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Overview of the 2022 WHO Classification of Familial Endocrine Tumor Syndromes

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Abstract
This review of the familial tumor syndromes involving the endocrine organs is focused on discussing the main updates on the upcoming fifth edition of the WHO Classification of Endocrine and Neuroendocrine Tumors. This review emphasizes updates on histopathological and molecular genetics aspects of the most important syndromes involving the endocrine organs. We describe the newly defined Familial Cancer Syndromes as MAFA-related, MEN4, and MEN5 as well as the newly reported pathological findings in DICER1 syndrome. We also describe the updates done at the new WHO on the syndromic and non-syndromic familial thyroid diseases. We emphasize the problem of diagnostic criteria, mention the new genes that are possibly involved in this group, and at the same time, touching upon the role of some immunohistochemical studies that could support the diagnosis of some of these conditions. As pathologists play an important role in identifying tumors within a familial cancer syndrome, we highlight the most important clues for raising the suspicious of a syndrome. Finally, we highlight the challenges in defining these entities as well as determining their clinical outcome in comparison with sporadic tumors. Instead of the usual subject review, we present the highlights of the updates on familial cancer syndromes by answering select questions relevant to practicing pathologists.

Keywords Familial tumor syndromes · Familial cancer syndromes · Hereditary tumor syndromes · Genetic tumor syndromes · Endocrine familial cancer syndromes

Introduction

In this manuscript, we will discuss the updates on the coming 2022 WHO Classification of Endocrine and Neuroendocrine Tumours on Familial Cancer Syndromes involving the Endocrine System. We present the newly described familial tumor syndromes involving the endocrine system, the main updates on the known syndromes, and the highlights of these syndromes focused on the most recent developments.

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Although some of the familial cancer syndromes have been described over 100 years ago, recognizable tumor-predisposing syndromes have been broadly documented during the last decades due to the fast-increasing use of DNA sequencing in diagnostic pathology, molecular pathology, and clinical genetics. The routine use of NGS will certainly continue to widen the spectrum of known predisposing genetic variants among patients with endocrine tumors.

A substantial number of patients with familial tumor syndromes present with a disease that does not alert the physician to be a familial disease but appears to be sporadic disease. A cautious clinical certification of familial syndromes that can be related with some cancers help diagnose germline-driven neoplasia. What appears to be a sporadic tumor is fitting less often so, due to the use of more powerful investigation. Consequently, more often new syndromes and tumors associated with these syndromes are being reported.

Pathologists have a crucial role in diagnosing tumors associated with the heritable syndromes. The characteristic morphological, immunophenotypic and molecular findings are addressed in this section. Pathologists must be attentive

of the histopathological features associated with distinct syndromes that should prompt consideration of germline screening. Information on underlying genetic variants might have an impact on the choice of therapy and surveillance guidelines.

We summarize all these entities emphasizing the pathologist's possibilities for recognizing the different familial cancer syndromes based on the histopathological and/or immunohistochemical features of the endocrine tissue involved on this syndrome.

Question 1: What Are the Newly Described Endocrine Familial Cancer Syndromes?

Three new familial cancer syndromes involving the endocrine organs and tissues have been defined over the last years. These syndromes are multiple endocrine neoplasia type 4 (MEN4), multiple endocrine neoplasia type 5 (MEN5), and MAFA-related insulinomatosis.

MEN4

MEN4 is a tumor syndrome, of an autosomal dominant, pattern caused by inactivating heterozygous germline mutations in the *CDKN1B* gene. The patients with this syndrome have a phenotype that mimics MEN1, as these patients develop tumors in the parathyroid, pituitary and pancreas (Fig. 1). These patients are identified with similar symptomatology as those with MEN1, but with negative *MEN1* genetic testing.

Regarding the pathological findings as clues for a MEN4 diagnosis, there is only limited data available on histopathology and with no clear differences from sporadic cases are reported. The occurrence of multiple tumors of the spectrum is the only known clue [1]. Hyperparathyroidism is

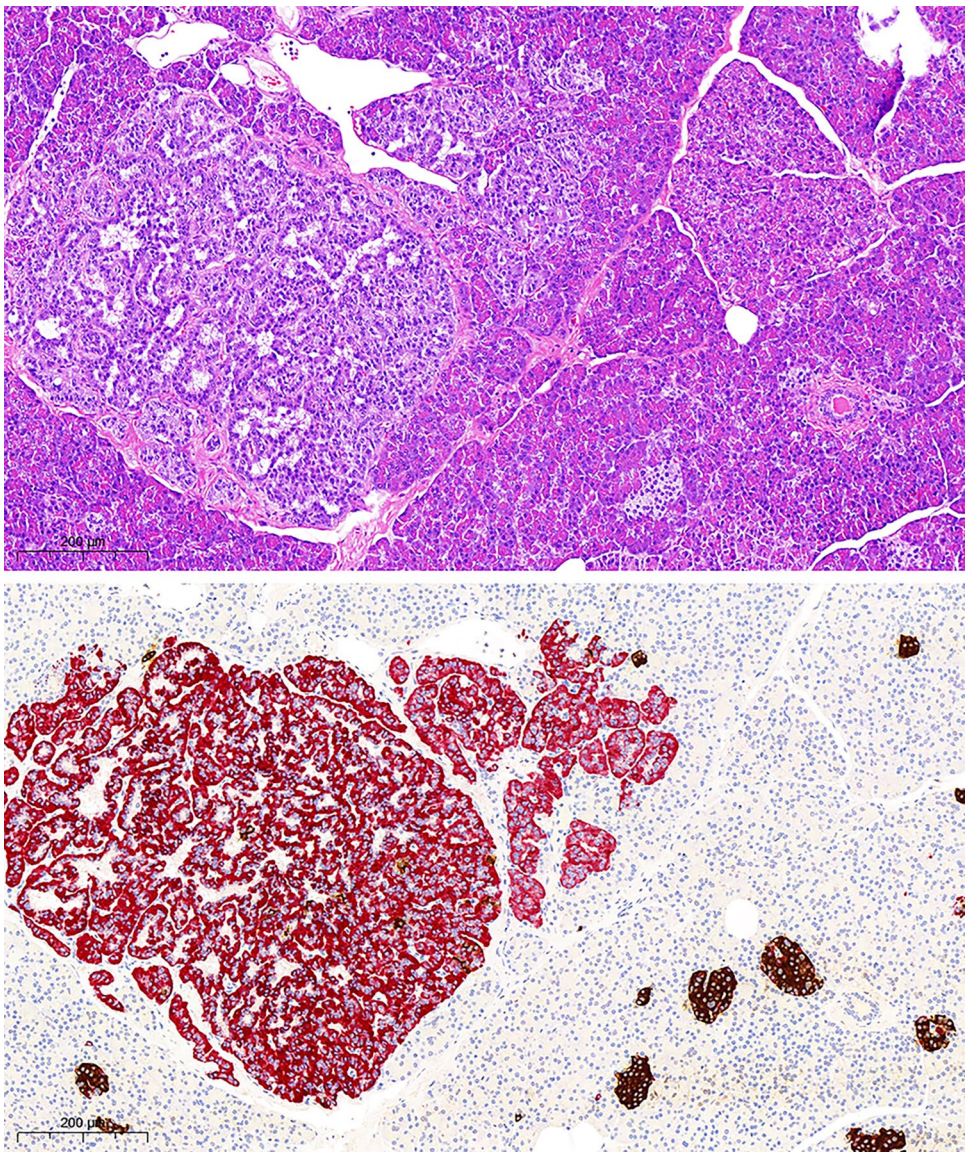

Fig. 1 Pancreatic neuroendocrine microadenoma. MEN1 patient with microadenoma, monohormonal staining for glucagon (red), single interspersed insulin-positive cells representing non-neoplastic b-cells as islet remnant

the frequently occurring symptom in about 75% of patients with this syndrome; uniglandular disease is frequent and no relapse after parathyroidectomy has been reported [2].

Overall, due to the inconstant presentation of MEN4, the recognition and the diagnosis of MEN4 can confirmed by genetic testing. Such genetic testing is recommended in patients with MEN1 phenotype, but are negative for *MEN1* mutations [3–5].

MEN5

Germline variants in the *MAX* tumor suppressor gene cause the autosomal dominant MEN5.

Patients develop pheochromocytomas of the adrenal medulla, which are often bilateral and can have multiple lesions within one adrenal gland [6]. Malignant and/or metachronous disease is common [7–10]. Less frequently, extra-adrenal sympathetic paragangliomas, ganglioneuromas [11], ganglioneuroblastoma, composite pheochromocytoma/ganglioneuroma and neuroblastomas are described [12]. Parathyroid adenomas and functional pituitary NET (prolactinomas or somatotropinomas) often occur after pheochromocytomas [13–15]. In contrast to MEN2, medullary thyroid carcinomas and C-cell hyperplasia are not described.

MAX-associated tumors are often multiple, bilateral and/or multicentric, but are indistinguishable from their sporadic counterparts.

Adrenal medullary hyperplasia may occur in this syndrome, although it is less common than in patients with MEN2 syndrome and SDH-deficient PPGL [16, 17].

At present, MAX immunohistochemistry in routine clinical practice is limited and it is not recommended as a screening test of *MAX* mutation [15].

MAFA-Related Familial Insulinomatosis MAFA-related familial insulinomatosis is an autosomal dominant syndrome caused by *MAFA* gene mutation sequence variants. This syndrome is characterized by multiple insulin-secreting pancreatic neuroendocrine tumors that usually present as adult-onset hyperinsulinemic hypoglycemia.

The pancreas of patients with this disorder grossly demonstrates multifocal small tumors that vary in size reaching up to around 1 cm.

The pancreas of patients with MAFA-related insulinomatosis shows the characteristic multicentric and innumerable insulin-producing beta cell proliferations ranging from dysplastic B cell cords to multifocal neuroendocrine trabecular microadenomas (< 5 mm) and solitary well-differentiated tumors (> 5 mm) (Fig. 2). The Ki-67 proliferative index is constantly < 2%.

The WHO chapter on this topic highlights that while the islets contain insulin, glucagon, pancreatic polypeptide, and somatostatin producing cells in normal distribution and numbers, the trabecular proliferations are exclusively positive for insulin, which helps distinguish the condition from MEN1 and glucagon cell adenomatosis and hyperplasia [18, 19]. The multifocal nature of the beta cell proliferations suggests that total pancreatectomy would be required for cure [20].

Question 2: What Familial Cancer Syndrome Has Diverse Primitive-Type Tumors? Which Tumors and Endocrine-Related Neoplasms Are Part of This Syndrome?

Heterozygous *DICER1* germline mutation causes DICER1 autosomal dominant familial tumor syndrome. Pleuropulmonary blastoma (PPB) is the most common primary malignant neoplasm of this syndrome involving the lung in young children. The previously called DICER1 PPB familial tumor predisposition syndrome was initially recognized in most cases because of the presence of PPB but also by several other unique and characteristic extrapulmonary tumors, have been described. DICER1 syndrome features several characteristic tumors and dysplastic conditions. Within the list of tumors associated with this syndrome are pediatric cystic nephroma, Sertoli-Leydig cell tumor, embryonal nasal chondromesenchymal hamartoma, gynandroblastoma, rhabdomyosarcoma of the cervix, primary central nervous system sarcoma, pituitary blastoma, embryonal tumor with multilayered rosettes-like cerebellar tumor, and ciliary body medulloepithelioma [21, 22] (Table 1). DICER1-associated presacral malignant teratoid neoplasm and other non-neoplastic associations are characterized by a second somatic mutation in DICER1.

From the endocrine pathology point of view, thyroid multinodular hyperplasia with unique findings as centripetal papillary hyperplasia, as well as neoplasms as follicular adenoma, differentiated (DTC) and poorly differentiated thyroid carcinoma (PDTC) [23], pituitary blastoma, and pineoblastoma.

In DTC, somatic *DICER1* alterations appear to be mutually exclusive with the most common somatic driver alterations including *BRAFV600E*, *RAS* mutations, and *RET* rearrangements [24–27].

The occurrence of a thyroid malignancy occurring in a younger patient, particularly if poorly differentiated or a macrofollicular variant of FTC should be considered as a clue of DICER1 involvement [26–29].

Pituitary Blastoma

Pituitary blastoma is an embryonal neoplasm within the sella turcica, composed of a mixture of primitive blastemal cells, neuroendocrine cells, and Rathke pouch epithelium, linked to germline and somatic *DICER1* variants.

