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# Inherited Endocrine Neoplasia— A Comprehensive Review from Gland to Gene

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## Abstract

**Purpose of the Review** There has been a significant expansion in our knowledge of inherited endocrine neoplasia. This review describes syndromic and non-syndromic hereditary endocrine tumours, associated genetic testing, and progress in the management of the disease.

**Recent Findings** Disease-targeted genetic testing for endocrine neoplasia is routinely available, including recently identified endocrine tumour susceptibility genes *GPR101*, *GCM2*, *DICER1*, and *ARMC5*. The recommendations for surveillance of those at risk of endocrine neoplasia are still evolving, as the evidence base is limited due to the rarity of these diseases. However, in MEN2, pre-emptive thyroidectomy is established surgical practice and may also be considered for other thyroid neoplastic conditions including *DICER1* and *PTEN*. In advanced MTC, targeted medical therapies are now licensed for use.

**Summary** Identifying patients with endocrine neoplasia formerly relied on clinical, biochemical, and radiological assessment. Increasingly, early genetic diagnosis identifies pre-symptomatic patients, enabling personalised medical care by informing ongoing surveillance and therapeutic interventions to improve outcomes.

**Keywords** Pituitary adenoma · Parathyroid tumour · Thyroid cancer · Neuroendocrine tumours · Adrenal tumours · Genetic testing

## Introduction

In this review, we take an endocrine gland–based approach to describe our current understanding of both syndromic and non-syndromic forms of endocrine neoplasia, highlighting recent discoveries which confirm widespread genetic heterogeneity and differential heredity of endocrine tumours. These insights are the result of genomic research and the exponential wealth of data generated from technological advances in molecular diagnostics.

Most endocrine tumours are sporadic and benign, but their presentation through secretory disturbance or compression symptoms as space-occupying lesions can lead to considerable morbidity. Their rarity, combined with multiple differing presentations, may result in diagnostic delay, although increasingly, many are detected incidentally during radiological investigations for other pathology. Disease-targeted sequencing is now widely available, such that molecular characterisation is becoming key to early diagnosis, possibly confirming a syndromic endocrine condition before additional features or tumours appear [1]. This review discusses inherited endocrine neoplasia of the pituitary, thyroid, parathyroid, and adrenal glands, as well as neuroendocrine tumours of the foregut and gastroenteropancreatic axis. It highlights clinical features that help identify index patients, to aid the clinician to consider genetic testing for each tumour type, and lists the genes implicated in endocrine tumour predisposition.

Confirmation of an inherited endocrine neoplasia condition provides an explanation for the diagnosis in the individual and confirms the pattern of inheritance (predominantly autosomal dominant with intrafamilial heterogeneity). Cascade genetic testing can then be undertaken in Clinical Genetics for family members, including children, if the condition develops in childhood. This enables confirmed at-risk relatives to access recommended lifelong surveillance or risk-reducing surgery for prevention and management of their endocrine susceptibility, whilst relieving those without the condition from the

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anxiety of disease burden. Although a full discussion of comprehensive management of each tumour is outside the scope of this review, relevant guidance for risk management of these conditions is referenced per syndrome (see Table 1). Unfortunately, treatment outcomes are less successful in inherited endocrine neoplasia compared to sporadic solitary endocrine neoplasia, as multiple tumours develop and disease often recurs. These challenges are best navigated by specialist multidisciplinary teams with expertise in recognising and treating the complexities of inherited endocrine neoplasia, where timing and order of interventions is crucial to optimise outcomes and minimise harm.

## Genetic Testing

Genetic testing is widely available for inherited endocrine neoplasia, and each of the genes discussed in this review is listed in Tables 1 and 2. In Table 1, the main clinical features of each syndrome are described, whereas in Table 2, the key sites of tumorigenesis for each inherited endocrine neoplasia gene are summarised.

Testing criteria help guide the clinician to order either single-gene analysis (e.g. selected *RET* exons in medullary thyroid cancer) or a small genetic panel, aiming to identify a germline pathogenic variant in a known inherited endocrine neoplasia gene [29]. Confirming the diagnosis influences therapeutic choices (including surgical strategy), surveillance programmes, and follow-up. However, sometimes, variants of unknown significance (VUS) are identified, which are uninformative in management and surveillance decisions or for familial cascade genetic testing. Variant reviews may reclassify some VUS to pathogenic or benign variants over time, providing clarity where a previously uninformative result existed. In order for the patient to benefit, an agreement should be reached between the clinician and the patient as to the follow-up plan in regard to the variant, for example recontacting the centre in 5 years' time to ask for an update. Additionally, hitherto unsolved cases with a clear syndromic form of endocrine neoplasia, or those with a confirmed family history of the disease, may benefit from extended genetic analysis, e.g. whole-exome sequencing, which may reveal a novel genetic cause for the disease, ending the diagnostic odyssey [30].

## Pituitary Gland

### Pituitary Adenoma

Pituitary adenomas are benign endocrine neoplasia of the adenohypophysis and represent the most common CNS neoplasm. The majority are sporadic, but < 5% are attributable to heritable causes [31].

