific case, both the 2001 Consensus and the 2012 Guidelines recommended that screening for PITs in MEN1 (prolactin and GH measurements and pituitary MRI) should start by the age of 5 years (8,10).

Recently, an NIH group investigated 19 patients with MEN1-associated ACTH- and non-ACTH-secreting tumors, and their etiology was determined in 14 of these cases (150). Eleven cases had Cushing's disease; three had ACTH-independent Cushing syndrome; three cases simultaneously had an ACTH-secreting tumor leading to Cushing's disease and non-secreting PIT microadenoma. Two of the three MEN1 patients with ACTH-independent CS also had ACC, and no ectopic ACTH secretion was identified. The etiology of hypercortisolism could not be defined in five patients, whereas in three cases, hypercortisolism appeared to resolve spontaneously (150).

The frequency of MEN1 mutations in MEN1-related tumors and their SET counterparts has been revised. MEN1 shows biallelic inactivation in 30% of some types of common variety endocrine tumors (e.g., parathyroid adenoma, gastrinoma, insulinoma, and bronchial carcinoid) but only 1-5% in sporadic PITs (151). Most functioning PETs in MEN1 are represented by gastrinomas (50-60%) and insulinomas (10%), and the first therapeutic option is essentially surgical (5,10,33-35). PETs in MEN1 are frequently found at the duodenum and rarely at the pancreas; they are usually malignant (60%), small (<1 cm) and multicentric; they are located on the duodenal mucosa (80%). PETs are the main cause of death of patients with MEN1 (60%) (33,35). Surgical approaches to gastrinomas frequently lead to no real cure, unless the surgery can be performed very early, before metastases. The main surgical alternatives are total and subtotal pancreatectomy, depending on the size and localization of the NF-PETs frequently associated with duodenal gastrinomas. The first option includes duodenotomy with resection of small and multiple duodenal gastrinomas, distal 80% subtotal pancreatic resection, and enucleation of lesser tumors in the head of the pancreas. Alternatively, pylorus-preserving pancreatoduodenectomy or pancreatoduodenectomy, as in the Whipple procedure, are performed in cases with large tumors localized in the head of the pancreas or with diffuse disease and all pancreatic tissue forbidding enucleation. The pancreatic tail may be spared in cases with limited local disease and normal endocrine and exocrine pancreatic functions. Exceptionally, a pancreas-preserving total duodenectomy has been performed in a patient with gastrinoma/MEN1. This surgical procedure, developed by Imamura et al., is invasive and complex and its use is still very limited. In patients with Zollinger-Ellison syndrome, the surgical procedure should be complemented by the excision of duodenal gastrinomas and regional lymph node metastases (33-35,152). Partial pancreatectomy, total pancreatoduodenectomy, and subtotal pancreatectomy-associated with resection of the small duodenal tumors (multiple nodulectomies) are the surgical options (33-35,152-154). In addition, gastric carcinoids are frequent in gastrinoma/MEN1 and require vigilance and adequate therapy (33).

There is a long-standing controversy as to the optimal timing for surgery in gastrinoma/MEN1 (77). Most doctors prefer to intervene surgically in gastrinoma/MEN1 cases presenting tumors larger than 2-3 cm. Conversely, a group from Uppsala, Sweden has significant clinical and surgical experience with MEN1, and they recommend surgery in PET/MEN1 cases presenting tumor dimensions as small as 1.0 cm (33,35,153,154). Because PETs are the second most common disease in MEN1, they play a pivotal role in the life expectancy and quality of life of MEN1 patients. Thus, screening with biochemical markers and endoscopic

ultrasound is recommended for early PET detection in asymptomatic MEN1-mutation positive cases. Surgery is currently recommended for all PET cases with tumors larger than 1.0 cm and no metastases, including NF-PETs. The latter strategy employs early and aggressive surgery before metastases can develop, which substantially reduces the risk for tumor recurrence and malignant progression (33-35,153,154). More recently, a high prevalence of combined NS-PET and gastrinoma occurrence has been documented, and patients were approached by distal 80% subtotal pancreatic resection associated with tumor enucleation at the pancreatic head. In Zollinger-Ellison syndrome, duodenotomy followed by excision of duodenal gastrinomas together with a clearance of regional lymph node metastases is recommended (152).

Most NF-PETs in MEN1 have a highly malignant behavior and are located at the pancreas (8,10). Thus, tumor serum markers such as PP and chromogranin-A have become increasingly important for the early detection of NF-PETs (153,154). Patients may also have increased levels of insulin/proinsulin, glucagon, and VIP values, without hormone excess syndrome (154). Studies of NF-PETs/MEN1 in the French GTE register revealed a low (4%) metastasis rate for tumors ≤10 mm and notably higher metastasis rates (15–52%) for larger tumors (155-157). However, the authors recommended surgery for NF-PETs greater than or equal to 2 cm, although they reported a 15% mortality risk from pancreatic surgery (155-157). Conversely, surgery for NF-PETs around or greater than 1.0 cm has been recommended by others because the metastasis rate is unacceptably high for larger tumors, and surgery has been performed in rather large series without mortality (35). As already mentioned, the preference of the Swedish group is to operate on functioning and NF-PETs in MEN1 using an early, aggressive surgical approach before metastases have developed. Excellent results have been reported for a long time with this approach (33,35,153,154). The surgical strategy is based on distal 80% subtotal pancreatic resection associated with the enucleation of tumors located in the head of the pancreas (152).

MEN1-related insulinomas are mostly benign (90%) and may develop at very early ages (10,153). The optimal timing to start clinical screening for insulinoma in MEN1 mutation carriers is 5 years of age (8,10). The simultaneous occurrence of insulinoma and multicentric NF-PETs is frequent in patients with MEN1. In addition, subtotal pancreatectomy associated with tumor enucleation at the pancreatic head is usually performed in cases with the MEN1/insulinomas. In conclusion, the early diagnosis and surgical treatment of PETs/MEN1 are critical topics for achieving a cure, as previously reported (33,35,153,154).

The timing for starting genetic screening in at-risk family members was first established by the 2001 consensus. Thus, clinical screening should start at 5 years of age for PITs and insulinomas in MEN1-mutation positive patients; at 8-10 years for HPT; and by 20 years for gastrinomas and NF-PETs, although the 2012 Clinical Practice Guidelines reduced the age for the latter procedure, which should begin at 10 years (8,10).

MEN1-associated primary HPT has a high penetrance, and almost all MEN1 cases will present HPT by 50 years of age, although most cases will exhibit the disease by 20 years of age (5,10,31). HPT/MEN1 usually develops 30 years earlier than its SET counterpart, although most patients will

exhibit the disease by 20 years of age (5,10,31). This condition affects all four parathyroid glands and is a monoclonal event, and it is frequently the first MEN1 presentation. Patients usually have early and severe bone demineralization and renal complications that were considered an important cause of death, at least until 1998 (45,46,158). It is still a matter of debate how to operate on HPT/MEN1 patients (48,51). PTx is advised by most surgeons and clinicians as the optimal approach to HPT/MEN1. However, there is a dispute as to whether subtotal or total PTx would be optimal for treating this condition (51,57,159,160). Subtotal PTx is largely applied, which usually leads to low rates of secondary hypoparathyroidism and may involve lesser surgical complications. However, one-third of cases may present HPT relapse/recurrence during the post-surgical follow-up, and substantial surgical difficulties may appear during parathyroid re-intervention (159). Conversely, total PTx followed by parathyroid auto-transplant to the non-dominant forearm is a valuable alternative and may have some advantages (48,51,160). First, post-surgical hypoparathyroidism is most frequently observed until 6-12 months after PTx. Subsequently, by months 12-15 after PTx, most patients will recover their normal serum PTH and calcium values, allowing the end of oral calcium and vitamin D supplementation (49,50). Our data have been confirmed by others (161). Thus, successful parathyroid auto-implants that were either cryopreserved or performed immediately after total PTx may secrete sufficient physiological amounts of PTH and achieve euparathyroidism (49,50,161,162). Additionally, the rate of relapse/recurrent HPT after total PTx is usually lower than in subtotal PTx, and when it occurs, the partial excision of the parathyroid implant requires only local forearm anesthesia (160).

In addition, there is some controversy as to when to operate on HPT/MEN1 cases, although several groups prefer to perform PTx as soon as there is a classical indication to recommend surgery (52,57,163). Notably, the criteria used to recommend PTx in HPT/MEN1 cases are the same as those used for sporadic primary HPT and include the presence of albumin-corrected total calcium at 1 mg/dl higher than the upper normal ranges, renal calculi, age at diagnosis lower than 50 years, and osteoporosis (163). Thus, severe bone mineral losses (Z-score <-2.0 or a T-score <-2.5 SD) constitute a classical recommendation for PTx in HPT/MEN1 cases (44,45,49,50). In addition, PTx usually leads to a substantial decrease in the gastrin serum levels in cases with associated gastrinoma and allows for the performance of concomitant preventive thymectomy (8,10,164). Alternatively, some authors prefer to postpone PTx in apparently asymptomatic primary HPT cases (31).

Lourenço Jr et al. recently suggested that the annual bone mineral density (BMD) analysis in HPT/MEN1 cases should start at ages as early as 20 years and include all three main bone sites because the proximal one-third of the distal radius (1/3DR) is severely affected in patients with HPT/MEN1 (44,45,165). If the 1/3DR is not approached, some cases with severe bone mineral losses may be missed (44,45,49,50). In addition, a short-term BMD improvement was recently noted after total PTx followed by parathyroid auto-transplant in HPT/MEN1 cases (49). As far as we know, only two studies have consistently evaluated BMD values after PTx in cases of MEN1-associated HPT (49,165). Concordantly, BMD exhibits a sharp short-term recovery at

the lumbar spine and femoral neck but not at the 1/3DR (49,50,165).