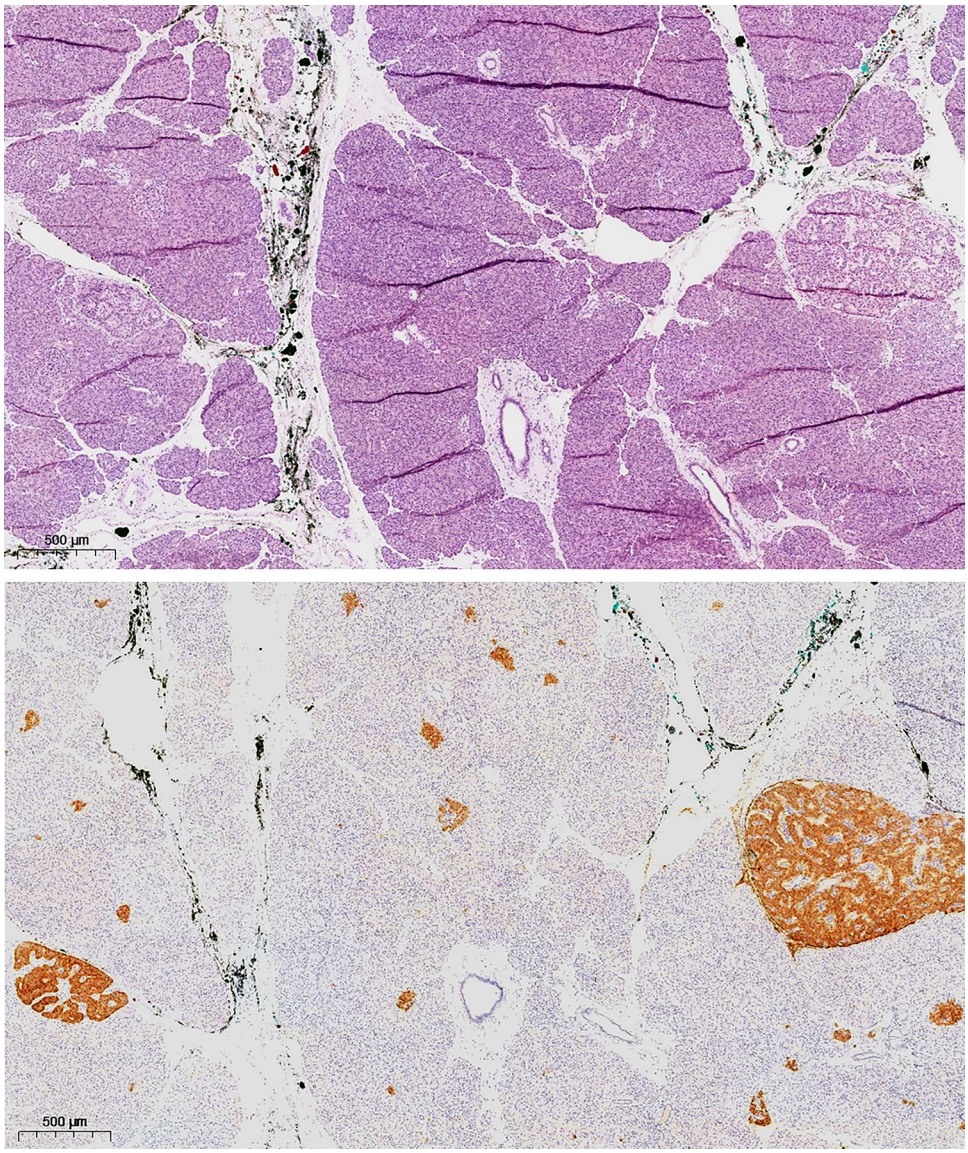

Fig. 2 Insulinomatosis patient with proven MAFA mutation, two microadenomas visible on HE, both positive for insulin (brown)

Pituitary blastoma is associated with Cushing disease in infants [30, 31].

Pituitary blastoma resembles fetal pituitary gland of ~11 weeks gestation and is composed of three cellular components including large, adenohypophysial neuroendocrine cells arranged in lobules or diffuse sheets, cuboidal or columnar primitive Rathke pouch epithelium with rosette or gland/follicle formation, and small undifferentiated-blastemal cells. Neuroendocrine cells variably express pro-opiomelanocortin-derivates including ACTH (Fig. 3), beta-endorphin, and melanocyte-stimulating hormone [32]. Unlike neuroendocrine cells, blastemal and Rathke pouch cells rarely show pituitary transcription factor expression [30].

Thyroblastoma

The accepted WHO definition of this newly described thyroid neoplasm is as follows: thyroblastoma is an embryonal high-grade thyroid neoplasm composed of primitive thyroid-like follicular cells surrounded by a small cell component, of also a primitive nature, and a mesenchymal stroma, which shows a variable differentiation.

Thyroblastoma likely arise due to somatic mutations in the *DICER1* gene. Thyroblastoma is not considered to be due to the germline mutations as in DICER1 syndrome. DICER1 mutations have been detected in all tested thyroblastoma cases.

Table 1 DICER1 syndrome phenotypes

DICER1 syndrome phenotypes	Age range in years (peak)	Specific for DICER1 syndrome
Most frequent phenotypes		
Pleuropulmonary blastoma[a]	(0–8)	High
Type I (cystic)	(0–2)	High
Type II (cystic and solid)	(1–5)	High
Type III (solid)	(1.5–6)	High
Type Ir (cystic)	Any age	High
Cystic nephroma	0–15 (0–4)	High
Ovarian Sertoli-Leydig cell tumor	2–40 (10–25)	High
Multinodular thyroid hyperplasia	2–40 (10–25)	Low, unless familial or age < 18 years
Moderately frequent phenotypes		
Embryonal rhabdomyosarcoma of uterine cervix[a]	4–45 (10–20)	High
Nasal chondromesenchymal hamartoma	5–25 (8–20)	Moderate
Differentiated thyroid carcinoma	5–45 (10–30)	Low, unless age < 18 years
Rare frequent phenotypes		
Pituitary blastoma	0–2	Very high
Anaplastic renal sarcoma[a]	2–20	High
Pineoblastoma	2–25 (2–10)	Moderate
Ciliary body medulloepithelioma	3–10	Moderate
Juvenile hamartomatous intestinal polyps	0–20 (0–4)	Low
Wilms tumor	3–8	Low
Embryonal rhabdomyosarcoma of bladder[a]	0–12	Undetermined
Cerebral sarcoma[a]	Undetermined	Undetermined
Very rare phenotypes		
Infantile cerebellar embryonal tumor	0–1	High
Ovarian embryonal rhabdomyosarcoma[a]	Undetermined	High
Gynandroblastoma	Undetermined	High
Presacral malignant teratoid tumor	Undetermined	High
PPB-like peritoneal sarcoma[a]	Undetermined	Likely high
Well-differentiated fetal lung adenocarcinoma	Undetermined	Low
Paratesticular sarcoma[a]	Undetermined	Low
Poorly differentiated thyroid carcinoma	Undetermined	Undetermined
Testicular stromal cell tumor	Undetermined	Undetermined
Mesenchymal hamartoma of the liver	0–8 (0–3)	Undetermined

Thyroblastoma is likely an underrecognized primitive thyroid neoplasm which has been previously diagnosed as the so-called malignant thyroid teratoma [33–35] or carcinosarcoma [36]. Due to the lack of standard terminology in earlier series, no epidemiological data is available.

Histologically, thyroblastoma is an embryonal neoplasm that mostly resembles thyroid parenchyma within the first trimester of prenatal development (Fig. 4). Thyroblastoma is composed of three cellular components including a component represented by fetal-type TTF1 + /PAX8 + /focal thyroglobulin + primitive-appearing thyroid follicles, fetal-type glands, and by primitive small round to oval cells, arranged into irregularly communicating solid aggregates and sheets with foci of necrosis and with an important mitotic activity. These components are bordered by a variably cellular primitive spindle cell stroma arranged into fascicles. These cells are usually positive for smooth muscle actin and may show focal positivity for desmin and myogenin. The small cells form focal periglandular cuffs. Foci of cartilage are seen in half of cases, but well-differentiated adult-type organoid structures, teratomatous components as pilosebaceous elements and skin adnexa are absent. The primitive small cell component express SALL4 but not OCT3/4 or PLAP [23, 33, 35, 36].

The detection of the germline mutation in *DICER1* allowed the identification of neoplasms and persist to recognize a number seemingly unrelated extrapulmonary neoplasms. DICER1 has also allowed us to identify histopathologic features of several overlapping morphologic characteristics of distinct entities.

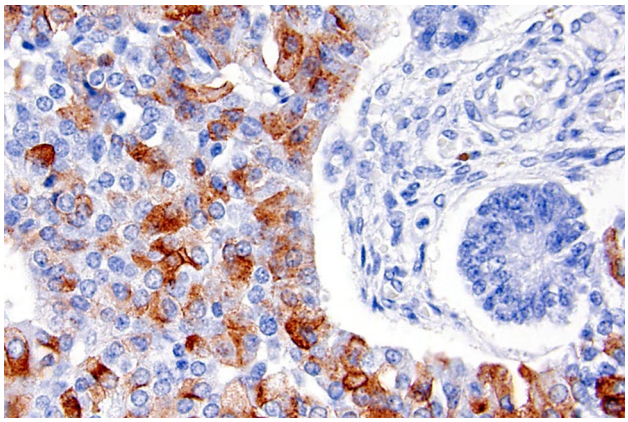

Fig. 3 Pituitary blastoma in a patient with DICER1 syndrome. Neuroendocrine cells staining for ACTH

The pathologists play an important role in identifying DICER1 mutation-related lesions. The characteristic thyroid findings should alert the pathologist of a familial DICER1-associated neoplasm. The pathologist should advise an appropriate testing on the tumor examined and should alert the clinician about a concern for a *DICER1* mutation-related disease.

Question 3: How Are the Familial Non-medullary Thyroid Carcinoma Classified in the New WHO?

Familial non-medullary thyroid carcinoma is extensively reviewed in the new 2022 WHO classification of endocrine and neuroendocrine tumors. This classification confirmed

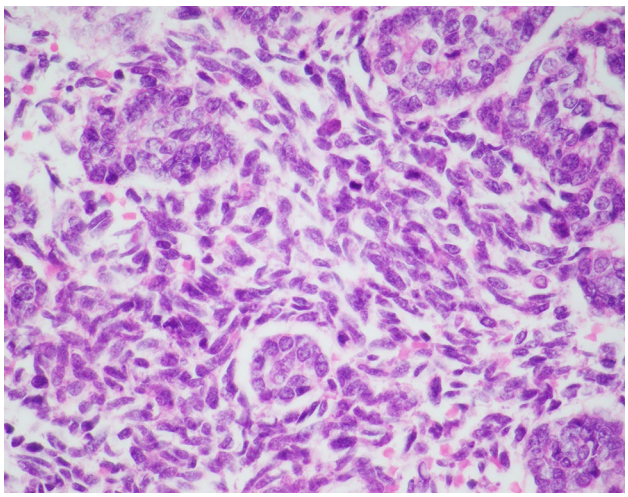

Fig. 4 Thyroblastoma in a young patient with DICER 1 somatic mutation shows primitive microfollicular structure surrounded by primitive spindle cells, mimicking a fetal thyroid at 12–13 weeks gestation

two large groups for familial thyroid cancer: (1) syndromic familial follicular cell-derived thyroid carcinoma and (2) non-syndromic familial follicular cell-derived thyroid carcinoma [37–39].

Syndromic familial follicular cell-derived thyroid carcinoma (SFNMTC) is a heterogeneous group of follicular cell-derived thyroid carcinomas that occur in families with a predominance of non-thyroid cancer [39–42]. SFNMTC includes PTEN hamartoma tumor syndrome (PHTS) [43, 44], familial adenomatous polyposis (FAP) [45], DICER1 syndrome [21], Carney complex (CNC) [46], and Werner syndrome (WS) [47] (Table 2). In SFNMTC, most of the clinical manifestations of non-thyroid lesions predominate and the genetic basis has been well established.

PHTS is mostly due to germline mutations in the *PTEN* gene [44, 48]. The mutations can also occur in the *PIK3CA*, *AKT1*, *SEC23B*, or *SDH* [49, 50] genes or due to germline *KLL* methylation epimutation [50].

FAP cases are caused by germline mutations in the *APC* gene [51, 52]. DICER1 syndrome is associated with heterozygous germline *DICER1* pathogenic variants that cause loss of function [53–55].