#### *AIP* Familial Isolated Pituitary Adenoma

Familial isolated pituitary adenoma (FIPA) describes pituitary adenoma occurring in at least two family members in the absence of other syndromic features. Up to 20% of FIPA pedigrees have pathogenic germline variants in *AIP*. The penetrance of pituitary adenoma with germline *AIP* pathogenic variants is 20–23% [32]. Clinical features of pituitary adenomas with predictive value for *AIP* disease include young onset (4–18 years), family history, growth hormone excess, and large tumour size, which may result in pituitary apoplexy [32]. Pituitary adenomas associated with germline pathogenic *AIP* variants have a poorer response to conventional treatments and a more aggressive natural history [33]; hence, germline testing in relatives may prevent significant morbidity.

Experts recommend surveillance with annual pituitary function tests and growth parameters from age 4 years, and 5-yearly MRI pituitary between age 10 and 50 years [2].

#### *GPR101* X-Linked Acrogigantism

*GPR101* X-linked acrogigantism is usually caused by de novo microduplication involving the *GPR101* gene (in germline or somatic mosaic forms) and results in pituitary adenoma and growth hormone hypersecretion [34••]. Recently, two familial cases have also been described [3]. Gigantism from growth hormone hypersecretion typically manifests before the age of 5 years.

#### Multiple Endocrine Neoplasia Type 1

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome caused by pathogenic germline variants in *MEN1*. It is classically characterised by predisposition to neoplasia of the parathyroids, pituitary, and gastroenteropancreatic neuroendocrine cells. Germline *MEN1* testing is recommended for individuals with both classical clinical MEN1 (≥ 2 primary tumour types) and atypical presentations (e.g. multiple parathyroid adenoma or multiple gastroenteropancreatic neuroendocrine tumours). First-degree relatives of probands should be offered germline *MEN1* testing, once a pathogenic variant is identified [4].

Approximately 3% of patients with pituitary adenomas have MEN1 [35], with the youngest reported occurrence aged 5 years [36]. Thirty to forty percent of MEN1 patients have clinically apparent pituitary adenoma [34••] and it is the presenting feature in 18% of MEN1 cases [37]. Prolactin-secreting adenomas are most common. Compared to sporadic disease, MEN1-related pituitary

**Table 1** Germline pathogenic variants predisposing to endocrine neoplasia listed by syndrome and main clinical features of each disease

| Syndrome | Gene | Function | Location | Endocrine tumours | Other clinical features | Management guidelines |
|---|---|---|---|---|---|---|
| Familial isolated pituitary adenoma [FIPA] | *AIP* | Tumour suppressor gene (TSG) | 11q13.2 | Pituitary somatotrophinomas and prolactinomas | Acromegaly, gigantism | [2] |
| X-linked acrogigantism [X-LAG] | *GPR101* | Oncogene | Xq26.3 | Pituitary hyperplasia or adenoma | Gigantism, coarse facial features, acanthosis nigricans | [3] |
| Multiple endocrine neoplasia type 1 [MEN1] | *MENIN* | TSG | 11q13.1 | Pituitary prolactinoma, parathyroid-four gland hyperplasia, GEP-NETs, duodenal gastrinomas most common, bronchial and thymic carcinoids, adrenal adenomas/hyperplasia, and ACC | Angiofibromas, lipomas, collagenomas, moderate risk of breast cancer | [4, 5•, 6, 7] |
| Multiple endocrine neoplasia type 4 [MEN4] | *CDKN1B* | TSG | 12p13.1 | Pituitary somatotrophinomas, parathyroid adenomas/hyperplasia, and PNETs | Later onset primary hyperparathyroidism (> 45 years) | [8] |
| Carney complex [CNC] | *PRKAR1A* | TSG | 17p12.1 | Pituitary somatotrophinomas, follicular thyroid adenomas, PPNAD | Lentigines, myxomas, schwannomas and large-cell calcifying Sertoli cell tumours, gynaecomastia, breast duct adenoma, psammomatous melanotic schwannoma, papillary, and follicular thyroid cancer | [9] |
| Multiple endocrine neoplasia type 2 [MEN2] | *RET* | Oncogene | 10q11.21 | Medullary thyroid cancer, parathyroid adenomas/hyperplasia, and PCC | Hirschsprung's disease, cutaneous lichen sclerosis, MEN2B only: marfanoid habitus, mucosal neuromas, ganglioneuromatosis, kidney malformations | [10•, 11••, 12] |
| Cowden/PTEN harmatoma tumour syndrome [PHTS] | *PTEN* | TSG | 10q23.31 | Thyroid adenoma, multinodular goitre, non-medullary thyroid cancer (follicular or papillary) | Trichilemmomas, acral keratoses, oral papillomatosis, Lhermitte–Duclos disease (cerebellar tumours), fibrocystic breast disease, breast cancer, uterine fibromas, endometrial cancer, macrocephaly (> 97th centile), gastrointestinal hamartomas, lipomas, fibromas, renal cell cancer, learning difficulties (IQ < 75) | [13] |
| Familial adenomatous polyposis [FAP] | *APC* | TSG | 5q22.2 | ACC, cribriform-morular variant of papillary thyroid cancer | Medulloblastoma, desmoid tumours, multiple adenomatous intestinal polyps including gastric and duodenal polyps, congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, fibromas, supernumerary teeth. | [14] |
| DICER1 | *DICER1* | TSG | 14q31.23 | Thyroid cysts and nodules, multinodular goitre, non-medullary thyroid cancer (follicular or papillary), Pituitary ACTH–secreting blastomas | Pineoblastoma, pleuropulmonary blastoma, ciliary body medulloepithelioma, medulloblastoma, cervical embryonal rhabdomyosarcoma, nasal chondromesenchymal hamartoma, hamartomatous intestinal polyps, cystic nephroma, Sertoli–Leydig cell tumours | [15•] |
| Familial isolated hyperparathyroidism [FIHP] | *GCM2* | Oncogene | 6p24.2 | Parathyroid adenomas/hyperplasia, rare cases of parathyroid carcinoma | Primary hyperparathyroidism only | [16] |
| Hyperparathyroidism-Jaw tumour [HPT-JT] | *CDC73* | TSG | 1q31.2 | Parathyroid carcinoma/single parathyroid adenoma | Ossifying fibromas of the mandible or maxilla, pancreatic cysts, renal cysts, renal hamartomas, renal cell cancer, uterine fibroids | [17, 18] |
| Von Hippel–Lindau [VHL] | *VHL* | TSG | 3p25.3 | PPGL, PNET (usually non-functioning) | Endolymphatic sac tumours, retinal, cerebellar and spinal haemangioblastomas, renal cell cancer, papillary cystadenoma of the epididymis and broad ligament | [19] |
| Neurofibromatosis type 1 [NF1] | *NF1* | TSG | 17q11.2 | GEP-NETs (somatostatinomas predominate), PCC | Axillary and inguinal freckling, café-au lait macules, Lisch nodules, neurofibromas, optic pathway gliomas, peripheral nerve sheath tumours, tibial dysplasia, moderate risk of breast cancer | [20] |
| Tuberous sclerosis complex [TSC] | *TSC1*<br>*TSC2* | TSG<br>TSG | 9q34.13<br>16p13.3 | PNETs-predominantly insulinoma | Learning difficulties, seizures, subependymal nodules, cortical dysplasias, subependymal giant cell astrocytomas, hypomelanotic | [21] |