Benign cutaneous tumors (collagenomas and angiofibromas, >70-80%) are highly prevalent in MEN1 and are an excellent clinical indicator for the early clinical diagnosis of MEN1 (8). Additionally, adrenal tumors are frequently found in patients with MEN1 (>40%) (5,10). Interestingly, glucose-dependent insulinotropic peptide receptor over-expression in adrenocortical hyperplasia without LOH at the 11q13 locus has been reported in MEN1 syndrome (166). Adrenal tumors/MEN1 are mostly non-secreting benign neoplasias, however periodic screening for secreting tumors and ACC are currently recommended (8,10).

Ongoing studies on the clinical heterogeneity in MEN1 are attempting to explain the marked intra- and inter-familial phenotypic variations. MEN1 non-synonymous SNPs, sequencing variants in other genes, copy number variations, iRNA, and epigenetic factors (e.g., DNA methylation) have been claimed as potential phenotypic modifiers (143). Accordingly, tissue-specific susceptibilities to MEN1-related tumors deserve further investigation, and possible genotype-phenotype correlations have been recently revised (143).

Recently, Zhang et al. and Lewis et al. confirmed that MEN1 patients have decreased insulin sensitivity, a higher prevalence of impaired fasting glucose compared with controls unrelated to MEN1 manifestations, and an increased risk of cardiovascular disease (167,168). Thus, it is important to search for glucose intolerance and diabetes in all MEN1-mutation carriers.

Carcinoid tumors are frequent in patients with MEN1 and may be mostly found in the gastric area (10%), bronchi (2%), and thymus (2%) (169). Thymic carcinoids are fast growing, highly aggressive malignant tumors and are prevalent (up to 3.5%) in some MEN1 series (170). Most affected cases are in heavy smoking males. Conversely, bronchial carcinoid/MEN1s have a less aggressive outcome and are more prevalent in women (169). Preventive transcervical thymectomy during PTx for HPT/MEN1 is usually effective in preventing the development of thymic carcinoids, although in other series, this surgical approach was not sufficient to prevent local and distant metastases (156,171).

Multiple endocrine neoplasia type 4

Not all patients with a MEN1 phenotype harbor a germline MEN1 mutation, even when considering patients with large deletions and intronic mutations. Thus, a new gene(s) has been proposed for cases with MEN1-like phenotypes and no MEN1 mutations. Concordantly, a female index-case with acromegaly from a pituitary GH-secreting tumor associated with primary HPT was described as carrying a germline mutation in the CDKN1B gene in 2006. In addition, her mutation-positive relative had a renal angiomyolipoma (54). Several other similar cases with MEN1-like phenotypes have been reported, supporting the idea that all MEN1 cases without MEN1 germline mutations should be screened for the CDKN1B gene (54,172,173). However, due to the limited number of affected cases reported so far (10 cases), the MEN4 phenotype has not been fully established (54).

Inherited pancreatic endocrine tumor syndromes

Familial PETs may occur in patients with MEN1, CS, VHL disease, NF1, and TSC (77). The relative frequency of PETs is higher in patients with MEN1 and VHL compared with CS,

NF1, and TSC. Preoperative assessment of the pancreas in MEN1 is highly critical because it may allow surgeons to better plan the approach and evaluate when and how to operate (167). Specifically, familial gastric stromal tumors may be found in patients with CS and differ from its SET counterpart (168). Surgery and radiofrequency ablation have been utilized to treat liver metastases from midgut and foregut carcinoids and PETs. Notably, a study of PETs in these syndromes provided insights into the possible pathogenesis of sporadic PETs and contributed to the clinical and therapeutic management of each inherited condition and their sporadic tumor counterparts.

Isolated familial acromegaly/gigantism

Acromegaly/gigantism has been a long-standing challenge. In Belgium, patients with acromegaly/gigantism are 3-5 times more prevalent than previously reported, yielding 1 case in 1,064 individuals (174). In 2012, de Herder described six of the most famous giants ever known in the last two or three centuries (175). One of these cases had a genetic predisposition to GH-secreting tumors and harbored a germline AIP mutation (65). Most patients with isolated familial somatotropinoma (IFS) do not harbor MEN1 germline mutations, but their tumors secrete high serum levels of GH and are associated with acromegaly/gigantism (176). The genetic cause of IFS has been linked to the same gene locus of MEN1, that is, 11q13, although no MEN1 germline mutation has been verified in these cases. In 2006, germline AIP mutations were reported in several IFS cases from Finland; soon after, these data were confirmed in Belgium and Brazil (41,177). The onset of a GH-secreting tumor in IFS cases occurs approximately 4-10 years earlier than sporadic PITs and these tumors are highly aggressive (37). After the AIP discovery, IFS cases have been referred to as FIPA (26,174). Interestingly, familial somatotropinoma leading to acromegaly/gigantism may also occur in the context of other IET syndromes, such as MEN1, CS, and autosomal dominant polycystic kidney disease (178,179).

Familial isolated pituitary adenoma

This entity is an autosomal inherited tumor syndrome characterized by the presence of a PIT that secretes GH and prolactin, although non-functioning PITs, Cushing's disease, and thyrotropinoma may also occur. PITs in patients with FIPA differ from sporadic PITs in several respects because they are more aggressive and expansive and usually have an earlier onset (<20 yr of age). Young FIPA patients often harbor macroadenomas that may be partially resistant to cabergoline therapy (174). The first description of AIP mutations was performed with a large group of patients with familial acromegaly/gigantism from Finland (42). Other authors have published similar data (41,180). Two Brazilian siblings with acromegaly and GH-secreting PITs were clinically reported in 2001, and a heterozygous AIP mutation was documented soon after (42,176). Another clinically unaffected 41-year-old brother carried this mutation on an apparently non-secreting pituitary micro-nodule (3 mm) and was documented in imaging studies. His 3-year-old mutated son was also unaffected (42). Overall, 5% of all PITs are related to MEN1, FIPA, CS, and MEN4 (26,37). Up to 25% of all FIPA cases harbor a germline AIP mutation, although AIP germline mutations have rarely been detected in apparently sporadic PITs. However, a high

prevalence of AIP mutations in macroadenoma cases younger than 30 years of age (10%) and in children with macroadenomas (>20%) have been verified (180). Furthermore, FIPA may have a relatively high prevalence in the general population because it accounts for up to 2-3% of PITs in some series. In groups at high risk of AIP mutations, genetic screening is recommended because it may lead to early diagnosis and treatment (180). Recently, an international consortium investigated 96 patients with germline AIP mutations and PITs and 232 matched AIP mutation-negative acromegaly controls. The group concluded that the first symptoms occurred in children/adolescents in 50% of cases, and most tumors were macroadenomas (93.3%). Tumor extension and invasion was common. GH-secreting tumors in FIPA were predominant (78.1%) and larger, with higher GH levels and occurrence two decades earlier, when compared with sporadic PITs (26). Gigantism was more common in the AIP-mutated group, and several cases presented less tumor shrinkage with somatostatin analogs *versus* the controls. Prolactinoma in FIPA was frequent in young males patients, and most required surgery or radiotherapy. These data indicate that the genetic screening associated with early diagnosis and treatment should be routinely considered in families with PITs/FIPA (26). Recently, genetic heterogeneity was suggested to occur in FIPA (181,182). In addition, the presence of ACC in a FIPA case suggested that AIP mutations may be lead to non-PIT tumors (181). In conclusion, AIP mutation analysis is recommended in young patients with FIPA.

Founding AIP mutations have been described in familial clusters from Finland, Polynesia, and Ireland. A large family presenting with multiple individuals with PITs secreting GH, prolactin, or both was reported in northern Finland. There were three cases of acromegaly or gigantism, and their genealogy could be traced to the 1700s. The phenotype was first postulated to represent a hereditary predisposition to pituitary adenomas (PAPs) with very low penetrance. A second family had two affected cases in two generations with somatotropinoma. In comparison to patients with sporadic PITs, patients with PAP were significantly younger at diagnosis, but there were no significant differences in tumor size. Six of the 15 patients diagnosed under 35 years of age (40%) in the population-based series had PAP. More recently, PAP cases have been referred to as FIPA (41). Highly aggressive PITs were reported in 2009 in a large FIPA Polynesian genealogy associated with a founding AIP mutation (183). In 2011, the AIP arg304-to-ter mutation was identified in DNA extracted from the teeth of an Irish patient with gigantism who lived from 1761 to 1783 (65). Decades prior, Harvey Cushing first examined the skeleton of this particular case described in 2011, identified an enlarged pituitary fossa, and ascribed his gigantism to a PAP. The same AIP germline mutation was identified in four contemporary northern Irish families who presented with gigantism, acromegaly, or prolactinoma, and they also harbored the same haplotypes. Thus, these individuals were postulated to share a common ancestor who lived approximately 57 to 66 generations earlier (65).

Familial Cushing's syndrome

This condition may be associated with MEN1 and CS and is rarely associated with FIPA; however, it may also occur in McCune-Albright syndrome (184). Accordingly, familial pituitary ACTH-secreting tumors leading to Cushing's

disease may occur in MEN1 syndrome (6). In addition, non-ACTH secreting Cushing's syndrome from adrenocortical carcinomas and adenomas may also occur in MEN1, and a few cases may present both ACTH-secreting and non-ACTH secreting tumors (150). Furthermore, pigmented adrenal hyperplasia is a non-ACTH secreting tumor frequently observed in patients with CS (37).

Familial papillary thyroid carcinoma

FPTC is usually more aggressive than sporadic PTC and may be associated with FAP/Gardner syndrome and Cowden syndrome (185). Over a decade ago, the search for FPTC susceptibility genes identified the following six potential loci: MNG1 (14q32), TCO (19p13.2), fPTC/PRN (1q21), NMTC1 (2q21), FTEN (8p23.1-p22), and the telomere-telomerase complex. Genes such as RET, TRK, MET, and TSHR were ruled out. The results have been partially contradictory, and further large-scale genetic studies using new molecular screening tests are warranted to elucidate the underlying genetic basis of FPTC (110).