CNC is caused by germline inactivating mutations of the *PRKAR1A* gene [46] and less commonly of the *PRKACB* gene [56], although a locus at 2p16 has also been identified in some cases of CNC without a *PRKAR1A* mutation [57].

WS is due to mutations in the *WRN* gene [58].

In patients with SFNMTC, the thyroid gland is usually multinodular with the presence of multiple, bilateral follicular cell nodules accompanying the thyroid carcinoma [42]. In addition, the histological pattern of the cribriform morular thyroid carcinoma (Fig. 5) associated with the characteristic nuclear and cytoplasmic positivity for β-catenin present in these tumors in FAP [52, 59], with the morular component staining for CD5 and CK5.

It has been well known that in the PHTS tumors, as tricholemmomas, gastrointestinal polyps, adult Lhermitte-Duclos disease/dysplastic gangliocytoma, and distinct thyroid nodules [60], loss of immunohistochemical expression of the PTEN protein is highly indicative of PHTS [39, 61].

Non-syndromic familial follicular cell-derived thyroid carcinoma (NSFNMTC) is a heterogeneous group of inherited thyroid cancer that occurs in families in which follicular cell-derived thyroid cancer is the predominant cancer. The genetic alterations of NSFNMTC are also heterogeneous and poorly understood, involving several candidate genes (and loci), some of which need to be confirmed [39, 42]. In most cases, these data are consistent with an autosomal dominant monogenic inheritance [39, 42], but a polygenic inheritance model has also been described [62].

NSFNMTC has been clinically defined in the WHO classification: (a) by the presence of follicular cell derived

Table 2 Syndromic familial follicular cell-derived (non-medullary) thyroid carcinoma (adapted from [37, 41])

Syndrome	Gene (locus), inheritance	Thyroid lesions and incidence	Other lesions present in the syndrome
PTEN hamartoma tumor syndrome	*PTEN* (10q23.31), AD	PTC (classical and follicular variant): 60% FTC: 14–45% HCC: ≈ 1% ATC: < 1% FTA (HCA, lipoadenoma, and microadenomas): 25% Multinodular thyroid hyperplasia and multiple adenomatous nodules: 43–75% C-cell hyperplasia Lymphocytic thyroiditis: 55%	Adult Lhermitte-Duclos disease (cerebellar tumors), facial trichilemmomas, acral keratosis, papillomatous papules, autism spectrum disorder; breast cancer, macrocephaly, endometrial carcinoma, multiple palmoplantar keratosis, multifocal cutaneous facial papules, macular pigmentation of the glans penis, multiple gastrointestinal (GI) hamartomas or ganglioneuromas, fibromas, genitourinary tumors (particularly renal cell carcinoma), genitourinary malformations, uterine fibroids, intellectual disability (IQ ≤ 75)
Familial adenomatous polyposis	*APC* (5q22.2), AD	Cribriform morular thyroid carcinoma: 16%	Adenomatous polyps of the large bowel, colorectal adenocarcinoma, duodenal adenomas and carcinomas, GAPPS, desmoid tumors, hepatobiliary tree tumors, hepatoblastoma, adrenocortical adenomas and carcinomas, brain tumors, CHRPE
DICER1 syndrome	*DICER1* (14q32.13), AD	TC (PTC, FTC, PDTC)* FTA MNG	Macrocephaly, pleuropulmonary blastoma (PPB), peritoneal PPB, pulmonary cysts and/or pneumothorax in a newborn or young child, ovarian tumors (Sertoli-Leydig cell tumor, gynandroblastoma, undifferentiated sarcomas, embryonal rhabdomyosarcoma), ciliary body medulloepithelioma, pituitary blastoma, central nervous system (CNS) sarcoma, CNS embryonal tumors, pineoblastoma, nasal chondromesenchymal hamartoma, multicystic hepatic lesions, cystic nephroma, presacral teratoid neoplasm
Carney complex	*PRKAR1A* (17q24.2), AD	TC (FTC, PTC): 15% MNG (follicular adenomatosis) FTA	*Major criteria*: spotty skin pigmentation (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa), myxoma (cutaneous, mucosal, cardiac, breast), GH-producing pituitary adenoma, primary pigmented nodular adrenocortical disease, blue nevus and epithelioid blue nevus (multiple), breast ductal adenoma (multiple), osteochondromyxoma, psammomatous melanotic schwannoma
Werner syndrome	*WRN* (8p12), AR	TC (FTC, PTC, ATC): 18%	Bilateral ocular cataracts, premature graying and/or thinning of scalp hair, short stature, chronic ulcers around the ankles, meningioma, melanoma, soft-tissue sarcomas, osteosarcomas, leukemia and preleukemic disorders, atherosclerotic disease, diabetes mellitus, hypogonadism

AD autosomal dominant, *AR* autosomal recessive, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *HCC* Hürthle cell carcinoma, *ATC* anaplastic thyroid carcinoma, *FTA* follicular thyroid adenoma, *HCA* Hürthle cell adenoma, *MNG* multinodular goiter, *PDTC* poorly differentiated thyroid carcinoma, *TC* thyroid carcinoma, *GAPPS* gastric adenocarcinoma and proximal polyposis of the stomach, *CHRPE* congenital hypertrophy of the retinal pigment epithelium

*Individuals with DICER1 syndrome had a 16-fold increased risk of thyroid cancer [63]

thyroid carcinoma in at least three first-degree relatives, or (b) by the existence of papillary thyroid carcinoma in two or more first-degree relatives, always in both cases, in the absence of a history of previous radiation and inherited cancer syndrome (Table 3). In these patients, the thyroid gland generally simulates a multinodular goiter macroscopically due to the frequent multicentricity and bilaterality of the thyroid carcinoma (usually papillary carcinoma) and to the association with hyperplastic nodules and adenomas [39, 42].

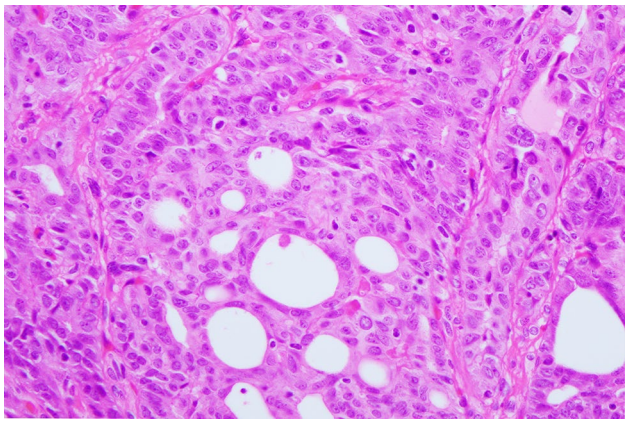

Fig. 5 Cribriform morular thyroid carcinoma associated with familial adenomatous polyposis syndrome. The cribriform-patterned areas lack fibrous stroma, the follicular-like structures lack colloid and the papillae are lined by cuboidal or tall cells with lacking PTC-like nuclear features

It is hoped that the clinical criteria established in this new WHO classification will facilitate the investigation of the genetic bases of NSFNMTC.

Question 4: What Are the Thyroid Pathology Findings in DICER 1 Syndrome?

The accepted definition of DICER1 syndrome at the 2022 WHO classification of tumor is an autosomal dominant tumor predisposition syndrome caused by heterozygous germline pathogenic variants in *DICER1*. It is characterized by increased incidence of benign and malignant lesions involving multiple organ systems, including pleuropulmonary blastoma, cystic nephroma, ovarian Sertoli-Leydig cell tumor, embryonal rhabdomyosarcoma of the uterine cervix and endocrine-related lesions such as multiple benign and malignant thyroid neoplasms, and pituitary blastoma.

Most patients with DICER1-related thyroid disease [23], feature MNG that consists of multiple benign follicular nodules with variable architecture and subtle atypia, or follicular adenomas including those with intrafollicular centripetal papillary growth [24, 25, 27, 42]. Early-onset, familial, or male MNG should prompt consideration of the presence of DICER1 syndrome.

Multinodular thyroid findings associated with *DICER1* syndrome shows characteristic multiple and bilateral nodules of follicular proliferations, as adenomatous nodules and macrofollicular-pattern nodules, well-circumscribed adenomas, and/or nodules displaying intrafollicular centripedal papillary growth (so-called papillary hyperplasia or papillary adenoma) without nuclear features of papillary thyroid carcinoma [24].

A high frequency of involutional change in the non-tumorous thyroid parenchyma, characterized by dilated macro-follicles, in the absence of subclinical or even clinical hyperthyroidism is a characteristic finding present in DICER1-related thyroid disease. The identification of variable involutional changes in the non-nodular thyroid parenchyma should raise suspicion of DICER1-related pathogenesis [24, 42].

Careful microscopic examination of thyroid nodules and examination of the non-lesional thyroid parenchyma offers further suspicions to the possibility of DICER1-related thyroid disease, as the gross findings are indistinguishable from multinodular hyperplasia [23].

Multifocal follicular cell proliferations with intrafollicular centripetal papillary projections, also known as papillary adenoma, are characteristic of this syndrome.

Persons with DICER1 syndrome have a 16-fold increased risk of thyroid cancer compared with the SEER rates [63]. The diagnosis of malignancy is restricted to tumors with invasive growth and is enriched in low-risk follicular-patterned DTCs [24, 28, 29, 42]. Germline *DICER1* mutations are associated with an increased risk of developing familial DTC. Pediatric FTCs have distinct genomic alterations and pathogenesis compared with adults, particularly those characterized by *DICER1* variants and should be considered in pediatric FTCs, especially in younger patients < 10 years of age.

Table 3 Clinical criteria for non-syndromic familial non-medullary thyroid carcinoma

Essential criteria
Follicular cell derived thyroid carcinoma in at least 3 first-degree relatives or Papillary thyroid carcinoma in 2 or more first-degree relatives
Always in both cases in the absence of prior known radiation exposure and familial cancer syndromes
Supportive criteria
Patient < 33 years
Affected family member/s < 45 years
Papillary thyroid carcinoma multifocal y/o bilateral
Papillary thyroid carcinoma in male, particularly in a young man
Background thyroid with a combination of benign lesions

Most carcinomas are well differentiated (usually classic, follicular variant or solid/trabecular variant of papillary thyroid carcinoma) [25, 64], but rare cases of poorly (high grade) differentiated carcinoma have been described [27]. The diagnosis of multinodular goiter with involutional changes, with or without differentiated thyroid carcinoma or poorly differentiated carcinoma in childhood or adolescence, should raise suspicion of DICER1 syndrome.

Childhood- and adolescent-onset neoplasms, as poorly differentiated thyroid carcinoma (PDTC) are genetically distinct from adult-onset PDTC in that they are strongly associated with DICER1 mutations and may herald DICER1 syndrome in a minority. PDTCs arising in childhood or adolescence are less common [27].

Thyroblastoma, a rare DICER1 gene-related primitive neoplasm, shows primitive microfollicular structure surrounded by primitive spindle cells rarely with heterologous elements, and likely arise due to somatic mutations in the *DICER1* gene [33, 35].

The occurrence of a thyroid malignancy occurring in a younger patient, particularly if poorly differentiated or a macrofollicular variant of FTC should be considered as a clue of DICER1 involvement [26–29]. Early-onset, familial, or male multinodular hyperplasia should prompt careful personal and family history focused on *DICER1*-associated tumors.

Question 5: The Familial Cancer Syndrome That Is Expanding on Its Recognition and on the Molecular Findings and These Tumors Are About Half of All Genetic Cases: Describe the Syndrome

SDH-deficient tumor syndromes are a group of syndromes characterized by succinate dehydrogenase (SDH)-deficient neoplasia, usually associated with pathogenic germline sequence variants in one of the *SDH* genes, which encodes the subunits of succinate dehydrogenase (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*) or with epimutation (promoter hypermethylation) of the *SDHC* gene.

A succinate dehydrogenase-deficient neoplasm refers to any tumor that shows loss of immunohistochemical expression of SDHB which serves as a marker of dysfunction of the SDH complex (also known as the mitochondrial complex 2), first demonstrated in 2005 [65] and the findings later confirmed [66, 67]. Although sporadic disease may rarely occur, most cases of SDH-deficient neoplasia arise in the syndromic setting, and therefore the occurrence of any SDH-deficient neoplasm is considered prima facie evidence of syndromic disease. Molecular mechanisms of the SDH-deficient tumor syndromes include germline mutations of one of the SDH genes encoding the subunits of succinate dehydrogenase (SDHA, SDHB, SDHC, SDHD, SDHAF2) or epimutation (promoter hypermethylation) of the SDHC gene.