**Table 1** (continued)

| Syndrome | Gene | Function | Location | Endocrine tumours | Other clinical features | Management guidelines |
|---|---|---|---|---|---|---|
| | | | | | macules, confetti skin lesions, facial angiofibromas, Shagreen patches, ungual fibromas, renal angiomyolipomas, renal cysts, renal cell cancer, cardiac rhabdomyomas, lymphangioleiomyomatosis of the lung | |
| Li-Fraumeni syndrome [LFS] | *TP53* | TSG | 17p11.2 | ACC | Early onset breast cancer, rhabdomyosarcoma, soft tissue sarcoma, choroid plexus, brain tumours, leukaemia, lung bronchoalveolar cancer, osteosarcoma | [22] |
| Lynch syndrome [LS] | EPCAM | TSG | 2p21 | ACC | Colorectal, endometrial, stomach, ovary, small bowel, hepatobiliary tract, urinary tract, brain, skin cancers | [23] |
| | *MLH1* | TSG | 3p22.2 | ACC | | |
| | *MSH2* | TSG | 2p21-16 | ACC | | |
| | *MSH6* | TSG | 2p16.3 | ACC | | |
| | *PMS2* | TSG | 7p22.1 | ACC | | |
| Macronodular adrenal hyperplasia | *ARMC5* | TSG | 16p.11.2 | PMAH | Cushing's syndrome, truncal obesity, round face, hypertension | [24] |
| Micronodular adrenal hyperplasia | *PDE11A* | TSG | 2q31.2 | i-PMAD | Cushing's syndrome, truncal obesity, round face, hypertension | [25] |
| Micronodular adrenal hyperplasia | *PDE8B* | TSG | 5q13.3 | PPNAD | Cushing's syndrome, truncal obesity, round face, hypertension | [25] |
| Micronodular adrenal hyperplasia | *PRKACA* | Oncogene | 19q13.3 | i-PMAD | Cushing's syndrome, truncal obesity, round face, hypertension | [26] |
| Major PPGL | *SDHA* | TSG | 5p15.33 | PPGL | High incidence of malignant disease, GIST, renal cell cancer | [27, 28••] |
| Major PPGL | *SDHAF2* | TSG | 11q12.2 | PPGL | Multiple HNPGL | [27, 28••] |
| Major PPGL | *SDHB* | TSG | 1p36.13 | PPGL, rare reports of pituitary adenomas and thyroid cancer | High incidence of malignant disease, renal cell cancer, GIST | [27, 28••] |
| Major PPGL | *SDHC* | TSG | 1q23.3 | PPGL | GIST | [27, 28••] |
| Major PPGL | *SDHD* | TSG | 11q23.1 | PPGL, rare reports of pituitary adenomas and thyroid cancer | Multiple HNPGL, GIST, renal cell cancer | [27, 28••] |
| Major PPGL | *FH* | TSG | 1q43 | PPGL | Papillary type 2 renal cell cancer, cutaneous and uterine leiomyomas | [27, 28••] |
| Major PPGL | *MAX* | TSG | 14q23.3 | PPGL | Bilateral PCC, malignant disease common | [27, 28••] |
| Major PPGL | *TMEM127* | TSG | 2q11.2 | Bilateral later onset PCC | HNPGL not yet described | [27, 28••] |
| Minor PPGL | *DNMT3A* | Oncogene | 2p23.3 | PPGL | Multiple PPGL | [27, 28••] |
| Minor PPGL | *EGLN1* | TSG | 1q42.2 | PPGL | PCC predominates, polycythaemia | [27, 28••] |
| Minor PPGL | *HIF2A* | TSG | 2p21 | PPGL | PPGL, polycythaemia | [27, 28••] |
| Minor PPGL | *KIF1B* | TSG | 1p36.22 | PPGL | Neuroblastoma, ganglioneuroma, PCC | [27, 28••] |
| Minor PPGL | *MDH2* | TSG | 7q11.23 | PPGL | Malignant PPGL | [27, 28••] |
| Minor PPGL | *MERTK* | Oncogene | 2q14.1 | PPGL | Medullary thyroid cancer | [27, 28••] |
| Minor PPGL | *MET* | Oncogene | 7q31.2 | PPGL | Papillary renal cell cancer | [27, 28••] |
| Minor PPGL | *SLC25A11* | TSG | 17p13.2 | PPGL | Multiple PPGL | [27, 28••] |