Familial isolated hyperparathyroidism

Most cases with primary HPT (95%) are sporadic; the remaining patients have inherited forms of HPT. At present, most HPT cases are asymptomatic (80%), whereas 20% are symptomatic cases (31). FIHPT may occur as part of either MEN1 syndrome or FIHPT/jaw tumor syndrome (HPT/JT) caused by HRPT2 germline mutations. Interestingly, HRPT2 mutations have been reported in 15% of parathyroid carcinoma cases, which rarely lead to HPT (186). HPT-JT is a rare inherited cancer syndrome that is usually associated with HPT and ossifying tumors of the maxilla/mandible, and it may harbor a germline HRPT2-inactivating mutation. HRPT2 encodes a 531-amino acid protein called parafibromin (186). Mild FIHPT may also occur in familial hypocalciuric hypercalcemia (FHH), an autosomal dominant disease with relative hypocalciuria. Most FHH cases are caused by a heterozygous CASR inactivating mutation, although homozygous or compound heterozygous CASR mutations can lead to severe neonatal HPT. Moreover, a homozygous CaSR germline missense mutation has been reported in FHH phenotypes, although most heterozygotes are normocalcemic. However, many FIHPT cases have no mutation in the MEN1, HRPT2, or CASR genes, suggesting that additional gene(s) are be involved.

Familial primary aldosteronoma

FPA is a relatively underdiagnosed condition, and it is the most frequent cause (5-15%) of secondary hypertension in adults (187). FPA has been mostly detected in non-smoker hypertensive patients. Due to a higher rate of cardiovascular complications relative to essential hypertension, the screening of at-risk groups for FPA is recommended (188). FPA is confirmed by a lack of aldosterone suppressibility following a sodium-loading test. CT scanning and adrenal venous sampling usually detect a unilateral source of aldosterone excess. Laparoscopic adrenalectomy is the treatment of choice, with excellent outcomes and low morbidity, in comparison with older, open approaches. Three genetic forms of FPA have been described so far, including familial hyperaldosteronism type I (FH-I), also known as glucocorticoid-remediable aldosteronism (GRA); familial hyperaldosteronism type II (FH-II); and familial hyperaldosteronism type III (FH-III).

Patients with FH-I/GRA have hypertension, high ACTH-dependent aldosterone secretion, renin suppression, and high levels of 18OH-cortisol and 18 oxocortisol. The genetic cause is an unequal recombination of CYP11B1 (11-β-hydroxylase)/CYP11B2 (aldosterone synthase) that leads to a chimeric CYP11B gene containing CYP11B1 sequences (including the promoter) at its 5' end and CYP11B2 sequences at its 3' end (187). This condition is very rare, and most patients develop severe hypertension in early life, although clinical heterogeneity is frequent. Genetic testing for FH-I/GRA is recommended for cases presenting with FPA before 20 years of age, a family history of FPA, and stroke at a young age (<40 years) (187). In 2011, a high prevalence of FH-I/GRA among hypertensive children in Chile was reported (3.1%). All cases from four unrelated families had a high aldosterone/renin ratio and low renin, whereas hypokalemia and high aldosterone levels were much less useful as markers of FPA. Genetic testing overcomes these difficulties, and the most widely used test is a long PCR-based method that amplifies the chimeric CYP11B1/B2 gene. FH-II is a non-glucocorticoid-remediable form of FPA, and it is indistinguishable from sporadic PA. This condition is relatively frequent (3-4%), and its molecular basis involves the 7p22 locus. The diagnosis of FH-II requires the presence of PA to be confirmed in at least two family members, and FH-I/GRA must be excluded. FH-II should be considered in hypertensive family members of PA patients. So far, this new condition was reported in one family, is characterized by severe hyperaldosteronism and resistance to common medical therapy, and requires bilateral adrenalectomy. A germline mutation in the KCNJ5 gene is the cause of FH-III.

Inherited adrenocortical carcinoma

Inherited adrenocortical tumors (carcinomas and adenomas) may occur in several conditions such as CS, LFS, Beckwith-Wiedemann syndrome (BWS), MEN1, NF1, FAP, and McCune Albright syndrome (90,107,108,189). Children with IACC are usually part of the classical tumor spectrum of LFS and BWS. The current recommendations regarding IACC screening and surveillance involve periodic biochemical and imaging studies in the index-cases, mutation analysis of all relatives who are at risk, and early diagnosis and surgical intervention.

Familial isolated pheochromocytoma/paraganglioma

FI-PHEO/paraganglioma has been associated with several inherited diseases such as MEN2; VHL; NF-1; and paraganglioma syndromes types 1, 3, and 4, which are caused by germline mutations in RET, VHL, NF1, SDH-D, SDH-C, and SDH-B, respectively (78,91,190). SDHx mutations are responsible for 6% and 9% of sporadic paragangliomas and PHEOs, respectively; in addition, they underlie 29% of pediatric cases and 38% of malignant tumors. More than 80% of familial aggregations of paraganglioma and PHEO are caused by these mutations (191). In addition, FI-PHEO/paraganglioma has been associated with TMEM127 and MAX mutations (23,24,25,192). Genetic screening for PHEO genes has been recommended in all cases with apparently sporadic PHEO/paraganglioma because approximately 30% of these patients may harbor a PHEO-related germline mutation. In a German series of apparently sporadic PHEOs, frequent mutations in the VHL and RET were found (57). In contrast, unsuspected germline mutations occurred in eight cases within a recent Italian series of 59 patients with apparently sporadic disease. The eight mutations were found in TMEM127 (n = 4), SDHB (n = 2), VHL (n = 1), and SDH-C (n = 1). Despite increased costs, the authors recommended systematic genetic screening in these patients because it might lead to a stricter follow-up, early diagnosis of recurrences in index-cases, and presymptomatic disease detection in at-risk relatives.

In 2012, a high incidence of paraganglioma type 1 syndrome was reported in Trentino, Italy, and affected cases were characterized by HNPs caused by the SDHD c.341A>G p.Tyr114Cys mutation. Patients had bilateral or multiple HNPs that were associated with a low prevalence of PHEO, malignant forms, and a high tumor penetrance. A common ancestor was dated back to the 14-15th century, with the mutation spreading from the Mocheni Valley isolate, which represents 1.5% of the region's population (64).

Pre-surgical care in asymptomatic FI-PHEO cases has some particularities. Because sustained or paroxysmal hypertension is detected in 90% of PHEO cases, α-adrenoceptor-blocking agents have been successfully administered to prevent hypertension before and during surgery for PHEO. With the discovery of asymptomatic PHEOs, many of them FI-PHEOs, this condition has been more frequently diagnosed than it was before modern imaging techniques were available. Accordingly, accumulated experiences with the use of α-adrenoceptor-blocking agents in asymptomatic PHEOs support the benefits of this procedure. Finally, cases with bilateral FI-PHEO are currently recommended to undergo cortical-sparing surgery using the retroperitoneoscopy access, which has a low recurrence rate and avoids lifelong cortisone substitution therapy in most cases. Thus, it would be prudent to recommend this surgical technique to all patients with bilateral PHEO.

Finally, more recent IET reviews have become available, and they provide further insights into these inherited tumor diseases (193-198).

◼ AUTHOR CONTRIBUTIONS

Toledo SP coordinated the review and worked intensively for months on this review project. Lourenço Jr. DM and Toledo RA reviewed carefully several articles and collaborated by discussing, commenting and writing part of the manuscript.

◼ REFERENCES

1. Leonard JM. Familial endocrine tumors. West J Med. 1980;132(4):352-33.
2. Neumann HPH, Vortmeyer A, Schmidt D, Werner M, Erlic Z, Cascon A, et al. Evidence of MEN-2 in the original description of classic pheochromocytoma. New Eng J Med. 2007;357(13):1311-5, http://dx.doi.org/10.1056/NEJMoa071407.
3. Wermer P. Genetic aspects of adenomatosis of endocrine glands. Am J Med. 1954;16(3):363-71.
4. Carney JA. Familial multiple endocrine neoplasia: the first 100 years. Am J Surg Pathol. 2005;29(2):254-74.

5. Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. Nat Rev Cancer. 2005;5(5):367-75.

6. Mulligan L, Marsh DJ, Robinson BG, Shuffenecker I, Zedenius J, Lips CJM, et al. Genotype-phenotype correlation in multiple endocrine neoplasia type 2: report of the International RET Mutation Consortium. J Intern Med. 1995;238(4):343-46, http://dx.doi.org/10.1111/j.1365-2796.1995.tb01208.x.

7. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. JAMA. 1996;276(19):1575-9, http://dx.doi.org/10.1001/jama.1996.03540190047028.

8. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658-71, http://dx.doi.org/10.1210/jc.86.12.5658.

9. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009;19(6):565-612, http://dx.doi.org/10.1089/thy.2008.0403.

10. Thakker RV, Newey J, Walls GV, Bilezikian J, Dralle H, Ebeling PR. et al. Clinical practice guidelines for multiple endocrine neoplasia type 1(MEN1). J Clin Endocrinol Metab. 2012;97(9):2990-3011, http://dx.doi.org/10.1210/jc.2012-1230.

11. Lips CJ, Höppener JW. Ethics: Genetic testing for MEN1-whose responsibility? Nat Rev Endocrinol. 2012;8(10):575-6, http://dx.doi.org/10.1038/nrendo.2012.164.

12. Toledo RA, Sekiya T, Longuini VC, Coutinho FL, Lourenço DM Jr, Toledo SP. Narrowing the gap of personalized medicine in emerging countries: the case of multiple endocrine neoplasias in Brazil. Clinics. 2012;67 Suppl 1:3-6, http://dx.doi.org/10.6061/clinics/2012(Sup01)02.

13. Dammann M, Weber F. Personalized medicine: caught between hope, hype and the real world. Clinics. 2012;67 Suppl 1:91-7, http://dx.doi.org/10.6061/clinics/2012(Sup01)16.

14. Carling T, Correa P, Hessman O, Hedberg J, Skogseid B, Lindberg D et al. Parathyroid MEN1 gene mutations in relation to clinical characteristics of nonfamilial primary hyperparathyroidism. J Clin Endocrinol Metab. 1998;83(8):2960-3, http://dx.doi.org/10.1210/jc.83.8.2960.