One major change in classification of the SDH-deficient tumor syndromes in the fifth edition blue book relates to use of the term "Carney triad." Carney triad was previously defined clinically as the association of SDH-deficient GIST, SDH-deficient paraganglioma, and pulmonary chondroma. Now the term Carney triad is restricted to syndromic SDH-deficient neoplasia where no underlying germline mutation is identified. Using this definition most cases of Carney triad are associated with promoter hypermethylation (epimutation) of the SDHC gene, although it is accepted that there will be some cases associated with germline mutation where the mutation is not identified by current methods.

There are some genotype–phenotype correlations so that different genes are more commonly associated with certain

Table 4 Clinicopathological features of SDH-deficient tumor syndromes

Gene	Most frequent location of pheochromocytoma/paraganglioma	SDH-deficient GIST	SDH-deficient RCC	SDH-deficient PitNET	Pulmonary chondroma
SDHD	Head and neck > intra-abdominal extra-adrenal > thoracic > adrenal	+	?	+	−
SDHAF2	Head and neck: most common (limited data)	+/−	?	+	−
SDHC	Head and neck (esp carotid body) > thoracic > intra-abdominal extra-adrenal	+	+ +	+	−
SDHB	Intra-abdominal extra-adrenal > thoracic > head and neck > adrenal	+	+ + +	+	−
SDHA	Intra-abdominal extra-adrenal > head and neck > adrenal > thoracic	+ + + (30% of SDH deficient GISTs)	+	+ +	−
SDHC promoter hypermethylation (Carney triad)	Intra-abdominal extra-adrenal > head and neck > thoracic	+ + + + (50% of SDH-deficient GIST)	−	−	+ + + +

Table 5 Clinical diagnostic criteria for the diagnosis of NF1 (two or more must be present [243]

1	> 6 café-au-lait macules > 5 mm in greatest diameter in prepubertal individuals and > 15 mm in greatest diameter after puberty
2	> 2 neurofibromas of any type or one plexiform neurofibroma
3	Axillary or inguinal freckling
4	Optic glioma
5	> 2 Lisch nodules (iris hamartomas)
6	A distinctive osseous lesion, such as sphenoid wing dysplasia or thinning of the cortex of long bones (with or without pseudarthrosis)
7	A first-degree relative (parent, sibling, or child) with NF1 diagnosed by the above criteria

tumor combinations and locations. These correlations are summarized in Tables 4 and 5. Briefly, SDHB mutations are more common in intra-abdominal extra-adrenal paragangliomas and/or metastatic paraganglioma, while mutations in the SDHD gene are more frequent in paragangliomas of the head and neck [67]. SDHA mutation is particularly associated with SDH-deficient GIST (30% of cases), as is SDHC mutation (50% of cases) [68–70]. SDHB mutation accounts for the great majority of SDH deficient renal carcinomas [71, 72] which are only rarely associated with SDHC or SDHA mutation and virtually never with SDHD mutations. Pulmonary chondromas are very rare outside the setting of Carney triad. In addition to loss of SDHA expression, tumors with biallelic inactivation of SDHA also show SDHA loss [73, 74].

SDHB and SDHA immunohistochemistry may be difficult to interpret in some cases, and a tumor should only be considered deficient if there is preserved expression in non-neoplastic cells which act as internal controls (Fig. 6).

About half of all syndromic phaeochromocytomas/paragangliomas are SDH-deficient. There are subtle, but inconsistent morphological clues to the diagnosis of SDH-deficient paraganglioma including well-formed, rounded nests of epithelioid cells, often with focally clear or vacuolated cytoplasm (Fig. 6a). [75]. SDH-deficient GISTs almost only every arise in the stomach and are characterized by multifocality, a plexiform/multinodular growth pattern, epithelioid cell type predominance, a subtle nested architecture, and frequent lymph node metastasis [67, 68, 76, 77]. Although they lack KIT or PDGFRA mutation, SDH-deficient GISTs show diffuse strong

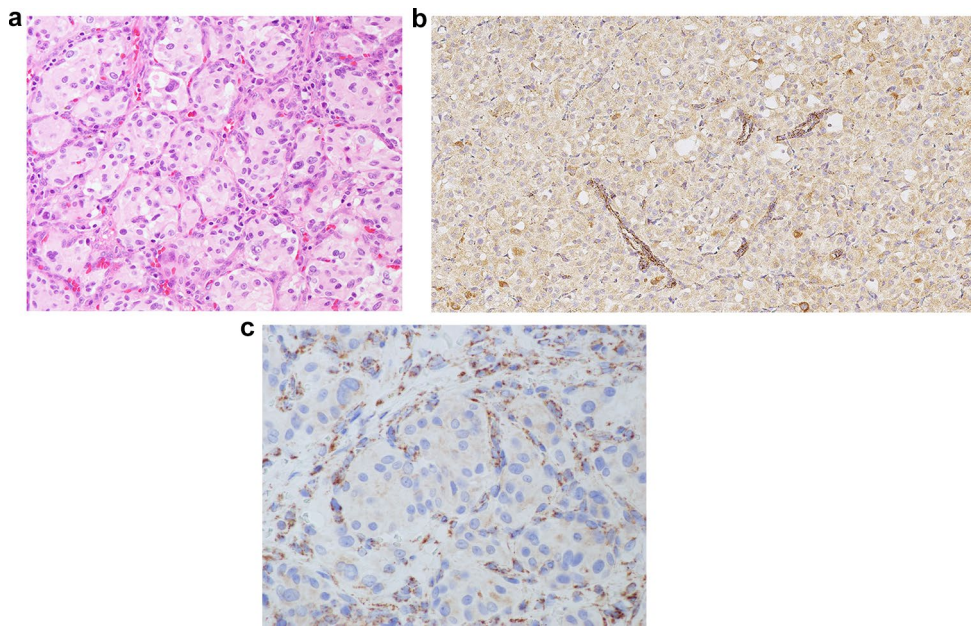

Fig. 6 **a** SDH-deficient paraganglioma with rounded nests of epithelioid cells with focally clear or vacuolated cytoplasm. **b** In this SDH-deficient renal cell carcinoma, all the neoplastic cells demonstrate definite, but weak and diffuse, expression of SDHB by IHC. This contrasts with the dense granular cytoplasmic expression seen in the non-neoplastic cells which serve as an internal positive control. Because the expression in the neoplastic cells is so weak and diffuse and contrast with the granular staining in the internal positive controls, in this case SDHB should be correctly interpreted as negative. The patient was subsequently showed to have a pathogenic SDHB mutation. **c** SDH-deficient paraganglioma, with SDH loss by the tumor cells; considered SDHB-deficient as there is preserved expression in non-neoplastic cells, as endothelial cells, which act as internal controls.

immunohistochemical expression of both KIT and DOG1 [67, 68, 77].

SDH-deficient renal carcinomas are now recognized as a distinct entity (Fig. 6b) [71, 72, 78–80]. Although variant morphology is increasingly recognized [71], the majority of SDH-deficient renal carcinomas show characteristic morphology being comprised of compact nests of bland cells with eosinophilic, but not oncocytic, cytoplasm. A characteristic, but inconstant feature of SDH-deficient renal carcinoma is the presence of cytoplasmic inclusions containing eosinophilic or bubbly pale material [71, 72, 78–80]. Tumor necrosis, nuclear atypia and variant morphologies signify higher grade transformation and are associated with worse prognosis [71].

There is less experience with SDH-deficient PitNETs/pituitary adenomas, but they may be more frequently prolactin producing [67, 81–84]. SDH-deficient pulmonary chondromas are distinguished from chondroid hamartomas by their smooth contour, and lack of mesenchymal elements such as fat or smooth muscle. SDHB IHC may be a less reliable marker of SDH-deficient pulmonary chondromas [67, 85].

In the era of widespread molecular testing performed to assess a range of malignancies, it is important to recognized that germline pathogenic variants in SDHA are relatively common and in some populations have been reported to be found in about 0.3% of unselected individuals [73], yet demonstrate a very low lifetime penetrance (estimated as 1.7%) [86]. Therefore, if identified by large panel sequencing outside the setting of SDH deficient neoplasia, SDHA germline variants may represent incidental findings of little clinical significance [73, 74].

Question 6: Immunohistochemistry Can Be a Reliable and Time-Saving Strategy in the Evaluation Germline Mutations in Patients with Familial Cancer Syndromes. What Are the Immunohistochemistry Markers That We Use Supporting the Diagnosis of a Familial Cancer Syndrome?

Immunohistochemistry has arisen as a cost-effective strategy in the evaluation either of somatic mutations in tumors and/or germline mutations in patients presenting with tumors associated with familial cancer predisposition syndromes [87]. The identification of at-risk kindreds enables screening and risk reduction approaches for patients with hereditary cancer predisposition syndromes. Immunohistochemistry markers are available for numerous familial cancer syndromes, including Carney Complex, cribriform-morular thyroid carcinoma in FAP, familial SDH-deficient pheochromocytoma/paraganglioma syndromes, medullary thyroid carcinoma and MEN2, MAX-related tumors (MEN5), hyperparathyroidism-jaw tumor syndrome, and glucagon cell hyperplasia and neoplasia. We summarize below the most useful markers used on the routine histopathology labs.

SDHB and SDHA Immunohistochemistry

Loss of immunohistochemical expression of SDHB is a marker of biallelic inactivation of any component of the SDH complex (that is SDHA, SDHB, SDHC, SDHD, or SDHAF2) [65–68, 75, 82, 88] and is also termed SDH deficiency. Because somatic mutations of the SDH genes are extremely rare outside the setting of germline mutation [89], SDH deficiency is prima facie evidence of an SDH-deficient tumor syndrome. In addition to showing loss of expression for SDHB, tumor associated with biallelic mutation of SDHA also show loss of expression for SDHA [73, 74].

Therefore, immunohistochemistry for SDHB is a cost-effective screening test for the SDH-deficient tumor syndromes (Fig. 6). However, SDHB immunohistochemistry does not replace genetic testing, as all presumptive syndromic cases should be confirmed with genetic testing. Furthermore, SDHB/A immunohistochemistry should be performed and interpreted with caution. True negative staining of SDHB/A requires the presence of an internal positive control in the non-neoplastic cells which should be distinctly granular and cytoplasmic (that is mitochondrial). In some case, the neoplastic cells demonstrate a diffuse cytoplasmic blush which contrasts with the darker and distinctly granular appearance of the staining in the internal controls. This pattern, which is commonly associated with SDHD mutation, should be correctly interpreted as being positive [67, 90] (Fig. 6).

Parafibromin Immunohistochemistry

Hyperparathyroidism jaw tumor (HPTJT) syndrome is an autosomal dominant disorder caused by germline mutation in the CDC73 gene which encodes the protein parafibromin. HPTJT syndrome presents with primary hyperparathyroidism usually due to a single parathyroid adenoma or carcinoma [91, 92]. Recurrent or new primary tumors occur with long-term follow-up in most patients [93–96].

Clinical clues to HPTJT syndrome include younger age of presentation (particularly if < 40 years), large tumors, and very high serum PTH and calcium [96–100]. Given its rarity in the general population parathyroid carcinoma is particularly common in patients with HPTJT and the lifetime risk approaches 15% [93, 95, 96, 98, 99, 101]. Therefore, the possibility of HPTJT syndrome should be considered in all patients with parathyroid carcinoma even in the absence of a family history [99, 102, 103].