**Table 2** Inherited endocrine neoplasia genes and key sites of tumorigenesis

| Tumour site | Brain | Pituitary | Para thyroid | Medullary thyroid | Non-medullary thyroid | Breast | Gastro-enteropancreatic | Adreno cortical cancer | Adreno cortical hyperplasia | Adrenal medulla/ PCC | Kidney | Endometrium |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | | | | | | | | | | | | |
| *AIP* | | * | | | | | | | | | | |
| *GPR101* | | * | | | | | | | | | | |
| *MEN1* | | * | * | | | * | * | * | * | | | |
| *CDKN1B* | | * | * | | | | * | | | | | |
| *PRKAR1A* | | * | | | * | * | | | * | | | |
| *RET* | | | * | * | | | | | | * | | |
| *PTEN* | * | | | | * | * | * | | | | * | * |
| *APC* | * | | | | * | | * | * | | | | |
| *DICER1* | * | * | | | * | | * | | | | * | |
| *GCM2* | | | * | | | | | | | | | |
| *CDC73* | | | * | | | | | | | | * | |
| *VHL* | * | | | | | | * | | | * | * | |
| *NF1* | * | | | | | * | * | | | * | | |
| *TSC1* | * | | | | | | * | | | | * | |
| *TSC2* | * | | | | | | * | | | | * | |
| *TP53* | * | | | | | * | | * | | | | |
| *EPCAM* | * | | | | | | * | * | | | | * |
| *MLH1* | * | | | | | | * | * | | | | * |
| *MSH2* | * | | | | | | * | * | | | | * |
| *MSH6* | * | | | | | | * | * | | | | * |
| *PMS2* | * | | | | | | * | * | | | | * |
| *ARMC5* | | | | | | | | | * | | | |
| *PDE11A* | | | | | | | | | * | | | |
| *PDE8B* | | | | | | | | | * | | | |
| *PRKACA* | | | | | | | | | * | | | |
| *SDHA* | | | | | | | * | | | * | | |
| *SDHAF2* | | | | | | | | | | * | | |
| *SDHB* | | | | | | | * | | | * | * | |
| *SDHC* | | | | | | | * | | | * | * | |
| *SDHD* | | | | | | | * | | | * | * | |
| *FH* | | | | | | | | | | * | * | * |
| *MAX* | | | | | | | | | | * | | |
| *TMEM127* | | | | | | | | | | * | | |
| *DNMT3A* | | | | | | | | | | * | | |
| *EGLN1* | | | | | | | | | | * | | |
| *HIF2A* | | | | | | | | | | * | | |
| *KIF1B* | | | | | | | | | | * | | |
| *MDH2* | | | | | | | | | | * | | |
| *MERTK* | | | | * | | | | | | * | | |
| *MET* | | | | | | | | | | * | * | |
| *SLC25A11* | | | | | | | | | | * | | |

adenomas are likelier to be larger, histologically invasive, multiple in number, and pluri-hormonal, although malignant transformation is rare [38].

Biochemical surveillance for pituitary adenoma in MEN1 includes annual prolactin and IGF-1 from age 5 years. Radiological surveillance should occur 3-yearly with pituitary MRI, starting at age 10 years [4].

#### Multiple Endocrine Neoplasia Type 4

MEN4 is an autosomal dominant syndrome caused by pathogenic germline variants in *CDKN1B*. Five to ten percent of individuals with clinical features of MEN1 lack pathogenic germline variants in *MEN1*. MEN4 pedigrees mirror the clinical features of MEN1 but are rare, with only 19 cases published to date [39•]. Pituitary adenomas occur in 37% reported MEN4 cases, the youngest presentation at 30 years [39•].