15. Lourenço DM Jr, Toledo RA, Coutinho FL, Margarido LC, Siqueira SA, dos Santos MA, et al. The impact of clinical and genetic screenings on the management of the multiple endocrine neoplasia type 1. Clinics. 2007;62(4):465-76, http://dx.doi.org/10.1590/S1807-59322007000400014.

16. Lourenço DM Jr, Coutinho FL, Toledo RA, Gonçalves TD, Montenegro FL, Toledo SP. Biochemical, bone and renal patterns in hyperparathyroidism associated with multiple endocrine neoplasia type 1. Clinics. 2012;67Suppl 1:99-108, http://dx.doi.org/10.6061/clinics/2012(Sup01)17.

17. Machens A, Niccoli-Sire P, Hoegel J, Frank-Raue K, van Vroonhoven TJ, Roeher HD, et al. Multiple Endocrine Neoplasia (EUROMEN) Study Group. Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med. 2003;349(16):1517-25.

18. Machens A, Dralle H. Familial prevalence and age of RET germline mutations: implications for screening. Clin Endocrinol (Oxf). 2008;69(1):81-87, http://dx.doi.org/10.1111/j.1365-2265.2007.03153.x.

19. Machens A, Dralle H. Multiple endocrine neoplasia type 2: achievements and current challenges. Clinics. 2012;67 Suppl 1:113-118, http://dx.doi.org/10.6061/clinics/2012(Sup01)19.

20. Toledo SP, dos Santos MA, Toledo RA, Lourenço DM Jr. Impact of RET proto-oncogene analysis on the clinical management of multiple endocrine neoplasia type 2. Clinics. 2006;61(1):59-70, http://dx.doi.org/10.1590/S1807-59322006000100011.

21. Correia-Deur JE, Toledo RA, Imazawa AT, Lourenço DM Jr, Ezabella MC, Tavares MR, et al. Sporadic medullary thyroid carcinoma: clinical data from a university hospital. Clinics. 2009;64(5):379-86.

22. Toledo RA, Wagner SM, Coutinho FL, Lourenço DM Jr, Azevedo JA, Long uini VC, et al. High penetrance of pheochromocytoma associated with the novel C634Y/Y791F double germline mutation in the RET protooncogene. J Clin Endocrinol Metab. 2010;95(3):1318-27, http://dx.doi.org/10.1210/jc.2009-1355.

23. Burnichon N, Cascón A, Schiavi F, Morales NP, Comino-Méndez I, Abermil N, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. Clin Cancer Res. 2012;18(10):2828-37, http://dx.doi.org/10.1158/1078-0432.CCR-12-0160.

24. Qin Y, Yao L, King EE, Buddavarapu K, Lenci RE, Chocron ES, et al. Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. Nat Genet. 2010;42(3):229-233, http://dx.doi.org/10.1038/ng.533.

25. Yao L, Schiavi F, Cascon A, Qin Y, Inglada-Pérez L, King EE, et al. Spectrum and prevalence of FP/TMEM127 gene mutations in pheochromocytomas and paragangliomas. JAMA. 2010;304(23):2611-9, http://dx.doi.org/10.1001/jama.2010.1830.

26. Daly AF, Tichomirowa MA, Petrossians P, Heliövaara E, Jaffrain-Rea ML, Barlier A, et al. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. J Clin Endocrinol Metab. 2010;95(11):E373-383, http://dx.doi.org/10.1210/jc.2009-2556.

27. Vezzosi D, Vignaux O, Dupin N, Bertherat J. Carney complex: Clinical and genetic 2010 update. Ann Endocrinol (Paris). 2010;71(6):486-493, http://dx.doi.org/10.1016/j.ando.2010.08.002.

28. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011;19(6):617-23.

29. Stratakis CA, Schussheim DH, Freedman SM, Keil MF, Pack SD, Agarwal SK, et al. Pituitary macroadenoma in a 5-year-old: an early expression of multiple endocrine neoplasia type 1. J Clin Endocrinol Metab. 2000;85(12):4776-80, http://dx.doi.org/10.1210/jc.85.12.4776.

30. Bausch B, Koschker AC, Fassnacht M, Stoevesandt J, Hoffmann MM, Eng C, et al. Comprehensive mutation scanning of NF1 in apparently sporadic cases of pheochromocytoma. J Clin Endocrinol Metab. 2006;91(9):3478-81, http://dx.doi.org/10.1210/jc.2006-0780.

31. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008; 93(9):3462-3470, http://dx.doi.org/10.1210/jc.2007-1215.

32. Lourenco DM Jr, Coutinho FL, Toledo RA, Gonçalvez TD, Montenegro FLM, Toledo SPA. Biochemical, bone, and renal patterns in hyperparathyroidism associated with multiple endocrine neoplasia type 1. Clinics. 2012;67 Suppl 1:99-108, http://dx.doi.org/10.6061/clinics/2012(Sup01)17.

33. Akerström G, Stålberg P, Hellman P. Surgical management of pancreatico-duodenal tumors in multiple endocrine neoplasia syndrome type 1. Clinics. 2012;67 Suppl 1:173-8, http://dx.doi.org/10.6061/clinics/2012(Sup01)29.

34. Machado MC. Surgical treatment of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. Clinics. 2012;67 Suppl 1:145-8, http://dx.doi.org/10.6061/clinics/2012(Sup01)24.

35. Oberg K. Diagnostic work-up of gastroenteropancreatic neuroendocrine tumors. Clinics. 2012;67 Suppl 1:109-12, http://dx.doi.org/10.6061/clinics/2012(Sup01)18.

36. Stratakis CA, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. J Clin Endocrinol Metab. 2001;86(9):4041-6, http://dx.doi.org/10.1210/jc.86.9.4041.

37. Stratakis CA, Tichomirowa MA, Boikos S, Azevedo MF, Lodish M, Martari M, et al. The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas in a large cohort of children, adolescents, and patients with genetic syndromes. Clin Genet. 2010;78(5):457-63, http://dx.doi.org/10.1111/j.1399-0004.2010.01406.x.

38. Machens A, Gimm O, Hinze R, Hoppner W, Bohem BO, Dralle H. Genotype-phenotype correlations in hereditary medullary thyroid carcinoma: oncological features and biochemical properties. J Clin Endocrinol Metab. 2001;86(3):1104-9, http://dx.doi.org/10.1210/jc.86.3.1104.

39. Hayashida CY, Alves VA, Kanamura CT, Ezabella MC, Abelin NM, Nicolau W, et al. Immunohistochemistry of medullary thyroid carcinoma and C-cell hyperplasia by an affinity-purified anti-human calcitonin antiserum. Cancer. 1993;72(4):1356-63, http://dx.doi.org/10.1002/1097-0142(19930815)72:4<1356::AID-CNCR2820720434>3.0.CO;2-0.

40. Tavares MR, Toledo SP, Montenegro FL, Moyses RA, Toledo RA, Sekyia T, et al. Surgical approach to medullary thyroid carcinoma associated with multiple endocrine neoplasia type 2. Clinics. 2012;67 Suppl 1:149-54, http://dx.doi.org/10.6061/clinics/2012(Sup01)25.

41. Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, et al. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. Science. 2006;312(5777):1228-30, http://dx.doi.org/10.1126/science.1126100.

42. Toledo RA, Lourenço DM Jr, Liberman B, Cunha-Neto MB, Cavalcanti MG, Moyses CB, et al. Germline mutation in the aryl hydrocarbon receptor interacting protein gene in familial somatotropinoma. J Clin Endocrinol Metab. 2007;92(5):1934-7, http://dx.doi.org/10.1210/jc.2006-2394.

43. Verges B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G, et al. Pituitary Disease in MEN Type 1 (MEN1): Data from the France-Belgium MEN1 Multicenter Study J. Clin. Endocrinol. Metab. 2002;87(2):457-65, http://dx.doi.org/10.1210/jc.87.2.457.

44. Lourenço Jr DM, Toledo RA, Mackowiak II, Coutinho FL, Cavalcanti MG, Correia-Deur, et al. Multiple endocrine neoplasia type 1 in Brazil: MEN1 founding mutation, clinical features, and bone mineral density profile. Europ J Endocrinol. 2008;159(3):259-74.

45. Lourenço DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correa-Deur JE, Toledo SP. Early-onset, progressive, frequent, extensive, and severe boné mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyrodism. J Bone Miner Res. 2010;25(11):2382-91, http://dx.doi.org/10.1002/jbmr.125.

46. Modigliani E, Coben R, Campos JM, Conte-Devolx B, Maes B, Boneu A, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d'etude des tumeurs a calcitonine. Clin Endocrinol (Oxf). 1998;48(3):265-73, http://dx.doi.org/10.1046/j.1365-2265.1998.00392.x.

47. Gill JR, Reyes-Mugica M, Iyengar S, Kidd KK, Touloukian RJ, Smith C, et al. Early presentation of metastatic medullary cancer on multiple endocrine neoplasia, type IIA: implications for therapy. J Pediatr. 1996;129(3):459-64, http://dx.doi.org/10.1016/S0022-3476(96)70084-7.

48. de Groot JWB, Links TP, Plukker JTM, Lips CJM, Hofstra RMW. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. Endocr Rev. 2006;27(5):535-60, http://dx.doi.org/10.1210/er.2006-0017.

49. Montenegro FL, Lourenço DM Jr, Tavares MR, Arap SS, Nascimento CP Jr, Massoni Neto LM, et al. Total parathyroidectomy in a large cohort of cases with hyperparathyroidism associated with multiple endocrine neoplasia type 1: experience from a single academic center. Clinics. 2012;67 Suppl 1:131-9, http://dx.doi.org/10.6061/clinics/2012(Sup01)22.

50. Coutinho FL, Lourenço DM Jr, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Bone mineral density analysis in patients with primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 after total parathyroidectomy. Clin Endocrinol (Oxf). 2010;72(4):462-8, http://dx.doi.org/10.1111/j.1365-2265.2009.03672.x.