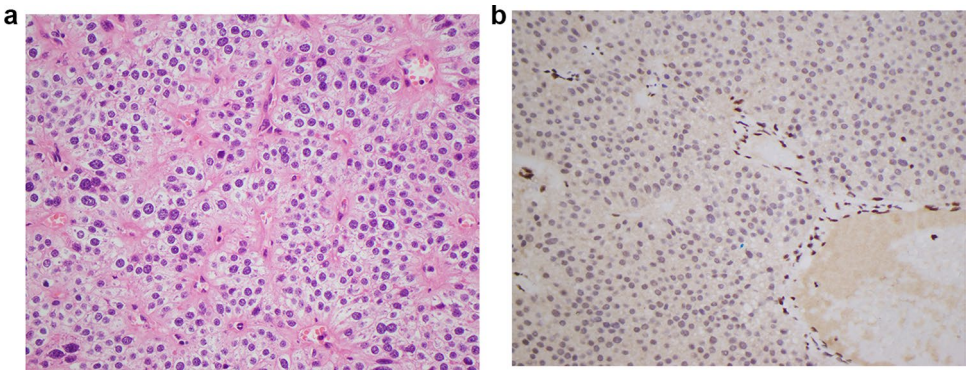

Fig. 7 **a** This parafibromin-deficient parathyroid tumor demonstrates typical morphological features being composed of cells with eosinophilic cytoplasm, frequently with perinuclear cytoplasmic clearing. There is nuclear enlargement, but with a relatively preserved N:C ratio and frequent binucleation. **b** Immunohistochemistry for parafibromin in a parafibromin-deficient parathyroid tumor. It is emphasized that significance is only placed on nuclear expression and that an internal positive control in non-neoplastic cells is required for parafibromin immunohistochemistry to be considered informative

Parathyroid tumors associated with biallelic CDC73 mutation/inactivation (with or without a germline mutation) are termed "parafibromin-deficient" [99]. Morphological clues include sheet-like growth, eosinophilic cytoplasm, perinuclear cytoplasmic clearing, nuclear enlargement occasionally with binucleation [91, 99] (Fig. 7a). Parafibromin is a difficult stain to perform and interpret, and it is emphasized that only nuclear expression of parafibromin is considered significant, and that for a tumor to be considered parafibromin-deficient, there should also be nuclear expression in non-neoplastic cells which act as an internal positive control [99, 102, 104]. It is emphasized that loss of immunohistochemical expression of parafibromin is seen in most, but not all, parafibromin-deficient parathyroid tumors (Fig. 7b) [87, 99, 102–105].

MAX Immunohistochemistry

At present, it appears that the overall utility of MAX immunohistochemistry in the pathology practice is limited and it is not recommended as a screening test of *MAX* mutation [15]. Some studies have suggested that loss of MAX immunoreactivity may occur only in *MAX*-related tumors carrying truncating mutations [7, 106]. However, MAX immunohistochemistry seems to have poor sensitivity and specificity as a marker of *MAX* mutation [107, 108].

PTEN Immunohistochemistry

PTEN is a tumor suppressor gene that maps to 10q23.3. PTEN regulates cell migration, cell growth, apoptosis, and cell cycle arrest. Lesional tissue in patients with Cowden syndrome (CS) has been found to have absent or decreased immunoexpression of PTEN.

Reduction or complete loss of PTEN expression in dysplastic gangliocytomas of cerebellum/adult Lhermitte-Duclos disease (LDD), a pathognomonic finding for Cowden syndrome, was demonstrated in 2003 [109]. Loss of PTEN expression in hamartomatous polyps from patients with CS was also confirmed [110].

Characteristic pathologic findings in thyroidectomy specimens suggestive of CS include multiple adenomatous nodules, follicular adenomas, associated with nodular hyperplasia, follicular carcinoma, and/or papillary thyroid carcinoma. Loss of PTEN expression in adenomatous thyroid nodules (Fig. 8), as well and in the thyroid carcinoma, whether in all nodules or in a subset of nodules, appears to be both sensitive and specific for CS. Loss of PTEN expression in adenomatous nodules (either in all nodules or heterogeneous) has been confirmed in thyroid lesions of patients with CS [39, 43, 60, 87].

Other Familial Thyroid Carcinomas

The functional study of some cases of NSFNMTC has evidenced immunohistochemical overexpression of HABP2, EGFR, phospholipase C beta 1, and NOP53 in thyroid carcinomas associated with pathogenic germline variants of the *HABP2*, *BROX*, *PLCB1*, and *NOP53* genes, respectively [111–114]. Although these immunohistochemical data could possibly help the pathologist in screening for this type of tumors, some of these susceptibility genes and immunohistochemical data still need to be confirmed.

Question 7: What Familial Cancer Syndrome Involves the Parathyroid Gland?

Familial cancer syndromes involving the parathyroid gland include MEN1, MEN2, HPT-JT, and MEN4. In MEN1,

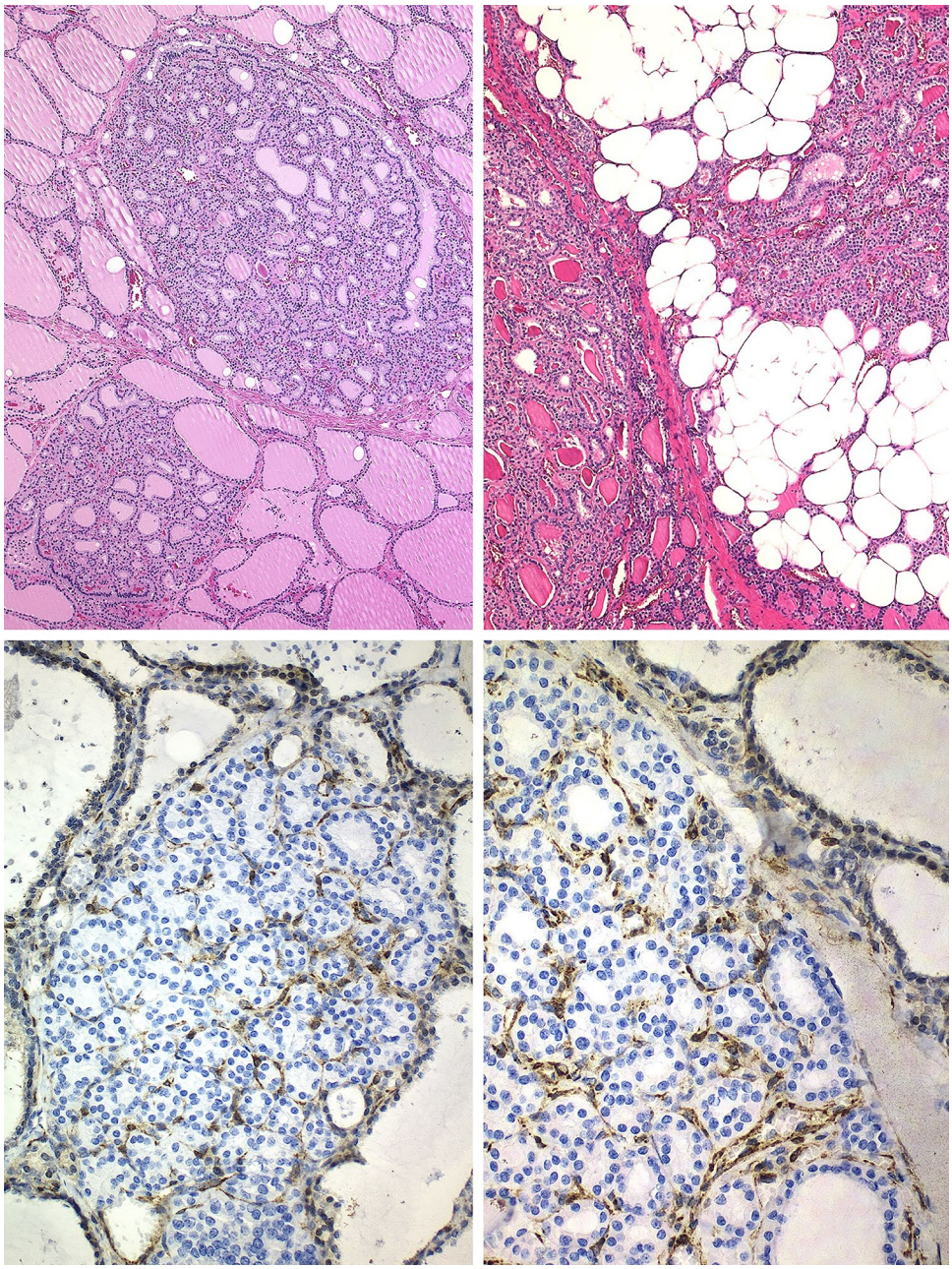

Fig. 8 Thyroid in PTEN hamartoma tumor syndrome (PHTS). The presence of several adenomatous nodules called "microadenomas" is characteristic (top left). Fatty infiltration and lipoadenomas (adenolipomas) are also common (top right). Immunohistochemical negativity for PTEN in all nodules or in a subset of nodule is a sensitive and specific indicator of PHTS (bottom). PTEN staining is only preserved in normal follicular cells and endothelial cells (internal control)

primary hyperparathyroidism is the most common feature, occurring in virtually all individuals with MEN1. The parathyroid disease in MEN1 usually involves multiple glands but can be asymmetrical and may occur in an asynchronous manner [115–117]. Historically, the term "parathyroid hyperplasia" has been used for this multiglandular disease, but it is now known that the lesions are composed of multiple monoclonal proliferations now referred to as multiglandular parathyroid disease or multiple multiglandular microadenomas [118]. Histologically, the parathyroids are hypercellular, may show nodular proliferations of predominantly chief cells but other cell types can be seen, and often lack a normal or atrophic appearing rim of non-lesional parathyroid tissue. MEN1-associated parathyroid disease generally behaves in a benign manner, and parathyroid carcinoma is are very rare in MEN1 [119].

Although MEN2 is characterized by medullary thyroid carcinoma and often associated with pheochromocytoma, parathyroid involvement occurs in approximately 3–35% of individuals with multiple endocrine neoplasia type 2A (MEN2A) [120]. Primary hyperparathyroidism is the first manifestation of MEN2A in less than 1% of cases [121]. Parathyroid disease is not a component of MEN2B. Parathyroid disease in MEN2A occurs a single gland disease

often regarded as adenoma and as multiglandular disease. The multi glandular disease historically has been regarded as "hyperplasia," but multiglandular disease in the setting of multiple endocrine neoplasia is more likely to represent multiple parathyroid neoplasms.

In HPT-JT, the parathyroid disease is the main and often the only feature of this disorder [93, 96, 99]. However, other tumors can occur including those involving the jaw and rarely tumors of the kidney and uterus [97, 122–124]. HPT-JT is an autosomal dominant disorder caused by heterozygous pathogenic germline sequence variants or deletions in the *CDC73* gene. *CDC73* is a tumor suppressor gene that encodes the protein parafibromin [101, 103, 125]. Individuals with HPT-JT generally present with primary hyperparathyroidism involving a single gland in most cases [91, 92]. Although with extended follow-up, metachronous tumors can occur [95]. With single gland involvement being the most common presentation of primary hyperparathyroidism in HPT-JT, most of the lesions identified are adenomas. However, in HPT-JT the lifetime risk of parathyroid carcinoma is up to 15% [98, 101]. Because parathyroid carcinoma is very uncommon, individuals diagnosed with parathyroid carcinoma are evaluated for the possibility of an underlying germline *CDC73* alteration–which is found in up to 30% of what were thought to be sporadic parathyroid carcinomas [99, 102, 103, 126, 127]. Although a variety of biomarkers may be used in the evaluation of parathyroid glands, parafibromin may be one of the most useful. Parathyroid tumors associated with biallelic CDC73 inactivation show complete nuclear loss of parafibromin in all neoplastic cells and are regarded as "parafibromin-deficient" (Fig. 7b) [99, 104, 128, 129]. However, the presence of parafibromin does not rule out the possibility of HPT-JT as point mutations of *CDC73* can result in preserved parafibromin expression [95, 102]. Most parafibromin deficient parathyroid tumors are associated with germline *CDC73* inactivation, but biallelic somatic only mutations do occur [99]. Regardless, the finding of a parafibromin-deficient parathyroid neoplasm is an indication for long-term follow-up and underlying genetic testing [99].

Question 8: What Familial Cancer Syndrome Involves the Paraganglia and Adrenal Medulla?

Pheochromocytoma occurs in approximately 50% of individuals with MEN2 [130, 131]. Paragangliomas (extra-adrenal pheochromocytoma) can occur in MEN2, but they are quite rare–approximately 1%–and may occur after a diagnosis of MEN2 [130]. Metastatic disease is very infrequent (0–3%) with pheochromocytomas in MEN2 [130, 132, 133]. Although individuals with MEN2 may present with pheochromocytoma (15%), these tumors are more often diagnosed either simultaneously (30%) with medullary thyroid carcinoma or after (55%) diagnosis of medullary thyroid carcinoma [130]. The pheochromocytomas symptomatic at diagnosis in 50–69% [130, 133]. In a large multinational study of 1210 individuals with MEN2, 563 had pheochromocytoma, 44% of which had bilateral disease and 56% had unilateral pheochromocytoma at presentation of the pheochromocytoma [130]. Thirty percent of those with unilateral pheochromocytoma subsequently developed a contralateral pheochromocytoma in a mean of 9 years [130].