Experts recommend biochemical surveillance for pituitary adenoma measuring IGF-1 annually, starting in adolescence [40•]. The role of radiological surveillance is not yet established.

#### Carney Complex

Carney complex (CNC) is an autosomal dominant syndrome caused by pathogenic germline variants in *PRKAR1A*. Patients develop distinctive mucocutaneous pigmentation, myxomatous tumours, and endocrine tumours.

Growth hormone–secreting pituitary adenomas occur in 10–12% of CNC patients [9]. Prolactin-secreting pituitary adenomas are documented but rarer.

Experts recommend annual biochemical surveillance for growth hormone IGF-1, and prolactin and radiological surveillance by pituitary MRI [9].

## Thyroid Gland

### Medullary Thyroid Carcinoma

The thyroid gland comprises two main histologically distinct cell types: follicular cells (derived from the endoderm) and parafollicular cells (derived from the neural crest). Parafollicular cells produce calcitonin in normal homeostasis. Parafollicular cells are the originating substrate of medullary thyroid cancer (MTC). MTC accounts for ~ 5% of all thyroid cancers.

Approximately 75% of MTC cases are non-familial. Twenty-five percent are attributable to autosomal dominant heritable MTC syndromes caused by activating germline pathogenic variants in specific exons of the *RET* proto-oncogene [41]. Germline testing for *RET* pathogenic variants is indicated in all MTC cases; with *RET* pathogenic variants identified in approximately 7% of apparently sporadic cases [41]. Current molecular *RET* testing for MEN2 includes exons 5, 7 and 8, in addition to classic 'hotspot exons' 10, 11, 13, 14, 15, and 16, to capture further MEN2A families [42, 43].

Of the two types of heritable MTC syndromes, multiple endocrine neoplasia type 2A (MEN2A) accounts for 95%, whilst multiple endocrine neoplasia type 2B (MEN2B) represents 5% [44].

#### MEN2A

In classical MEN2A, over 95% develop MTC, up to 50% develop phaeochromocytoma and up to 30% primary hyperparathyroidism [44], which is mild or asymptomatic in 85% [43]. Rarely, some MEN2A families with exon 10 *RET* pathogenic variants develop Hirschsprung's disease in infancy (approximately 7%), predating the onset of endocrine neoplasia [45]. Up to 10% MEN2A cases with exon 11 pathogenic variants develop cutaneous lichen amyloidosis [46]. Familial MTC (FMTC), describing families with *RET* pathogenic variants where only MTC has occurred, is now considered part of the MEN2A disease spectrum [47].

#### MEN2B

In MEN2B, all patients develop MTC and 50% develop phaeochromocytoma. All have characteristic extra-thyroidal features which include mucosal neuromas on the lips and tongue, thickened corneal nerves, ptosis, upper eyelid eversion, marfanoid habitus, and gastrointestinal dysfunction [10•].

Germline pathogenic *RET* variants in MEN2B arise *de novo* in 90% of cases [48]. Diagnosis is often delayed, as reduced or absent tear production (alacrima), and intestinal ganglioneuromatosis (key early signs of MEN2B) are underrecognised, and extra-thyroidal features of marfanoid habitus and mucosal neuromas are not always apparent before age 5 years. Most cases of MEN2B present with metastatic MTC in the second decade of life, which may result in shortened survival [10•]. Tyrosine kinase therapy for advanced MTC is available, resulting in highly variable improved progression-free survival, but its use is limited by toxicity and has not resulted in improved overall survival [11••].

#### Thyroid Management in MEN2A and MEN2B

Thyroidectomy is always advisable in hereditary MTC syndromes, preferably as a risk-reducing measure ahead of MTC developing, so correct timing is crucial [12]. Late thyroidectomy leads to adverse morbidity and mortality from MTC. Early thyroidectomy risks iatrogenic hypoparathyroidism [49].

The age for effective intervention and extent of surgery is determined by genotype, which predicts aggressiveness of MTC development [12]. In MEN2B thyroidectomy in the first year is recommended as delays may result in a failure to achieve surgical cure before onset of metastasis [10•]. *RET* germline testing at birth in known kindreds is therefore urgent. In MEN2A, high-risk genotypes (RET 634 codons) should undergo thyroidectomy by age 5 years, whereas for moderate risk MEN2A genotypes, thyroid surgery may be delayed beyond 5 years, subject to satisfactory assessment and MDT discussion [47].

### Non-medullary Thyroid Cancer

Ninety-five percent of thyroid cancers are non-medullary thyroid cancers (NMTC), of which 5% are attributable to heritable syndromes [50]. These syndromes are heterogeneous and lack the genotype–phenotype correlations observed in MTC.

#### Carney Complex

More than 60% of individuals with CNC have cystic or nodular thyroid disease on ultrasonography and, up to 10% of those develop NMTC. Annual thyroid ultrasound surveillance from the time of CNC diagnosis is recommended [9].