51. Coutinho FL, Lourenco DM Jr, Toledo RA, Montenegro FL, Toledo SP. Post-surgical follow-up of primary hyperparathyroidism associated with multiple endocrine neoplasia type 1. Clinics. 2012;67 Suppl 1:169-72, http://dx.doi.org/10.6061/clinics/2012(Sup01)28.

52. Giusti F, Tonelli F, Brandi ML. Primary hyperparathyroidism in multiple endocrine neoplasia type 1: when to perform surgery? Clinics. 2012;67 Suppl 1:141-4, http://dx.doi.org/10.6061/clinics/2012(Sup01)23.

53. Melmed S. Acromegaly. N Engl J Med. 2006;355(24):2558-73.

54. Pellegata NS. MENX and MEN4. Clinics. 2012;67 Suppl 1:13-18, http://dx.doi.org/10.6061/clinics/2012(Sup01)04.

55. Toledo RA, Sekiya T, Horvath A, Faucz F, Fragoso MC, Longuini VC, et al. Assessing the emerging oncogene protein kinase C epsilon as a candidate gene in families with Carney complex-2. Clin Endocrinol (Oxf). 2012;76(1):147-8, http://dx.doi.org/10.1111/j.1365-2265.2011.04144.x.

56. Erlic Z, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, et al. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. Clin Cancer Res. 2009;15(20):6378-85, http://dx.doi.org/10.1158/1078-0432.CCR-09-1237.

57. Tonelli F, Giudici F, Cavalli T, Brandi ML. Surgical approach in patients with hyperparathyroidism in multiple endocrine neoplasia type 1: total versus partial parathyroidectomy. Clinics. 2012;67 Suppl 1:155-60, http://dx.doi.org/10.6061/clinics/2012(Sup01)26.

58. Falchetti A, Brandi ML. Multiple endocrine neoplasia type I variants and phenocopies: more than a nosological issue? J Clin Endocrinol Metab. 2009;94(5):1518-20, http://dx.doi.org/10.1210/jc.2009-0494.

59. Nunes AB, Ezabella MC, Pereira AC, Krieger JE, Toledo SP. A novel Val648Ile substitution in RET protooncogene observed in a Cys634Arg multiple endocrine neoplasia type 2A kindred presenting with an adrenocorticotropin-producing pheochromocytoma. J Clin Endocrinol Metab. 2002;87(12):5658-61, http://dx.doi.org/10.1210/jc.2002-020345.

60. Peltonen L, Palotie A, Lange K. Use of population isolates for mapping complex traits. Nat Rev Genet. 2000;1(3):182-90, http://dx.doi.org/10.1038/35042049.

61. Frank-Raue K, Rybicki LA, Erlic Z, Schweizer H, Winter A, Milos I, et al. International RET Exon 10 Consortium. Risk profiles and penetrance estimations in multiple endocrine neoplasia type 2A caused by germline RET mutations located in exon 10. Hum Mutat. 2011;32(1):51-8, http://dx.doi.org/10.1002/humu.21385.

62. Machens A, Dralle H. Prophylactic thyroidectomy in RET carriers at risk for hereditary medullary thyroid cancer. Thyroid. 2009;19(6):551-4, http://dx.doi.org/10.1089/thy.2009.0144.

63. Pinto EM, Billerbeck AE, Villares MC, Domenice S, Mendonça BB, Latronico AC. Founder effect for the highly prevalent R337H mutation of tumor suppressor p53 in Brazilian patients with adrenocortical tumors. Arq Bras Endocrinol Metabol. 2004;48(5):647-50.

64. Schiavi F, Demattè S, Cecchini ME, Taschin E, Bobisse S, Del Piano A, et al. The endemic paraganglioma syndrome type 1: origin, spread, and clinical expression. J Clin Endocrinol Metab. 2012;97(4):E637-41.

65. Chahal HS, Stals K, Unterlander M, Balding DJ, Thomas MG, Kumar AV, et al. AIP mutation in pituitary adenomas in the 18th century and today. New Eng. J. Med. 2011;364(1):43-50, http://dx.doi.org/10.1056/NEJMoa1008020.

66. Knudson AG Jr, 1971. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A. 1971;68(4):820-3, http://dx.doi.org/10.1073/pnas.68.4.820.

67. Koch CA, Pack K, Chrousos GP. The molecular pathogenesis of hereditary and sporadic adrenocortical and adrenomedullary tumors.

68. Lips CJ, Landsvater RM, Höppener JW, Geerdink RA, Blijham G, van Veen JM, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. N Engl J Med. 1994;331(13):828-35.

69. Sanso GE, Domene HM, Garcia R, Pusiol E, Roque M, Ring A, et al. Very early detection of RET proto-oncogene mutation is crucial for preventive thyroidectomy in multiple endocrine neoplasia type 2 children: presence of C-cell malignant disease in asymptomatic carriers. Cancer. 2002;94(2):323-30, http://dx.doi.org/10.1002/cncr.10228.

70. Puñales MK, da Rocha AP, Meotti C, Gross JL, Maia AL. Clinical and oncological features of children and young adults with multiple endocrine neoplasia type 2A. Thyroid. 2008;18(12):1261-8, http://dx.doi.org/10.1089/thy.2007.0414.

71. Diaz RE, Wohllk N. Multiple endocrine neoplasia; the Chilean experience. Clinics. 2012;67 Suppl 1:7-11, http://dx.doi.org/10.6061/clinics/2012(Sup01)03.

72. Pieterman CR, Schreinemakers JM, Koppeschaar HP, Vriens MR, Rinkes IH, Zonnenberg BA et al. Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome. Clin Endocrinol (Oxf). 2009;70(4):575-81, http://dx.doi.org/10.1111/j.1365-2265.2008.03324.x.

73. Lips CJ, Höppener JW, Van Nesselrooij BP, Van der Luijt RB. Counselling in multiple endocrine neoplasia syndromes: from individual experience to general guidelines. J Intern Med. 2005;257(1):69-77, http://dx.doi.org/10.1111/j.1365-2796.2004.01429.x.

74. Gopie JP, Vasen HF, Tibben A. Surveillance for hereditary cancer: Does the benefit outweigh the psychological burden? -A systematic review.Crit Rev Oncol Hematol. 2012;83(3):329-40, http://dx.doi.org/10.1016/j.critrevonc.2012.01.004.

75. Erlic Z, Hoffmann MM, Sullivan M, Franke G, Peczkowska M, Harsch I, et al. Pathogenicity of DNA variants and double mutations in multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome. J Clin Endocrinol Metab. 2010;95(1):308-13, http://dx.doi.org/10.1210/jc.2009-1728.

76. Barontini M, Levin G, Sanso G. Characteristics of pheochromocytoma in a 4- to 20-year-old population. Ann N Y Acad Sci. 2006;1073(8):30-7.

77. Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer. 2008;113(7 Suppl):1807-43, http://dx.doi.org/10.1002/cncr.23648.

78. Offergeld C, Brase C, Yaremchuk S, Mader I, Rischke HC, Gläsker S, et al. Head and neck paragangliomas: clinical and molecular genetic classification. Clinics. 2012;67 Suppl 1:19-28, http://dx.doi.org/10.6061/clinics/2012(Sup01)05.

79. von Dücker L, Walz MK, Voss C, Arnold G, Eng C, Neumann HP. Laparoscopic organ-sparing resection of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors. World J Surg. 2011;35(3):563-7, http://dx.doi.org/10.1007/s00268-010-0878-5.

80. Asher KP, Gupta GN, Boris RS, Pinto PA, Linehan WM, Bratslavsky G. Robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma: the National Cancer Institute technique. Eur Urol. 2011;60(1):118-24, http://dx.doi.org/10.1016/j.eururo.2011.03.046.

81. Weisbrod AB, Liewehr DJ, Steinberg SM, Patterson EE, Libutti SK, Linehan WM, et al. Association of type O blood with pancreatic neuroendocrine tumors in Von Hippel-Lindau syndrome. Ann Surg Oncol. 2012;19(6):2054-9, http://dx.doi.org/10.1245/s10434-012-2276-8.

82. Mannelli M, Lenders JW, Pacak K, Parenti G, Eisenhofer G. Subclinical phaeochromocytoma. Best Pract Res Clin Endocrinol Metab. 2012;26(4):507-15, http://dx.doi.org/10.1016/j.beem.2011.10.008.

83. Ali T, Kandil D, Piperdi B. Long-term disease control with sunitinib in a patient with metastatic pancreatic neuroendocrine tumor (NET) associated with Von Hippel-Lindau syndrome (VHL). Pancreas. 2012;41(3):492-3, http://dx.doi.org/10.1097/MPA.0b013e31822a645e.

84. Stratakis CA, Carney JA, Lin JP, Papanicolaou DA, Karl M, Kastner DL, et al. Carney complex, a familial multiple neoplasia and lentiginosis syndrome. Analysis of 11 kindreds and linkage to the short arm of chromosome 2. J Clin Invest. 1996;97(3):699-705, http://dx.doi.org/10.1172/JCI118467.

85. Vezzosi D, Bertherat J, Groussin L. Pathogenesis of benign adrenocortical tumors. Best Pract Res Clin Endocrinol Metab. 2010;24(6):893-905, http://dx.doi.org/10.1016/j.beem.2010.10.005.

86. Carney JA, Stratakis CA. Virilizing ovarian stromal tumor in a young woman with Carney complex. Am J Surg Pathol. 2011;35(10):1592-1599.

87. Nozières C, Berlier P, Dupuis C, Raynaud-Ravni C, Morel Y, Chazot FB, et al. Sporadic and genetic forms of paediatric somatotropinoma: a retrospective analysis of seven cases and a review of the literature. Orphanet J Rare Dis. 2011;24;6:67, http://dx.doi.org/10.1186/1750-1172-6-67.