In the large multinational study of 563 individuals with MEN2 with pheochromocytoma, the mean age at diagnosis of the first pheochromocytoma was 45 years for those with *RET* mutation involving exon 10 (codon 609, 611, 618, 620), 37 years for those involving exon 11 (codon 634), and 27 years for those involving exon 16 (codon 918) [130]. Of individuals with pheochromocytoma in this large study, 84% of the pheochromocytomas were identified in individuals with *RET* mutation involving codon 634 [130]. In a study from Japan, all individuals with pheochromocytomas occurring in the setting of MEN2 with a *RET* mutation involving code on 918 developed pheochromocytoma by age 56 years, while the penetrance of pheochromocytoma was 25% by age 30 years, 52% by age 50 years, and 88% by age 77 years in individuals with a codon 634 mutation [134]. The penetrance pheochromocytoma in individuals with mutations involving codons other than 634 and 918 was 32% [134].

Unlike some other syndrome-associated pheochromocytomas, those in the setting of MEN2 histologically appear indistinguishable from sporadic pheochromocytomas. In the setting of MEN2, pheochromocytomas are often bilateral may be associated with adrenal medullary hyperplasia, or in this setting micro-pheochromocytomas–a clonal process. Composite pheochromocytomas can also be seen in MEN2 [135].

Pheochromocytomas, often bilateral and multifocal in one gland occur in the setting of MEN5 due to pathogenic *MAX* germline variants. The median age reported at pheochromocytoma occurrence is 34 years [6]. Extra-adrenal sympathetic paragangliomas, ganglioneuromas, neuroblastomas, and pituitary neuroendocrine tumors are also reported [15].

Question 9: What Are the New Findings Within the Classical Familial Cancer Syndromes?

MEN1 is characterized by primary hyperparathyroidism, the most common manifestation of MEN1 and is present in almost all individuals with MEN1. The parathyroid disease in MEN1 is multiglandular and can be asymmetrical and asynchronous [115–117, 136, 137]. Historically, the multiglandular disease in MEN1 has been referred to as parathyroid

"hyperplasia." However, recent genetic studies have shown the multiglandular parathyroid lesions in MEN1 are multiple monoclonal proliferations and regarded as multiple multiglandular adenomas [118]. Other tumors significantly associated with MEN1 include pituitary adenomas/pituitary neuroendocrine tumors and duodenum-pancreatic neuroendocrine tumors [115–117]. In addition to these characteristic tumors, a variety of other endocrine and non-endocrine tumors can occur in the setting of MEN1 including bronchopulmonary neuroendocrine tumors, thymic neuroendocrine tumors, adrenal cortical carcinomas, pheochromocytomas, collagenomas, facial angiofibromas, leiomyomas, lipomas, leiomyomas, hibernomas, and breast cancers have also been described [138–143].

Increasing data of genotype–phenotype associations in the setting of MEN2 have led a greater understanding of the features of the disease is well as to improved prognostic risk classification [120]. Classic MEN2A, which accounts for approximately 95% of MEN2, is associated with medullary thyroid carcinoma (90%), pheochromocytoma (30%), and primary hyperparathyroidism (10%), while MEN2A with cutaneous lichen amyloidosis has slightly greater prevalence of MTC (95%), pheochromocytoma (50%), and primary hyperparathyroidism (15%), and MEN2A with Hirschsprung disease has slightly less prevalence of MTC (80%), pheochromocytoma (20%), and primary hyperparathyroidism (5%) [120]. In MEN2B, which accounts for approximately 5% of MEN2, has a prevalence of MTC of 100%, pheochromocytoma of 50%, ganglioneuromatosis of 100%, Marfanoid habitus 70%, corneal nerve hypertrophy 45%, and alacrima 40% [120]. *RET* germline variants are numerous, and not all are pathogenic. Numerous RET germline variants that continue to be reported often in association with hereditary medullary thyroid carcinoma must be carefully considered in this setting as it is much more complex than the conventional MEN2A (classic type, with Hirschsprung disease, with cutaneous lichen amyloid, and familial isolated medullary thyroid carcinoma) and MEN2B disease associated with *RET* mutation many pathologists learned about decades past in medical school. The classification and genotype–phenotype correlation is often looked at as medullary thyroid carcinoma risk groups with those carrying M918T mutations as being of highest risk well those with variants involving codon 634 and A883F as high risk, and those with variants involving codon 533, 609, 611, 618, 620, 630, 631, 666, 768, 790, 804, 891, and 912 as moderate risk [144]. However there remains significant variability both within a family and among families regarding the age of onset and aggressive miss of medullary thyroid carcinoma that is remains difficult to explain or predict with an individual [120].

Primary hyperparathyroidism is the characteristic feature of HPT-JT. Unlikely multiglandular parathyroid disease in MEN1, often there is only a single gland involvement in HPT-JT although additional tumors can occur with long-term follow-up [92, 93, 95, 96, 99]. What is particularly striking about the primary hyperparathyroidism in HPT-JT is the markedly increased incidence in parathyroid carcinoma occurring in up to 15% [98, 101]. HPT-JT is caused by germline sequence variants or deletions in the *CDC73* gene, a tumor suppressor gene, that encodes the protein parafibromin [101, 103, 125]. A variety of biomarkers have been used in the evaluation of parathyroid glands, and recent work with the immunohistochemical marker parafibromin has shown utility both in raising the possibility of underlying *CDC73* inactivation and diagnostically in diagnosing parathyroid carcinoma. Tumors with complete nuclear loss of parafibromin in all neoplastic cells are regarded as "parafibromin-deficient" (Fig. 7b) [99, 104, 128, 129]. Complete loss of nuclear parafibromin in all neoplastic cells is not definitive of an underlying *CDC73* in activation as it can also be seen in rare biallelic somatic only mutations [99]. As 40–80% of sporadic parathyroid carcinomas have inactivating *CDC73* mutations and frequent loss of heterozygosity of the *CDC73* locus, complete loss of nuclear parafibromin immunoexppression in the tumor cells may be a supportive biomarker of malignancy in the appropriate setting [102, 104, 126, 127, 145–147]. As two thirds of parafibromin-deficient parathyroid tumors are associated with pathogenic germline *CDC73* variants, so assessment for the likelihood of HPT-JT syndrome is recommended [99, 126, 127]. Recently, morphologic indications of a parathyroid-parafibromin-deficient tumor include a sheet-like growth, perinuclear cytoplasmic clearing, nuclear enlargement, eosinophilic cytoplasm, occasional multinucleated cells, and arborizing vasculature [91, 99]. Cystic change may also occur [93, 99, 101]. In addition to the parathyroid glands, other tumors occur in the setting of HPT-JT such as those involving the jaw, kidney, and uterus [97, 122–124]. Ossifying fibromas of the jaw, more often affecting the mandible than the maxilla, are often incidental findings in the setting of HPT-JT [124, 148]. Although historically it was thought that renal disease (cysts, adenomas, Wilms tumors, mixed epithelial and stromal tumors) was relatively common in HPT-JT, however clinically significant renal pathology is actually quite uncommon in HPT-JT [93, 95–99, 123, 149, 150]. Other than possibly uterine adenosarcomas, it is now thought that the amount of uterine pathology occurring in the setting of HPT-JT may be common benign disease simply found through screening [95, 97, 123].

Von Hippel Lindau (VHL) is a complex disease with types 1, 2A, 2B, and 2C having different manifestations and are associated with different genetic alterations the *VHL* gene. Manifestations of VHL include hemangioblastomas which occur in 80% of individuals with VHL and most often

affect the cerebellum, followed by the spinal cord and brainstem, but can also affect the retina [151]. CNS hemangioblastomas are associated with bigger risk of death, while retinal hemangioblastomas are much less likely lethal but they are associated with blindness [152, 153]. Although renal cysts are common in VHL, 40% of individuals developed clear cell renal cell carcinoma which is often multicentric, bilateral, often cystic, and often low stage at diagnosis and may be associated with multiple small "clear cell tumorlets" in the renal parenchyma and renal cysts [154–156]. Rare clear cell papillary-like renal cell may also occur, but often lack the keratin 7 and CAIX immunopositivity of conventional clear cell papillary renal cell carcinoma [155, 157]. The possibility of a progression in renal disease starting with renal cysts in the setting of VHL has been suggested. The pathogenesis of other manifestations of VHL occur continue to be studied including endolymphatic sac tumors [158, 159], pheochromocytomas and/or paragangliomas [160], pancreatic neuroendocrine tumors, cysts and serous cystadenomas [161–164], neuroendocrine tumors of the ampulla, duodenum, gallbladder, and common bile duct [165, 166], epididymal papillary cystadenomas [167], and rarely papillary cystadenomas of the broad ligament and mesosalpinx [168, 169]. Screening to earlier detect malignancies may improve outcome, and clinical surveillance guidelines have been published [170, 171].

Neurofibromatosis 1 (NF1) is characterized by multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, plexiform neurofibromas, Lisch nodules, optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, phaeochromocytoma (adrenal paraganglioma), duodenal and pancreatic neuroendocrine tumors, and choroidal freckling.

Duodenal NET in NF1 patients arise in association with the major or minor ampulla, show a tubular growth pattern and frequent psammoma-bodies [172]. In contrast to sporadic and MEN1 associated D-NET, a strong expression of Somatostatin is found [173, 174]. Co-occurrence with gangliocytic paragangliomas, adenoma/adenocarcinoma (MiNEN) and gastro-intestinal stromal tumors (GIST) are described [172, 175–178].

While NF1-associated pheochromocytomas may be bilateral, they do not differ from their non-familial counterparts harboring somatic NF1 mutations, which are found in about 20% of sporadic pheochromocytomas [179]. These pheochromocytomas are more frequently of composite type [180].

NF1-related pancreatic NET are indistinguishable from sporadic PanNET, and no microadenomatosis is described in contrast to MEN1 and VHL-associated familial PanNET.

Question 10: Which Endocrine Familial Cancer Syndromes Involves the Skin? Which Skin Lesions Can Be Identified on These Syndromes?

NF1

Neurofibromatosis 1 (NF1) is characterized by multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, plexiform neurofibromas, Lisch nodules, optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, phaeochromocytoma (adrenal paraganglioma), duodenal and pancreatic neuroendocrine tumors, and choroidal freckling.

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PTEN-Hamartoma Tumor Syndrome PHTS comprises diverse disorders caused by mutations in the phosphatase and tensin homolog (*PTEN)* gene. PHTS patients have diverse presentations and various phenotypes. Cowden syndrome (CS) is the principal PTEN-related disorder. CS is characterized by multiple neoplasms and hamartomas, mucosal papillomatosis, and skin lesions, trichilemmomas [60]. Trichilemmomas are usually located in the mid-face and are multiple in this disease. Trichilemmomas and mucocutaneous papillomatous papules are one of the first signs of the disease.

According to the International Cowden Consortium operational diagnostic criteria [181], many skin lesions are considered as pathognomonic or a major criterion for diagnosis.

Pathognomonic criteria include adult Lhermitte-Duclos disease (cerebellar tumors), facial trichilemmomas, acral keratosis, papillomatous papules, and the known autism-spectrum disorder.

The major criteria include breast carcinoma, macrocephaly, endometrial carcinoma, multiple palmoplantar

keratosis, macular pigmentation of the glans penis, multifocal cutaneous facial papules, and multiple gastrointestinal ganglioneuromas or hamartomas.

Minor criteria include single gastrointestinal hamartoma or ganglioneuroma, lipomas, fibromas, fibrocystic breast disease, renal cell carcinoma, genitourinary malformations, uterine fibroids, and intellectual disability (IQ ≤ 75).

Please note that non-medullary thyroid cancer is a major criteria and FTA and MNG are minor criteria.

MEN2

Cutaneous lichen amyloidosis is the most common cutaneous manifestation of MEN2A, including familial isolated medullary thyroid carcinoma. In individuals with MEN2A-associated cutaneous lichen amyloidosis, almost all RET mutations involve codon 634 [182], although families with involvement of other codons such as V804M [182, 183], S891A [182, 184], G513D [184], and C611Y [185] have been reported. Interestingly, a family with MEN2A with V804M mutation had individuals with dermal hyperneury, a cutaneous lesion more characteristic of MEN2B, and one family member had multiple sclerotic fibromas, a cutaneous feature seen in PTEN tumor syndrome [186].