#### PTEN Hamartoma Tumour Syndrome

PTEN hamartoma tumour syndrome (PHTS) is an autosomal dominant spectrum of clinical entities (including Cowden syndrome) caused by pathogenic germline variants in *PTEN*. PHTS clinical findings include hamartomas, macrocephaly, neurodevelopmental disorders, and thyroid, breast, endometrial, and kidney tumours.

Thyroid lesions are common. In one study, 71% of patients had thyroid lesions including multinodular goitre and adenoma [51]. The incidence of thyroid neoplasia by age 70 years is up to 38% [52] with NMTC diagnosed as young as age 7 years [53].

Surveillance by annual thyroid ultrasound is recommended, starting at either age 18 years, or 5–10 years before the earliest known thyroid cancer diagnosis in the family [54]. Certain authors recommend consideration of prophylactic total thyroidectomy in patients who have thyroid nodules, an enlarging goitre, or are unable to tolerate routine thyroid surveillance due to learning difficulties [55].

#### Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome caused by pathogenic germline variants in *APC*. The typical phenotype involves hundreds of adenomatous colonic polyps.

There are several extra-colonic manifestations (listed in Table 1), including an estimated 1–2% lifetime incidence of NMTC (typically papillary thyroid carcinoma) [56]. The histology is distinctive, characterised as the "cribriform-morular" variant. This histology alone warrants clinical evaluation for FAP because thyroid cancer can predate clinically detectable colonic abnormalities in ~ 40% of cases [57]. One suggested surveillance programme is annual thyroid ultrasound starting in late teenage years [14], but this is not offered routinely in most centres due to the indolent nature of the disease.

#### *DICER1* Syndrome

*DICER1* syndrome is autosomal dominant, caused by pathogenic germline variants in *DICER1*. It predisposes to pleiotropic tumours, especially pleuropulmonary blastoma, cystic nephroma, and ovarian Sertoli–Leydig cell tumours.

One study reported a significantly higher cumulative risk of multinodular goitre, and a 16-fold risk of NMTC in *DICER1* syndrome patients compared to baseline [58]. The efficacy of thyroid ultrasound surveillance is unknown, but recommended from age 8 years, particularly in children who have already received prior chemotherapy or radiotherapy for other malignancies [15•]. In some individuals with multinodular goitre, risk-reducing thyroidectomy may be advised.

## Parathyroid Gland

### Parathyroid Adenoma

Parathyroid adenomas are benign endocrine neoplasia of the parathyroid glands, accounting for 93% of cases of primary hyperparathyroidism (PHPT) [59]. More than 10% of cases of primary hyperparathyroidism arise from heritable genetic causes [60••]. Clinical suspicion and biochemical testing should help to differentiate familial hypocalciuric hypercalcaemia from PHPT. Heritable predisposition to PHPT results in multiple parathyroid adenomas or hyperplasia, whereas sporadic forms are typically singular.

#### Germline-Activating *GCM2*-Pathogenic Variants in Familial Isolated Hyperparathyroidism

Familial isolated hyperparathyroidism (FIHP) describes PHPT in at least two family members in the absence of other syndromic features. An emerging disease entity involves FIHP pedigrees with pathogenic germline-activating variants in *GCM2*. One study reported that *GCM2* pathogenic variants accounted for 18% of genetically uncharacterised FIHP and found that parathyroid

adenomas in this population were significantly larger in size than genetically uncategorised FIHP [16].

#### MEN1

An estimated 1–18% of patients with parathyroid adenomas have MEN1 [4]. Ninety-five percent of MEN1 patients develop parathyroid adenoma [61], and hyperparathyroidism is the presenting clinical feature in 90% of cases of MEN1 [60••].

Surgical approaches recommended are subtotal or total thyroidectomy with bilateral cervical thymectomy [4]. There is a high risk of recurrent hyperparathyroidism even following subtotal parathyroidectomy, attributed to ectopic or supernumerary glands and regrowth of remnant or autografted parathyroid tissue [62]. Calcimimetic agents have a role in the medical management of some cases of recurrent MEN1 hyperparathyroidism [63].

Biochemical surveillance for hyperparathyroidism in MEN1 involves annual serum calcium and parathyroid hormone from age 8 years [4].

#### MEN4

In one study, 100% of patients with molecularly confirmed MEN4 developed hyperparathyroidism of later onset (> 45 years) [39•]. Annual biochemical surveillance for hyperparathyroidism is recommended [40•].

#### MEN2A

Up to 30% of patients with MEN2A develop hyperparathyroidism (often asymptomatic), with the prevalence depending on the mutant *RET* codon [47].

Annual biochemical surveillance for hyperparathyroidism is recommended, starting at age 11 or 16 years, depending on the exact *RET* pathogenic variant [47].

#### Hyperparathyroidism-Jaw Tumour Syndrome

Hyperparathyroidism-Jaw Tumour syndrome (HPT-JT) is an autosomal dominant syndrome caused by pathogenic germline variants in *CDC73*. It is characterised by PHPT, ossifying tumours of the jaw, renal cysts, and uterine tumours [17]. Annual biochemical surveillance for hyperparathyroidism should be arranged, as recurrent hyperparathyroidism is common. Screening for other aspects of the disease is recommended [18].