88. Anselmo J, Medeiros S, Carneiro V, Greene E, Levy I, Nesterova M, et al. A large family with Carney complex caused by the S147G PRKAR1A mutation shows a unique spectrum of disease including adrenocortical

cancer. J Clin Endocrinol Metab. 2012;97(2):351-359, http://dx.doi.org/10.1210/jc.2011-2244.

89. Morin E, Mete O, Wasserman J, Joshua AM, Asa SL. Carney complex with adrenal cortical carcinoma. J Clin Endocrinol Metab. 2012;97(2):E202-206, http://dx.doi.org/10.1210/jc.2011-2321.

90. Bertherat J. Adrenocortical cancer in Carney complex: a paradigm of endocrine tumor progression or an association of genetic predisposition factors ? J Clin Endocrinol Metab. Metab. 2012;97(2):387-390, http://dx.doi.org/10.1210/jc.2011-3327.

91. Briassoulis G, Kuburovic V, Xekouki P, Patronas N, Keil MF, Lyssikatos C, Stajevic M, Kovacevic G, Stratakis CA. Recurrent left atrial myxomas in Carney complex: a genetic cause of multiple strokes that can be prevented. J Stroke Cerebrovasc Dis. 2012;21(8):914.e1-8, http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2012.01.006.

92. Welander J, Söderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. Endocr Relat Cancer. 2011;18(6):R253-276, http://dx.doi.org/10.1530/ERC-11-0170.

93. Lodish MB, Stratakis CA. Endocrine tumours in neurofibromatosis type 1, tuberous sclerosis and related syndromes. Best Pract Res Clin Endocrinol Metab. 2010;24(3):439-449, http://dx.doi.org/10.1016/j.beem.2010.02.002.

94. Uhlmann EJ, Plotkin SR. Neurofibromatoses. Adv Exp Med Biol. 2012;724:266-77, http://dx.doi.org/10.1007/978-1-4614-0653-2_20.

95. Stumpf DA, Alksne JF, Annegers JF,Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45(5):575-578.

96. Brunetti-Pierri N, Doty SB, Hicks J, Phan K, Mendoza-Londono R, Blazo M, et al. Generalized metabolic bone disease in Neurofibromatosis type I. Mol Genet Metab. 2008;94(1):105-111, http://dx.doi.org/10.1016/j.ymgme.2007.12.004.

97. Wang W, Nyman JS, Ono K, Stevenson DA, Yang X, Elefteriou F. Mice lacking Nf1 in osteochondroprogenitor cells display skeletal dysplasia similar to patients with neurofibromatosis type I. Hum Mol Genet. 2011;20(20):3910-3924, http://dx.doi.org/10.1093/hmg/ddr310.

98. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998;13(12):624-628, http://dx.doi.org/10.1177/088307389801301206.

99. Arva NC, Pappas JG, Bhatla T, Raetz EA, Macari M, Ginsburg HB, et al. Well-differentiated pancreatic neuroendocrine carcinoma in tuberous sclerosis--case report and review of the literature. Am J Surg Pathol. 2012;36(1):149-153, http://dx.doi.org/10.1097/PAS.0b013e31823d0560.

100. Ehninger D. From genes to cognition in tuberous sclerosis: implications for mTOR inhibitotr-based treatment approaches. Neuropharmacol. 2013;68(5):97-105, http://dx.doi.org/10.1016/j.neuropharm.2012.05.015.

101. Malkin D. Li-fraumeni syndrome. Genes Cancer. 2011;2(4):475-484, http://dx.doi.org/10.1177/1947601911413466.

102. Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. Cancer. 2012;118(5):1387-1396, http://dx.doi.org/10.1002/cncr.26390.

103. Else T. Association of adrenocortical carcinoma with familial cancer susceptibility syndromes. Mol Cell Endocrinol. 2012;351(1):66-70, http://dx.doi.org/10.1016/j.mce.2011.12.008.

104. Ribeiro RC, Sandrini F, Figueiredo B, Zambetti GP, Michalkiewicz E, Lafferty AR et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proc Natl Acad Sci USA. 2001;98(16):9330-9335., http://dx.doi.org/10.1073/pnas.161479898.

105. Latronico AC, Pinto EM, Domenice S, Fragoso MC, Martin RM, Zerbini MC, et al. An inherited mutation outside the highly conserved DNA-binding domain of the p53 tumor suppressor protein in children and adults with sporadic adrenocortical tumors. J Clin Endocrinol Metab. 2001;86(10):4970-4973, http://dx.doi.org/10.1210/jc.86.10.4970.

106. Garritano S, Gemignani F, Palmero EI, Olivier M, Martel-Planche G, Le Calvez-Kelm F, et al. Detailed haplotype analysis at the TP53 locus in p.R337H mutation carriers in the population of Southern Brazil: evidence for a founder effect. Hum Mutat. 2010;31(2):143-150, http://dx.doi.org/10.1002/humu.21151.

107. Pinto EM, Ribeiro RC, Kletter GB, Lawrence JP, Jenkins JJ, Wang J, et al. Inherited germline TP53 mutation encodes a protein with an aberrant C-terminal motif in a case of pediatric adrenocortical tumor. Fam Cancer. 2011;10(1):141-146, http://dx.doi.org/10.1007/s10689-010-9392-z.

108. Ribeiro RC, Pinto EM, Zambetti GP, Rodriguez-Galindo C. The International Pediatric Adrenocortical Tumor Registry initiative: contributions to clinical, biological, and treatment advances in pediatric adrenocortical tumors. Mol Cell Endocrinol. 2012;351(1):37-43, http://dx.doi.org/10.1016/j.mce.2011.10.015.

109. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000;37(11):828-830, http://dx.doi.org/10.1136/jmg.37.11.828.

110. Son EJ, Nosé V. Familial follicular cell-derived thyroid carcinoma. Front Endocrinol (Lausanne). 2012;3:61. doi: 10.3389.

111. Wohllk N, Schweizer H, Eric Z, Schmid KW, Walz MK, Raue F, et al. Multiple endocrine neoplasia type 2. Best Pract Res Clin Endocrinol

Metab. 2010;24(3):371-387, http://dx.doi.org/10.1016/j.beem.2010.02.001.

112. Raue F, Frank-Raue K. Genotype-phenotype correlation in multiple endocrine neoplasia type 2. Clinics. 2012;67 Suppl 1:69-75, http://dx.doi.org/10.6061/clinics/2012(Sup01)13.

113. Wagner SM, Zhu S, Nicolescu AC, Mulligan LM. Molecular mechanisms of RET receptor-mediated oncogenesis in multiple endocrine neoplasia 2. Clinics. 2012;67 Suppl 1:77-84, http://dx.doi.org/10.6061/clinics/2012(Sup01)14.

114. Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. J Clin Endocrinol Metab. 2011;96(5):E863-868, http://dx.doi.org/10.1210/jc.2010-1921.

115. Agrawal N, Jiao Y, Sausen M, Leary R, Bettegowda C, Roberts NJ, et al. Exomic Sequencing of Medullary Thyroid Cancer Reveals Dominant and Mutually Exclusive Oncogenic Mutations in RET and RAS. J Clin Endocrinol Metab. 2013;98(2):E364-369, http://dx.doi.org/10.1210/jc.2012-2703.

116. Qi XP, Ma JM, Du ZF, Ying RB, Fei J, Jin HY, et al. RET germline mutations identified by exome sequencing in a Chinese multiple endocrine neoplasia type 2A/familial medullary thyroid carcinoma family. PLoS One. 2011;6(5):e20353, http://dx.doi.org/10.1371/journal.pone.0020353.

117. Conzo G, Circelli L, Pasquali D, Sinisi A, Sabatino L, et al. Lessons to be learned from clinical management of a MEN2A patient bearing a novel 634/640/700 mutation of the RET prto-oncogene. Clin Endocrinol. Clin Endocrinol 2012;77(6):934-936, http://dx.doi.org/10.1111/j.1365-2265.2012.04412.x.

118. Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, et al. Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. J Clin Endocrinol Metab. . 2008;93(3):682-687.

119. Berndt I, Reuter M, Saller B, Frank-Raue K, Groth P, Grussendorf M, et al. A new hot spot for mutations in the ret protooncogene causing familial medullary thyroid carcinoma and multiple endocrine neoplasia type 2A. J Clin Endocrinol Metab. 1998;83(3):770-774, http://dx.doi.org/10.1210/jc.83.3.770.

120. Cosci B, Vivaldi A, Romei C, Genignani F, Landi S, Ciampi R, et al. In silico and in vitro analysis of rare germline allelic variants of RET oncogene associated with mrdullary thyroid carcinoma. Endocr Relat Cancer. 2011;18(5):603-612, http://dx.doi.org/10.1530/ERC-11-0117.

121. Machens A, Frank-Raue K, Lorenz K, Rondot S, Raue F, Dralle H. Clinical relevance of RET variants G691S, L769L, S836S and S904S to sporadic medullary thyroid cancer. Clin Endocrinol (Oxf). 2012;76(5):691-697 , http://dx.doi.org/10.1111/j.1365-2265.2011.04293.x.

122. Ceolin L, Siqueira DR, Ferreira CV, Romitti M, Maia SC, Leiria L, et al. Additive effect of RET polymorphisms on sporadic medullary thyroid carcinoma susceptibility and tumor aggressiveness. Eur J Endocrinol. 2012;166(5):847-854.

123. Lendvai N, Tóth M, Valkusz Z, Bekő G, Szücs N, Csajbók E, et al. Over-representation of the G12S polymorphism of the SDHD gene in patients with MEN2A syndrome. Clinics. 2012;67 Suppl 1:85-89, http://dx.doi.org/10.6061/clinics/2012(Sup01)15.

124. Menko FH, van der Luijt RB, de Valk IA, Toorians AW, Sepers JM, van Diest PJ, et al. Atypical MEN type 2B associated with two germline RET mutations on the same allele not involving codon 918. J Clin Endocrinol Metab. Metab. 2002;87(1):393-397, http://dx.doi.org/10.1210/jc.87.1.393.