MEN2A-related cutaneous lichen amyloid occurs more commonly in women with a mean age of 20 to 30 years but can occur individuals as young as 3 years of age [182, 187, 188]. In kindreds with cutaneous lichen amyloidosis, the skin lesion is a second most frequent manifestation–second only to medullary thyroid carcinoma and affecting approximately 51% of the individuals [182]. Additionally, the pruritus associated with cutaneous lichen amyloidosis and lichen amyloid itself may appear more than two decades before neoplastic disease in MEN2A and may be the first manifestation of MEN2A [182, 189]. The relationship between MEN2A and cutaneous lichen amyloid remains unclear. MEN2A-associated cutaneous lichen amyloidosis usually affects the interscapular of the back. The cutaneous lichen amyloidosis are pruritic and may appear as multiple infiltrated papules which can be overlying plaques [190]. The pruritis is thought to result in scratching and subsequent epidermal hyperplasia, keratinocytes damage with deposition of keratin positive material in the dermis in continuity with the dermal epidermal junction [182]. Unlike the amyloid in the thyroid associated with medullary thyroid carcinoma which is calcitonin [191], the amyloid in cutaneous lichen amyloid in MEN2A is positive for keratin and negative for calcitonin [192].

Mucocutaneous neuromas are a manifestation of MEN2B, but they are not pathognomonic of MEN2B as they can be seen sporadically as well as in association with *PTEN* mutations on 10q23.31 [193]. Extra-endocrine features of MEN2B to be are important to recognize as they usually preceded a diagnosis of a neoplasm such as medullary thyroid carcinoma or pheochromocytoma [133, 194]. A recent retrospective, multi center, international study of individuals with M918T RET mutation found all 287 with available data had at least one extra-endocrine feature of disease [133]. Neuromas and ganglioneuromas often affect the intestines but also frequently involved the tongue (62%), lips (53%), and eyelid or conjunctiva (19%) [120, 133]. Mucosal neuromas may be the first manifestation of MEN2B. Individuals with mutations of M918T, A883F, and double *RET* germline variants can all be associated with extra-endocrine manifestations of MEN2B [120].

The histologic features of mucosal neuromas can appear like that of a solitary neuroma or may appear as irregular hyperplastic nerves with a thickened perineurium. The term dermal hyperneury is a type of small nerve hypertrophy with prominent dermal nerve fibers that are enlarged in size. This can occur sporadically as a cell lesion or with multiple lesions in can occur with syndromes, particularly MEN2B [195, 196]. Dermal hyperneury has also been identified in normal appearing skin in individuals with MEN2B [195]. The skin shows an increase in organized nerve tissue, with aggregated nerve fascicles or trunks containing parallel masses of spindle cells and nerve fibers [195]. The fascicles are enlarged in size and more frequent in number [195].

Question 11: What Is the Role of the Pathologist in Diagnosing Syndromic Familial Non-medullary Thyroid Carcinoma?

Syndromic familial non-medullary thyroid carcinoma (SFNMTC) is defined in the new 2022 WHO classification as a heterogeneous group of familial follicular cell-derived carcinomas with a predominance of non-thyroid cancer. SFNMTC is a good example of how the advancement of molecular biology has made it possible to establish genotype–phenotype correlations that can be useful for the pathologist in daily practice [39, 42]. SFNMTC includes PHTS [44], FAP [45], DICER1 syndrome [21], CNC [46] and WS [47] (Table 2). The pathologist should be aware of the characteristics of these syndromes, which include extrathyroid neoplasms, some of which given their rarity, could alert to the hereditary basis of the disease [39, 42]. In all these syndromes, thyroid gland involvement is typically multinodular and both lobes are affected [39, 42].

In PHTS (Cowden syndrome, Cowden disease, and Bannayan-Riley-Ruvalcaba syndrome) [44], the thyroid gland is characteristically multinodular showing multiple, bilateral, well-defined, and/or encapsulated follicular cell micro- and macroscopic nodules [41, 43, 197–203]. Several adenomatous nodules called “microadenomas” coexist with follicular cell derived carcinoma and support an

adenoma-carcinoma pathogenetic sequence [37, 197, 200]. Thyroid cancer is mainly papillary thyroid carcinoma (both classic and follicular variants) and follicular thyroid carcinoma [37, 197, 201]. Lipoadenomas (adenolipomas) are common [197, 201]; trabecular-like growth patterns as well as clear and oncocytic cells have also been described [43, 197, 202, 203]. Adipose infiltration and thyroiditis are also typical [197, 198, 203]. In some cases of PHTS, there is thyroiditis and C-cell hyperplasia, but there is no increased risk of medullary carcinoma [202–204]. The immunohistochemical determination of the PTEN protein is a good diagnostic tool since its negativity in the nodules or in a subset of nodules (Fig. 8), while preserving positivity in the endothelial cells (positive controls), is an indicator which is both sensitive and specific for PHTS [39, 42, 61, 201].

Cribriform morular thyroid carcinoma (CMTC) occurs in about 16% of patients with FAP [205]. While sporadic CMTC usually presents macroscopically as a single nodule, the cases associated with FAP are usually multifocal and bilateral [52, 59, 206, 207]. Macroscopically, CMTC is well delimited, encapsulated and/or partially lobed by fibrosis bands. Histologically, there is a variable proportion of cribriform, papillary, follicular, solid, trabecular, and morular growth patterns [52, 59, 207, 208]. The

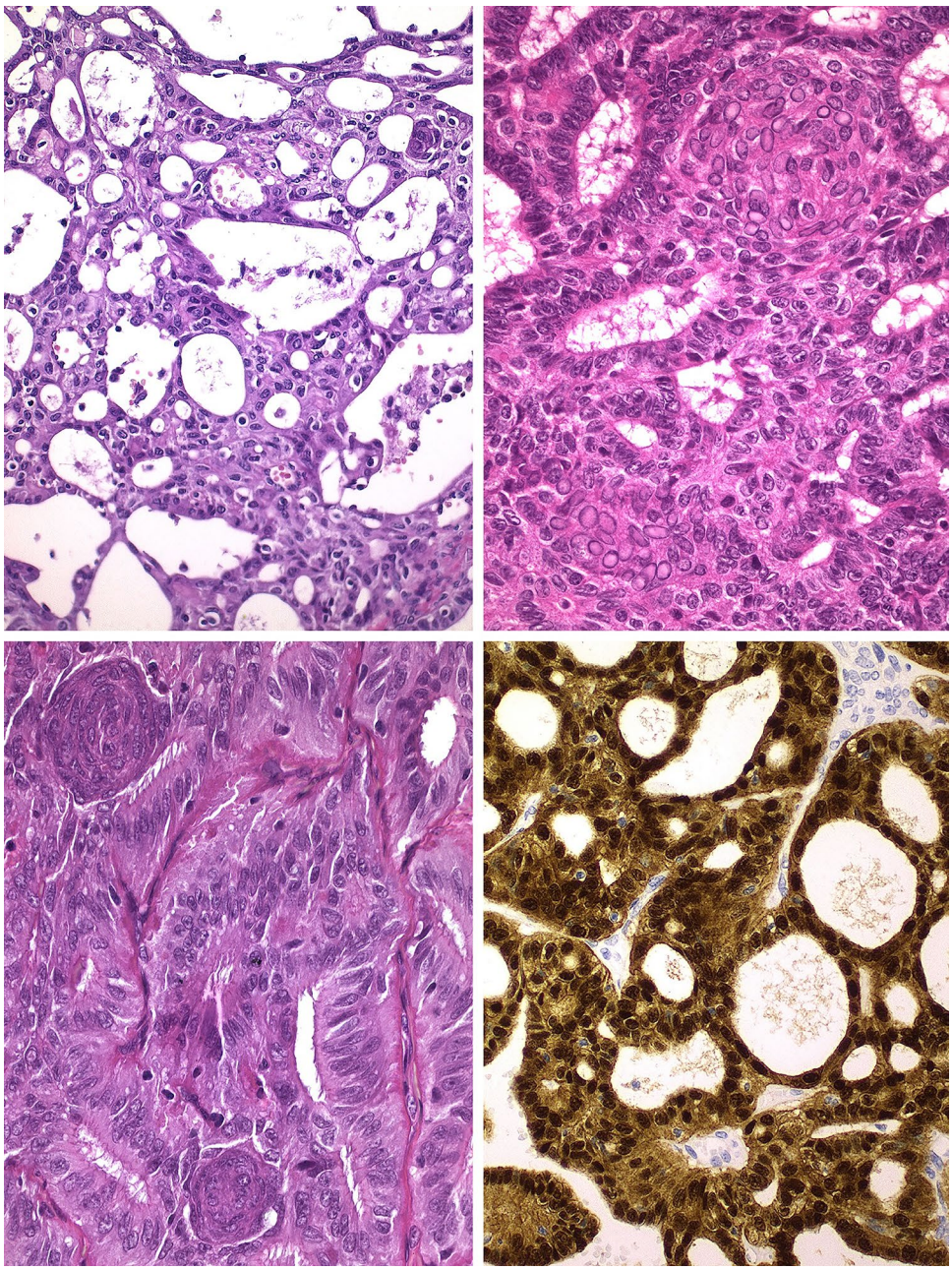

Fig. 9 Cribriform morular thyroid carcinoma. This thyroid tumor associated with familial adenomatous polyposis is characterized by a variable mix of cribriform (top left), follicular (top right), papillary, trabecular (bottom left), and morular (top and bottom) growth patterns. In morular structures, there are some peculiar biotin-rich optically clear nuclei (top right). Strong nuclear and cytoplasmic positivity for beta-catenin is the hallmark of this neoplasm (lower right)

cribriform patterned areas lack fibrous stroma, the follicular structures lack colloid and the papillae are lined by cuboidal or tall cells. Spindle cell trabecular areas may adopt a hyalinizing trabecular tumor-like pattern. Squamous morulae lack keratinization and show occasional nuclei with peculiar chromatin clearance (rich in biotin). Strong nuclear and cytoplasmic staining for beta-catenin is the characteristic finding of CMTC (Fig. 9) [42, 52, 59, 208]. Tumor cells are also positive for TTF1 (clones 8G3G7/1 and SPT24), epithelial membrane antigen, pankeratins (AE1/AE3), vimentin, estrogen, and progesterone receptors, and negative for keratin 20, calcitonin, and WT1 [52, 59]. Thyroglobulin is negative and the PAX8 (clone BC12 or polyclonal antisera) shows focal or negative staining in the CMTC [52, 59]. Morulae are positive for beta-catenin, keratin 5, CD10, CDX2, CD5, and CA19.9, but negative for TTF1, PAX8, E-cadherin, and estrogen and progesterone receptors [52, 59]. Although CMTC generally has a good prognosis, some high-grade tumors showing necrosis, high mitotic index, Ki-67 of 15–60%, neuroendocrine differentiation and/or *TERT* promoter mutations have behaved aggressively [209–213].

In patients with DICER1 syndrome, the thyroid gland is multinodular due to multiple benign (multinodular goiter) and malignant nodules [24, 25]. There are nodules with intrafollicular centripetal papillary pattern of growth, adenomatous nodules and involutional changes [24, 25]. The presence of cells with "intermediate" nuclei is common and in papillary patterned areas especially should not lead to a false diagnosis of papillary thyroid carcinoma. The majority of the carcinomas are the typical well differentiated thyroid carcinomas (usually classic, follicular variant or solid/trabecular variant of papillary thyroid carcinoma) [25, 64], but rare cases of poorly (high grade) differentiated carcinoma have been described [27]. The diagnosis of multinodular goiter with involutional changes, with or without differentiated thyroid carcinoma or poorly differentiated carcinoma in childhood or adolescence, should raise suspicion of DICER1 syndrome. Thyroblastoma, a rare neoplasm composed of primitive follicular cells surrounded by a small cell component and mesenchymal stroma with heterologous elements, should also raise suspicion of DICER1 syndrome [33, 35].

The thyroid gland in CNC is multinodular due to the presence of encapsulated and non-encapsulated follicular cell proliferations [214–217]. This "follicular adenomatosis" [213] or multiple adenomatous nodules, involves the entire gland in a manner equivalent to the multiple adenomatous nodules or microadenomas described in PHTS. Some follicular adenomas with intrafollicular centripetal papillary growth pattern can cause hyperthyroidism ("toxic" adenoma); oncocytic (Hürthle cell) adenomas have also been described [215]. The incidence of thyroid cancer (both papillary and follicular types) [214–216, 218] is around 15% [216], and these malignant tumors are not morphologically different from their sporadic counterpart.

In WS, the risk of thyroid involvement by cancer is estimated to be around 18%. The predominant thyroid cancer is follicular thyroid carcinoma, followed by papillary thyroid carcinoma and anaplastic thyroid carcinoma [219]. The benign follicular thyroid adenoma is also seen in these patients. Interestingly, anaplastic thyroid carcinoma presents clinically at younger ages than sporadic anaplastic thyroid carcinoma, reflecting the premature biological aging associated with this syndrome [42].