### Parathyroid Carcinoma

Parathyroid carcinoma is a rare malignant endocrine neoplasia that accounts for 0.3–2.1% of cases of PHPT [64]. Unlike parathyroid adenoma, parathyroid carcinoma typically causes strong symptomatology of hypercalcaemia and is associated with higher parathyroid hormone levels at presentation. Preoperative management to reduce hypercalcaemia and correct biochemical abnormalities and hydration are crucial for safe care. However, parathyroid carcinoma is commonly clinically indistinguishable from other causes of PHPT and is often discovered intra-operatively. Curative surgery may be achieved by *en bloc* resection at first operation [17]. Patients with recurrent or incurable disease may benefit from Cinacalcet and Denosumab therapy.

Parathyroid carcinoma occurs in 15–37% of HPT-JT cases [17, 18]. Individuals with apparently sporadic parathyroid carcinomas are found to have germline *CDC73* pathogenic variants in 20–33% of cases, indicating undiagnosed HPT-JT [18]. Germline *CDC73* testing is indicated in apparently sporadic cases of parathyroid carcinoma. Parathyroid carcinoma is also a rare feature of MEN1 [65] and MEN2A [66]. Germline-activating pathogenic variants in *GCM2* were identified in 17.4% of patients with sporadic parathyroid carcinoma [67], highlighting the need to consider this an alternative inherited cause of parathyroid carcinoma, other than HPT-JT.

### Bronchial and Thymic Neuroendocrine Tumours

Most bronchial and thymic neuroendocrine tumours (NETs) occur sporadically. Non-functioning tumours typically present with a cough, recurrent infections, or haemoptysis. Functioning tumours present with symptoms of hormonal excess, e.g. ectopic ACTH secretion resulting in Cushing's syndrome. Bronchial NETs are found in 5% of patients with MEN1, and thymic carcinoids in 2–8%. The possibility of MEN1 should be considered during assessment, with genetic testing offered if another feature of MEN1 disease is found or there is a relevant family history. Metastatic disease occurs in 20%, with poor outcomes [68]. In MEN1 NETs Surveillance from age 15 years by chest CT or MRI is recommended [4].

## Gastroenteropancreatic NETs

Gastroenteropancreatic NETs (GEP-NETs) comprise ~ 1–3% of pancreatic neoplasms. Heritable endocrine cancer syndromes (MEN1, MEN4, Von Hippel–Lindau [VHL], neurofibromatosis type 1 [NF1], and tuberous sclerosis [TS]) account for > 10% of GEP-NETs [69]. Thirty to forty percent of GEP-NETs are non-functioning neoplasms, presenting late due to mass effect or liver metastases [70••]. Functioning GEP-NETs present early due to clinical manifestations from hypersecretion of peptide hormones including insulin, gastrin, glucagon, and vasoactive intestinal peptide. These tumours are located either in the duodenum or the pancreas [70••].

### MEN1

GEP-NET is the presenting clinical feature in 32% of MEN1 patients [37]. Eighty to one hundred percent of MEN1 patients reportedly have microscopic non-functioning GEP-NETs. There is an 84% penetrance of clinically apparent GEP-NET in MEN1 by age 80 years, and GEP-NET contributes to 19–100% of deaths in MEN1 [71].

The most common clinically apparent functional GEP-NETs are gastrinomas (54% risk) and insulinomas (18% risk). Twenty-five percent of all gastrinomas and 4% of all insulinomas are caused by MEN1 [71]. Gastrinomas and insulinomas both present earlier in MEN1 than in sporadic forms, with a 10-year earlier onset for gastrinoma reported (onset age 33.2 years vs age 43.5 years) [72]. Gastrinomas are usually located in the duodenum.

GEP-NETs in MEN1 occur as multiple tumours, which may necessitate an aggressive surgical approach to reduce risk of metastasis. However, medical management using proton-pump inhibitors and somatostatin analogues for gastrinoma patients is increasingly successful, as a non-surgical option [4, 70].

Biochemical surveillance for GEP-NETs in MEN1 is recommended with annual plasma gastrin, glucagon, vasointestinal polypeptide, pancreatic polypeptide, chromogranin A, and insulin paired with fasting glucose. Recommended radiological surveillance includes annual pancreato-duodenal MRI, CT, or EUS [4].

### Von Hippel–Lindau Syndrome

VHL syndrome is an autosomal dominant syndrome caused by pathogenic germline variants in *VHL* [19]. It is classically associated with central nervous system and retinal hemangioblastomas, clear cell renal cell carcinomas, phaeochromocytomas and paragangliomas, endolymphatic sac tumours, epididymal cystadenomas, and pancreatic lesions.

Pancreatic lesions in VHL are common (77% of cases) and may involve true cysts, serous cystadenomas, and GEP-NETs. GEP-NETs in VHL are usually non-functioning [73]. In one VHL case series, 17% of individuals developed GEP-NET and 8% of this subgroup had metastatic GEP-NET [74].