125. Elisei R, Cosci B, Romei C, Agate L, Piampiani P, Miccoli P, et al. Identification of a novel point mutation in the RET gene (Ala883Thr), which is associated with medullary thyroid carcinoma phenotype only in homozygous condition. J Clin Endocrinol Metab. 2004;89(11):5823-5827, http://dx.doi.org/10.1210/jc.2004-0312.

126. Mukherjee S, Zakalik D. RET codon 804 mutations in multiple endocrine neoplasia 2: genotype-phenotype correlations and implications in clinical management. Clin Genet. 2011;79 (1):1-16, http://dx.doi.org/10.1111/j.1399-0004.2010.01453.x.

127. Lindsey SC, Kunii IS, Germano-Neto F, Sittoni MY, Camacho CP, Valente FO, et al. Extended RET Gene Analysis in Patients with Apparently Sporadic Medullary Thyroid Cancer: Clinical Benefits and Cost. Horm Cancer. 2012;3(4):181-186, http://dx.doi.org/10.1007/s12672-012-0109-7.

128. Moore SW, Zaahl M. The Hirschsprung's-multiple endocrine neoplasia connection. Clinics. 2012;67 Suppl 1:63-67, http://dx.doi.org/10.6061/clinics/2012(Sup01)12.

129. Quedas EP, Longuini VC, Sekiya T, Coutinho FL, Toledo SP, Tannuri U, et al. RET haplotype, not linked to the C620R activating mutation, associated with Hirschsprung disease in a novel MEN2 family. Clinics. 2012;67 Suppl 1:57-61, http://dx.doi.org/10.6061/clinics/2012(Sup01)11.

130. Hyndman BD, Gujral TS, Krieger JR, Cockburn JG, Mulligan LM. Multiple functional effects of RET kinase domain sequence variants in Hirschsprung disease. Hum Mutat. 2013;34 (1): 132-142, http://dx.doi.org/10.1002/humu.22170.

131. Mian C, Sartorato P, Barollo S, Zane M, Opocher G. RET codon 609 mutations: a contribution for better clinical managing. Clinics. 2012;67 Suppl 1:33-36, http://dx.doi.org/10.6061/clinics/2012(Sup01)07.

132. Vasen HF, Nieuwenhuijzen Kruseman AC, Moers AM, Lips CJ, Beukers EK, et al. MEN-2 syndrome: the value of screening and central registration; a study of six kindreds in The Netherlands. Am J Med. 1987;35 (2-3):101-103.

133. Lips CJ, Landsvater RM, Höppener JW, Geerdink RA, Blijham G, van Veen JM, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. N Engl J Med. 1994;331(13):828-835.

134. Ezabella MC, Hayashida CY, Bisi H, Leite MO, Borelli A, Abelin NM, et al. Early detection of medullary thyroid carcinoma in multiple endocrine neoplasia type II. Rev Hosp Clin Fac Med Sao Paulo. 1990;45(3):105-109.

135. Machens A, Dralle H. Simultaneous medullary and papillary thyroid cancer: a novel entity? Ann Surg Oncol. 2012;19(1):37-44, http://dx.doi.org/10.1245/s10434-011-1795-z

136. Toledo SP, Lourenço DM Jr, Santos MA, Tavares MR, Toledo RA, Correia-Deur JE. Hypercalcitoninemia is not pathognomonic of medullary thyroid carcinoma. Clinics. 2009;64(7):699-706.

137. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007;92(2):450-455.

138. Romei C, Mariotti S, Fugazzola L, Taccaliti A, Pacini F, Opocher G, et al. Multiple endocrine neoplasia type 2 syndromes (MEN 2): results from the ItaMEN network analysis on the prevalence of different genotypes and phenotypes. Eur J Endocrinol. 2010;163(2):301-308.

139. Da Silva AM, Maciel RM, Da Silva MR, Toledo SR, De Carvalho MB, Cerutti JM. A novel germ-line point mutation in RET exon 8 (Gly(533)Cys) in a large kindred with familial medullary thyroid carcinoma. J Clin Endocrinol Metab. 2003;88(11):5438-5443, http://dx.doi.org/10.1210/jc.2003-030997.

140. Muzza M, Cordella D, Bombled J, Bressac-de Paillerets B, Guizzardi F, Francis Z, et al. Four novel RET germline variants in exons 8 and 11 display an oncogenic potential in vitro. Eur J Endocrinol. 2010;162(4):771-777.

141. Hisano M, Vicentini FC, Srougi M. Retroperitoneoscopic adrenalectomy in pheochromocytoma. Clinics. 2012;67 Suppl 1:161-167, http://dx.doi.org/10.6061/clinics/2012(Sup01)27.

142. Schlumberger M, Massicotte MH, Nascimento CL, Chougnet C, Baudin E, Leboulleux S. Kinase inhibitors for advanced medullary thyroid carcinoma. Clinics. 2012;67 Suppl 1:125-129, http://dx.doi.org/10.6061/clinics/2012(Sup01)21.

143. Lips CJ, Dreijerink KM, Hoppener JW. Variable clinical expression in patients with a germline MEN1 disease gene mutation: clues to a genotype-phenotype correlation. Clinics. 2012;67 Suppl 1:49-56, http://dx.doi.org/10.6061/clinics/2012(Sup01)10.

144. Lairmore TC, Piersall LD, DeBenedetti MK, Dilley WG, Mutch MG, Whelan AJ, et al. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). 2004;239 (5):637-645.

145. Machens A, Schaaf L, Karges W. Age-related penetrance of endocrine tumors in multiple endocrine neoplasia type 1(MEN1): a multicentre study of 258 gene carriers. Clin Endocrinol 2007;67(4):613-622.

146. Syro LV, Scheithauer BW, Kovacs K, Toledo RA, Londoño FJ, Ortiz LD, et al. Pituitary tumors in patients with MEN1 syndrome. Clinics. 2012;67 Suppl 1:43-48, http://dx.doi.org/10.6061/clinics/2012(Sup01)09.

147. de Herder WW. Familial gigantism. Clinics. 2012;67 suppl 1: 29-32, http://dx.doi.org/10.6061/clinics/2012(Sup01)06

148. Ortiz LD, Syro LV, Scheithauer BW, Rotondo F, Uribe H, Fadul CE, et al. Temozolomide in aggressive pituitary adenomas and carcinomas. Clinics. 2012;67 Suppl 1:119-123, http://dx.doi.org/10.6061/clinics/2012(Sup01)20.

149. Farrell WE, Azevedo MF, Batista DL, Smith A, Bourdeau I, Horvath A, et al. Unique gene expression profile associated with an early-onset multiple endocrine neoplasia (MEN1)-associated pituitary adenoma. J Clin Endocrinol Metab. 2011;96 (11): E1905-914 , http://dx.doi.org/10.1210/jc.2011-1127.

150. Simonds WF, Varghese S, Marx SJ, Nieman LK. Cushing's syndrome in multiple endocrine neoplasia type 1. Clin Endocrinol (Oxf). 2012;76 (3):379-386, http://dx.doi.org/10.1111/j.1365-2265.2011.04220.x.

151. Agarwal SK, Ozawa A, Mateo CM, Marx SJ. The MEN1 gene and pituitary tumours. Horm Res. 2009;71 Suppl 2:131-138, http://dx.doi.org/10.1159/000192450.

152. Norton JA, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK, et al. Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia-type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. Ann Surg. 2008;247(3):501-510, http://dx.doi.org/10.1097/SLA.0b013e31815efda5.

153. Skogseid B, Rastad J, Åkerström G. Pancreatic endocrine tumors in multiple endocrine neoplasia type I. Doherty GM, Skogseid B, editors. Surgical Endocrinology Philadelphia, PA: Lippincott, Williams & Wilkins; 2001. pp. 511-524.

154. Åkerström G, Stålberg P. Surgical management of MEN-1 and -2: State of the art. Surg Clin N Am. 2009;89(5):1047-1068.

155. Triponez F, Goudet P, Dosseh D, Cougard P, Bauters C, Murat A, et al. Is surgery beneficial for MEN1 patients with small (<or = 2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. World J Surg. 2006;30(5):654-662 .

156. Triponez F, Dosseh D, Goudet P, Cougard P, Bauters C, Murat A, et al. Epidemiology data on 108 MEN 1 patients from the GTE with isolated nonfunctioning tumors of the pancreas. Ann Surg. 2006;243(2):265-272, http://dx.doi.org/10.1097/01.sla.0000197715.96762.68.

157. Goudet P, Murat A, Binquet C, Cardot-Bauters C, Costa A, Ruszniewski P, et al. Risk factors and causes of death in MEN1 disease. A GTE (Groupe d'Etude des Tumeurs Endocrines) cohort study among 758 patients. World J Surg. 2010;34(2):249-255 .

158. Burgess JR, Greenaway TM, Shepherd JJ. Expression of the MEN-1 gene in a large kindred with multiple endocrine neoplasia type 1. J Intern Med. 1998;243(6):465-470, http://dx.doi.org/10.1046/j.1365-2796.1998.00275.x.

159. Burgess JR, David R, Parameswaran V, Greenaway TM, Shepherd JJ. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. Arch Surg. 1998;133(2):126-129, http://dx.doi.org/10.1001/archsurg.133.2.126.

160. Wells SA Jr, Stirman JA Jr, Bolman RM 3rd, Gunnells JC. Transplantation of the parathyroid glands. Clinical and experimental results. Surg Clin North Am. 1978;58(2):391-402..

161. Scholten A, Schreinemakers JM, Pieterman CR, Valk GD, Vriens MR, Borel Rinkes IH. Evolution of surgical treatment of primary hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. Endocr Pract. . 2011;17(1):7-15, http://dx.doi.org/10.4158/EP10050.OR.

162. Cohen MS, Dilley WG, Wells SA Jr, Moley JF, Doherty GM, Sicard GA, et al. Long-term functionality of cryopreserved parathyroid autografts: a 13-year prospective analysis. Surgery. 2005;138(6):1033-1034, http://dx.doi.org/10.1016/j.surg.2005.09.029.