Although an unusual "villous" papillary thyroid has been described present in a patient with Marfan syndrome [220], the usefulness of this "villous" pattern for the recognition of Marfan syndrome needs confirmation.

The pathologist usually has an important role when facing these morphological and/or immunohistochemical clues and alert clinicians to the possibility of these inherited syndromes, which must be genetically confirmed. Identifying these syndromes will facilitate cancer screening, genetic counseling, and appropriate treatment. In fact, total thyroidectomy is usually recommended in these cases due to the multicentricity of the lesions and the risk of progression to carcinoma [39, 41, 42, 197, 199].

Question 12: How Does the 2022 WHO Classification Approach Non-syndromic Familial Non-medullary Thyroid Carcinoma?

The new 2022 WHO classification of thyroid tumors defines the NSFNMTC as a heterogeneous group of hereditary thyroid cancers that encompasses a variety of familial tumor syndromes characterized by a predominance of follicular cell-derived carcinomas or non-medullary thyroid carcinomas.

NSFNMTC has a prevalence ranging from 4.5 to 10% depending on the criteria of different series [221–225], reaching up to 13.5% in some areas with less diversity of population [226]. NSFNMTC has a heterogeneous and poorly understood genetic basis, with most pedigrees supporting a monogenic and autosomal dominant mode of inheritance with reduced penetrance and variable expressiveness [39, 42, 227]; a polygenic mode of inheritance has also recently been proposed however [62] (Table 6). NSFNMTC shares the same somatic mutations [224, 228–233] and signaling pathways (MAPK/ERK and PI3K/AKT) [234] as its sporadic counterpart, which fits in with the absence of both cytological and histopathological differences between NSFNMTC and sporadic carcinomas. There are, however, certain clinico-pathological features that may suggest the familial character of NSFNMTC [39, 42]. Patients with familial thyroid cancer are generally diagnosed on an average of 5 years earlier (≈ 43 years) than patients with sporadic

Table 6 Susceptibility genes and chromosomal loci associated with non-syndromic familial follicular cell (non-medullary) thyroid carcinoma

Susceptibility genes			Chromosomal loci		
Gene	Loci	References	Proposed gene	Loci	References
BROX	1q41	[112]	*fPTC/PRN*	1q21	[244, 245]
PLEKHG5	1p36.31	[246]	*NMTC3*	2q21	[247–249]
ANXA3	4q21.21	[246]	Unknown	6q22	[244]
SAPCD1	6p21.33	[246]	*FTEN*	8p23.1-p22	[250]
POT1	7q31.33	[251–254]	*PTCSC1*	8q24.22	[255]
FOXE1	9q22.33	[230, 256, 257]	*MNG1*[$]	14q32.13	[258]
HABP2	10q25.3	[111, 259]	*TCO/TCO1**	19p13.2	[247, 248, 260–263]
SRGAP1	12q14.2	[264]			
NTN4	12q22	[246]			
NKX2-1	14q13.3	[265, 266]			
SERPINA1	14q32.13	[246]			
DUOX2	15q21.1	[228]			
MAP2K5	15q23	[267]			
SRRM2	16p13.3	[268]			
P2RX5	17p13.2	[246]			
FKBP10	17q21.2	[246]			
*NDUFA13**	19p13.11	[269]			
*TIMM44**	19p13.2	[270]			
NOP53	19q13.33	[114]			
PLCB1	20p12.3	[113, 241]			
CHEK2	22q12.1	[231, 271–273]			

*These genes are associated with oncocytic (Hürthle cell) thyroid tumors

[$]These cases are probably due to germline DICER1 gene mutation

carcinomas [221, 224, 235–238]. Furthermore, each new generation is diagnosed at an earlier age [225, 239], although a bias due to the greater number of examinations in these families has been proposed to explain this clinical anticipation [240]. The frequent multicentricity, bilaterality and/or association of NSFNMTC with benign nodules is also characteristic and can clinically (and grossly) simulate a multinodular goiter in its presentation [39, 42].

Microscopically, most NSFNMTCs are papillary thyroid carcinomas, including cases measuring ≤ 1 cm in diameter, classical, follicular and other variants of papillary carcinoma; other types of differentiated thyroid carcinoma, including oncocytic variants, have also been reported (Table 6). Typically, tumor multifocality combined with a background of hyperplastic nodules, follicular adenomas and Hashimoto's thyroiditis should alert to their possible hereditary nature [39, 42]. Additionally, the coexistence of NSFNMTC with multiple benign follicular nodules is consistent with a sequential tumorigenic model [227, 235]. Patients with germline *PLCB1* mutation usually present with multinodular goiter of adolescent onset and increased risk of progression to papillary thyroid carcinoma [113, 241]. Interestingly, this form of multinodular goiter is characterized by the presence of multiple well-defined nodules with a micropapillary pattern (papillary adenomata) on a normal-appearing thyroid background, in contrast with the diffuse involvement of conventional multinodular goiter [241, 242].

The functional study of some cases of NSFNMTC has evidenced immunohistochemical overexpression of HABP2, EGFR, phospholipase C beta 1, and NOP53 in thyroid

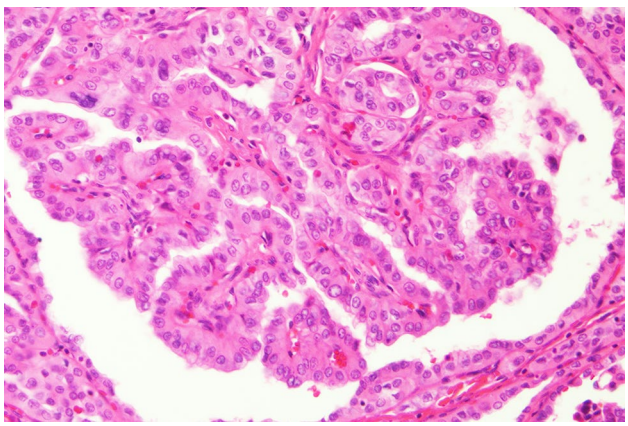

Fig. 10 Non-syndromic familial follicular cell-derived thyroid carcinoma associated with renal cell carcinoma shows the characteristic thyroid tumor morphological features. Although these thyroid tumors may mimic renal structures, they are positive for TTF1, PAX8, and thyroglobulin

Table 7 Familial cancer syndromes with involvement of the endocrine system

Disease/phenotype	Inheritance	Gene(s)	Encoded protein(s)	Normal protein function
Multiple endocrine neoplasia type 1	AD	*MEN1*	Menin	DNA repair and regulation of apoptosis (tumor suppressor)
Multiple endocrine neoplasia type 2A	AD	*RET*	RET	Normal development of nerve cells
Multiple endocrine neoplasia type 2B	AD	*RET*	RET	Normal development of nerve cells
Multiple endocrine neoplasia type 4	AD	*CDKN1B*	p27	Prevention of aberrant cell division (tumor suppressor)
Multiple endocrine neoplasia type 5 (MAX-related tumors)	AD	*MAX*	MAX	MAX protein is an essential component of the MYC/MAX/MXD1 network of transcription factors that regulate cell proliferation, differentiation, and apoptosis
Hyperparathyroidism-jaw tumor syndrome	AD	*CDC73*	Parafibromin	Parafibromin is a critical component of the polymerase-associated factor 1 complex (PAF1C) that binds to RNA polymerase II and controls transcription
Von Hippel–Lindau syndrome	AD	*VHL*	VHL	Ubiquitination and degradation of HIF (tumor suppressor)
SDH-deficient tumor syndromes				Dysfunction of the SDH complex enzyme causes the accumulation of succinate which acts as an oncometabolite involved in a broad spectrum of tumorigenic pathways including hypoxic regulation and epigenetic reprogramming
–PGL1	AD; PT	*SDHD*	SDHD	
–PGL2	AD; PT	*SDHAF2*	SDHAF2	
–PGL3	AD	*SDHC*	SDHC	
–PGL4	AD	*SDHB*	SDHB	
–PGL5	AD	*SDHA*	SDHA	
Neurofibromatosis type 1	AD	*NF1*	Neurofibromin (NF1)	Negative regulation of RAS
Carney complex	AD	*PRKAR1A*	PRKAR1A	A regulatory subunit; PRKAR1A mutation results in overactive protein kinase A
McCune–Albright syndrome	Post-Zygotic	*GNAS*	$G_s\alpha$	The alpha subunit of a G protein; signal transduction from seven transmembrane receptors to the cAMP second messenger
DICER1 syndrome	AD	*DICER1*	DICER1	Processing microRNAs in the RNA interference pathway
Glucagon cell hyperplasia and neoplasia	AR	*GCGR*	GCGR	Deficient glucagon signaling in the liver causes a disturbance in a feedback mechanism between the liver and the glucagon cells
MAFA-related familial insulinomatosis	AD	*MAFA*	MAFA	MAFA plays a critical role as a transcription factor regulating B cell function and proliferation leading to glucagon cell hyperplasia
Syndromic familial non-medullary thyroid carcinoma*				
Non-syndromic familial non-medullary thyroid carcinoma**				

AD autosomal dominant, *AR* autosomal recessive, *AD;PT* autosomal dominant with paternal transmission (maternally imprinted, clinical disease is inherited only from paternal carrier)

*See Table 2; **See Table 6

carcinomas associated with pathogenic germline variants of the *HABP2*, *BROX*, *PLCB1*, and *NOP53* genes, respectively [111–114]. Lower immunostaining for CHEK2 protein in thyroid tumors has also been detected in patients with *CHEK2* gene mutations [231]. Although these immunohistochemical data could possibly help the pathologist in screening for this type of tumors, some of these susceptibility genes and immunohistochemical data still need to be confirmed.

Given the absence of specific microscopic features in NSFNMTC in most cases; the familial papillary thyroid carcinoma-renal cell carcinoma show some specific features of these thyroid carcinomas (Fig. 10), the new 2022 WHO classification of thyroid tumors has established as essential clinical criteria for the diagnosis and identification of NSFNMTC: (a) the presence of a follicular cell-derived thyroid carcinoma appearing in at least 3 first-degree relatives, or (b) the presence of papillary thyroid carcinoma in 2 or more first-degree relatives. In both cases, always in the absence of previous known ionizing radiation exposure and other cancer syndromes (Table 3). Although the second criterion is less selective, this approach could avoid the loss of hereditary cases which could benefit from more appropriate treatment [226, 235, 236, 238].

Conclusions

The prior WHO Classification of Tumors of the Endocrine Organs, edited in 2017, covered a specific section on familial cancer syndromes. That section contained chapters on 12 syndromes associated with endocrine tumors.

With the rapidly increasing use of molecular genetic techniques including next-generation sequencing (NGS) in both diagnostic pathology and molecular and clinical genetics, numerous new constitutional gene mutations have been identified in tumors, resulting in clinically recognizable tumor-predisposing syndromes. Within the last few years, other three new syndromes involving the endocrine organs were recognized: MAFA-related insulinomatosis, MEN4, and MEN5. These familial cancer syndromes are associated with a range of benign and malignant neoplasms involving multiple organ systems and are not limited to the endocrine system.

The present 2022 WHO classification of tumors of endocrine organs now describes and gives updates on 15 syndromes associated with endocrine lesions and tumors (summarized on Table 7). Besides the addition of the newly discovered familial diseases, due to new genetic and molecular findings and clinical and pathological correlation, familial follicular cell-derived thyroid carcinoma or non-medullary thyroid carcinoma, is now accepted to be classified as syndromic and non-syndromic familial follicular cell-derived/non-medullary thyroid carcinoma. This topic is covered in 2 chapters that highlight the important role the pathologist plays in recognizing some of these diseases.

The addition on immunohistochemistry, as a reliable and time-saving approach in the assessment either somatic mutations in tumors and/or germline mutations in patients with familial cancer syndromes, has improved the pathologist's ability to raise the possibility of dealing with a tumor as part of a familial cancer syndrome.

Author Contribution All authors contributed to the study conception and design. The original draft of the manuscript was written in parts by all authors and Vania Nosé have finalized the manuscript.

Declarations

Ethical Approval All evaluations performed in this analysis do not involve any individual patient's data but was still performed in accordance with the ethical standards of the institutional review board. The opinions or assertions contained herein are the private views of the authors.

Consent Statement No personally identifiable information is included and thus informed consent is not applicable.

Conflict of Interest The authors declare no competing interests.

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