163. Bilezikian JP, Potts JT Jr, Fuleihan Gel-H, Kleerekoper M, Neer R, Peacock M, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab. 2002;87(12):5353-5361, http://dx.doi.org/10.1210/jc.2002-021370.

164. Brandi ML. Parathyroid gland: Hyperparathyroidism in MEN1 syndrome: time to operate? Nat Rev Endocrinol. 2010;6(11):604--605, http://dx.doi.org/10.1038/nrendo.2010.131.

165. Burgess JR, David RB, Greenaway TM, Parameswaran V, Shepherd JJ. Osteoporosis in multiple endocrine neoplasia type 1: severity, clinical significance, relationship to primary hyperparathyroidism and response to parathyroidectomy. Arch Surg. 1999;134(10):1119-1123, http://dx.doi.org/10.1001/archsurg.134.10.1119.

166. Costa MH, Domenice S, Toledo RA, Lourenço DM Jr, Latronico AC, Pinto EM, et al. Glucose-dependent insulinotropic peptide receptor overexpression in adrenocortical hyperplasia in MEN1 syndrome without loss of heterozygosity at the 11q13 locus. Clinics. 2011;66 (4):529-533.

167. Lewis MA, Thompson GB, Young WF Jr. Preoperative assessment of the pancreas in multiple endocrine neoplasia type 1.World J Surg. Surg. 2012;36(6):1375-8131.

168. Zhang L, Smyrk TC, Young WF Jr, Stratakis CA, Carney JA. Gastric stromal tumors in Carney triad are different clinically, pathologically, and behaviorally from sporadic gastric gastrointestinal stromal tumors: findings in 104 cases. Am J Surg Pathol. 2010;34(1):53-64.

169. Lips CJ, Lentjes EG, Höppener JW. The spectrum of carcinoid tumours and carcinoid syndromes. Ann Clin Biochem. 2003;40(Pt 6):612-627, http://dx.doi.org/10.1258/000456303770367207.

170. Ferolla P, Falchetti A, Filosso P, Tomassetti P, Tamburrano G, Avenia N, Daddi G, Puma F, Ribacchi R, Santeusanio F, Angeletti G, Brandi ML. Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: the Italian series. J Clin Endocrinol Metab. 2005;90(5):2603-2609, http://dx.doi.org/10.1210/jc.2004-1155.

171. Burgess JR, Giles N, Shepherd JJ. Malignant thymic carcinoid is not prevented by transcervical thymectomy in multiple endocrine neoplasia type 1. Clin Endocrinol (Oxf). 2001;55 (5):689-693, http://dx.doi.org/10.1046/j.1365-2265.2001.01348.x.

172. Georgitsi M, Raitila A, Karhu A, van der Luijt RB, Aalfs CM, Sane T, et al. Germline cdkn1b/p27kip1 mutation in multiple endocrine neoplasia. J Clin Endocrinol Metab. 2007;92(8):3321-3325, http://dx.doi.org/10.1210/jc.2006-2843.

173. Agarwal SK, Mateo CM, Marx SJ. Rare germline mutations in cyclin-dependent kinase inhibitor genes in multiple endocrine neoplasia type 1 and related states. J Clin Endocrinol Metab. 2009;94(5):1826-1834, http://dx.doi.org/10.1210/jc.2008-2083.

174. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirova MA, Beckers B. High Prevalence of Pituitary Adenomas: A Cross-Sectional Study in the Province of Liège, Belgium. J Clin Endocrinol Metab. 2006;9 1 (12):4769-4775, http://dx.doi.org/10.1210/jc.2006-1668.

175. De Herder WW. Acromegalic gigantism, physicians and body snatching. Past or present? Pituitary. 2012;15(3): 312-318, http://dx.doi.org/10.1007/s11102-012-0389-5.

176. Jorge BH, Agarwal SK, Lando VS, Salvatori R, Barbero RR, Abelin N, et al. Study of the multiple endocrine neoplasia type 1, growth hormone-releasing hormone receptor, Gs alpha, and Gi2 alpha genes in isolated familial acromegaly. J Clin Endocrinol Metab. 2001;86 (2):542-544, http://dx.doi.org/10.1210/jc.86.2.542.

177. Daly AF, Vanbellinghen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA, et al. Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. J Clin Endocrinol Metab. 2007;92(5):1891-1896, http://dx.doi.org/10.1210/jc.2006-2513.

178. Rothenbuhler A, Stratakis CA. Clinical and molecular genetics of Carney complex. Best Pract Res Clin Endocrinol Metab. 2010;24(3):389-399, http://dx.doi.org/10.1016/j.beem.2010.03.003.

179. Syro LV, Sundsbak JL, Scheithauer BW, Toledo RA, Camargo M, Heyer CM, et al. Somatotroph pituitary adenoma with acromegaly and autosomal dominant polycystic kidney disease: SSTR5 polymorphism and PKD1 mutation. Pituitary. 2012;15(3):342-349, http://dx.doi.org/10.1007/s11102-011-0325-0.

180. Vasilev V, Daly A, Naves L, Zacharieva S, Beckers A. Clinical and genetic aspects of familial isolated pituitary adenomas. Clinics. 2012;67 Suppl 1:37-41, http://dx.doi.org/10.6061/clinics/2012(Sup01)08.

181. Toledo RA, Mendonca BB, Fragoso MC, Soares IC, Almeida MQ, Moraes MB, et al. Isolated familial somatotropinoma: 11q13-loh and gene/protein expression analysis suggests a possible involvement of aip also in non-pituitary tumorigenesis. Clinics. 2010;65(4):407-415, http://dx.doi.org/10.1590/S1807-59322010000400010.

182. Toledo RA, Lourenço DM Jr, Toledo SP. Familial isolated pituitary adenoma: evidence for genetic heterogeneity. Front Horm Res. 2010; 38:77-86 , http://dx.doi.org/10.1159/000318497.

183. Jennings JE, Georgitsi M, Holdaway I, Daly AF, Tichomirowa M, Beckers A, et al. Aggressive pituitary adenomas occurring in young patients in a large Polynesian kindred with a germline R271W mutation in the AIP gene. Eur J Endocrinol. 2009;161(5):799-804

184. Carney JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. Am J Surg Pathol. 2011;35(9):1311-1326.

185. McDonald TJ, Driedger AA, Garcia BM, Van Uum SH, Rachinsky I, Chevendra V et al. Familial papillary thyroid carcinoma: a retrospective analysis. J Oncol. 2011;2011:948786.

186. Domingues R, Tomaz RA, Martins C, Nunes C, Bugalho MJ, Cavaco BM. Identification of the first germline HRPT2 whole-gene deletion in a patient with primary hyperparathyroidism. Clin Endocrinol (Oxf). 2012;76(1):33-38., http://dx.doi.org/10.1111/j.1365-2265.2011.04184.x.

187. Mulatero P, Tizzani D, Viola A, Bertello C, Monticone S, Mengozzi G, et al. Prevalence and Characteristics of Familial Hyperaldosteronism. The PATOGEN Study (Primary Aldosteronism in TOrino-GENetic forms). Hypertension. 2011;58(5):797-803, http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.175083.

188. Funder JW, Carey RM, Fardela C, Gomez-Sanchez C, Mantero F, Stowasser M, et al. Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93(9):3 266-281.

189. Eng C, Crossey PA, Mulligan LM, Healey CS, Houghton C, Prowse A, et al. Mutations in the RET proto-oncogene and the von Hippel-Lindau disease tumour suppressor gene in sporadic and syndromic phaeochromocytomas. J Clin Genet. 1995;32(12):934-937.

190. Qin Y, Buddavarapu K, Dahia PL. Pheochromocytomas: from genetic diversity to new paradigms. Horm Metab Res. 2009;41(9):664-671, http://dx.doi.org/10.1055/s-0029-1215590.

191. Dahia PL, Hao K, Rogus J, Colin C, Pujana MA, Ross K, et al. Novel pheochromocytoma susceptibility loci identified by integrative genomics. Cancer Res. 2005;65(21):9651-c-9658, http://dx.doi.org/10.1158/0008-5472.CAN-05-1427.

192. Neumann HP, Sullivan M, Winter A, Malinoc A, Hoffmann MM, Boedeker CC, et al. Germline mutations of the TMEM127 gene in patients with paraganglioma of head and neck and extraadrenal abdominal sites. J Clin Endocrinol Metab. 2011;96(8):E1279-282, http://dx.doi.org/10.1210/jc.2011-0114.

193. Melmed S. Pathogenesis of pituitary tumors. Nat Rev Endocrinol. 2011;7(5):257-266, http://dx.doi.org/10.1038/nrendo.2011.40.

194. Falchetti A, Marini F, Luzi E, Giusti F, Cavalli L, Cavalli T, et al. Multiple endocrine neoplasia type 1 (MEN1): not only inherited endocrine tumors. Gen Med. 2009;11(12):825-835 , http://dx.doi.org/10.1097/GIM.0b013e3181be5c97.

195. Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protrin (AIP) gene. Endocr Rev. 2013;34(2):239-277, http://dx.doi.org/10.1210/er.2012-1013.

196. Machens A, Dralle H. Multiple endocrine neoplasia type 2 and the RET protooncogene: from bedside to bench to bedside. Mol Cell Endocrinol. 2006,9;247(1-2):34-40, http://dx.doi.org/10.1016/j.mce.2005.10.028.

197. Jaffrain-Rea ML, Angelini M, Gargano D, Tichomirowa MA, Daly AF, Vanbellinghen JF, et al. Expression of aryl hydrocarbon receptor (AHR) and AHR-interacting protein in pituitary adenomas: pathological and clinical implications. Endocr Relat Cancer. 2009;16(3):1029-1043, http://dx.doi.org/10.1677/ERC-09-0094.

198. Romei C, Pardi E, Cetani F, Elisei R. Genetic and Clinical Features of Multiple Endocrine Neoplasia Types 1 and 2. J Oncol. 2012;2012:705036.