A recommended surveillance protocol for GEP-NET in VHL is annual MRI from age 10 years [29]. Treatment is by surgical resection, although the risk of metastasis is considered low for GEP-NETs that are < 3 cm in size, have doubling time > 500 days, and lack pathogenic variants in *VHL* exon 3 [74].

### Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous syndrome caused by pathogenic germline variants in *NF1*. Its hallmarks are multiple café-au-lait macules and cutaneous neurofibromas. Other features are listed in Table 1. Thirty to fifty percent of cases arise as de novo *NF1* pathogenic germline variants or due to somatic mosaicism [20].

There is up to a 10% lifetime risk of GEP-NET in NF1, commonly duodenal somatostatinoma [71]. NF1 accounts for 48% of cases of all duodenal somatostatinomas. Thirty percent of these somatostatinomas metastasise. As with sporadic duodenal somatostatinomas, they rarely manifest clinically with a hypersecretion syndrome [75]. There are no consensus surveillance protocols for GEP-NET in NF1.

### Tuberous Sclerosis Complex

TSC is an autosomal dominant neurocutaneous syndrome caused by pathogenic germline variants in *TSC1* and *TSC2*. Typical features include multiple benign hamartomas of the brain, eyes, heart, lung, liver, kidney, and skin.

There is approximately a 1% lifetime risk of GEP-NET in TSC [71], usually in individuals with *TSC2* pathogenic variants [76]. Non-functioning GEP-NETs have been most commonly reported, followed by insulinoma and gastrinoma [77]. There are no consensus surveillance protocols for GEP-NET in TSC, but abnormalities may be detected during the recommended 1–3 yearly MRI surveillance for renal lesions [21].

## Tumours of the Adrenal Cortex

### Adrenocortical Cancer

Five to ten percent of adrenocortical cancer (ACC) cases occur in patients with cancer-predisposing syndromes. These include Li-Fraumeni syndrome [LFS] (2–4% ACC), Lynch syndrome [LS] (3% ACC), and MEN1 (1–2% ACC) [78•]. ACC is often the first presenting tumour in LFS and LS, but in MEN1, BWS, and FAP, patients are commonly already being monitored for their condition when ACC is diagnosed.

#### Li-Fraumeni Syndrome

Germline pathogenic variants in *TP53* result in LFS. This rare syndrome predisposes individuals to multiple early onset cancers, including ACC, which occurs in 3–10% of LFS children [78•]. All patients presenting with ACC should be screened for *TP53* pathogenic variants across all exons (Chompret testing criteria). *TP53* pathogenic variants arise de novo *in* up to 20% cases [78•]. A founder *TP53* pathogenic variant in southern Brazil, p.R337H, accounts for 95% of childhood-onset ACC cases [78•]. Surveillance programmes for LFS in children and adults are being introduced which include screening for ACC [79].

### Lynch Syndrome

Germline pathogenic variants in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* result in LS, an adult-onset autosomal dominant cancer predisposition syndrome with many manifesting tumour types: colorectal, endometrial, ovarian, small bowel, pancreatic, and transitional cell of the ureter or renal pelvis. ACC is one of the rarer LS tumours and occurs in 3% adults with LS. ACC tumours demonstrate mismatch repair deficiency. If *TP53* testing is negative in ACC, MMR testing could be utilised to screen cases for LS [80]. At present, surveillance of ACC in LS is not recommended.

### MEN1

Adrenal hyperplasia and benign adenomas are common in adults with MEN1; 45–55% are affected [81]. ACC is identified in 1–2% of MEN1 cases, sometimes from a precursor lesion which has evolved into ACC [82]. Adrenal imaging and biochemical surveillance is routine in MEN1 [4].

## Micronodular and Macronodular Adrenal Hyperplasia

Bilateral adrenal hyperplasia has two distinct forms, primary macronodular adrenal hyperplasia (PMAH) or micronodular bilateral adrenal hyperplasia (MiBAH). They account for 2% of pituitary-independent Cushing's syndrome and present as bilateral disease in patients with autonomous cortisol secretion [24]. Many inherited causes of hypercortisolism are now known.

Recently, germline *ARMC5* pathogenic variants have been identified in familial and sporadic forms of PMAH [83•]. Ten to fifty-five percent of PMAH patients harbour *ARMC5* pathogenic germline variants germline, with a second somatic hit resulting in disease [84].

MiBAH is more complex, with three subgroups described, primary pigmented nodular adrenocortical disease (PPNAD), isolated-PPNAD, and isolated micronodular adrenocortical disease (i-MAD) [25]. PPNAD is the most common tumour in CNC [85]. Isolated PPNAD arises in patients with *PRKAR1A*, *PDE8B*, and *PDE11A* pathogenic variants whereas patients with *PRKACA* copy number gains or *PDE11A* pathogenic variants present with i-MAD [25]. Adrenal imaging and biochemical surveillance is routine in CNC [9]. Bilateral adrenalectomy is required to achieve surgical cure.

# Tumours of the Adrenal Medulla

## Phaeochromocytomas and Paragangliomas

Phaeochromocytomas (PCC) are neuroendocrine tumours arising from chromaffin cells of the adrenal medulla. Paragangliomas (PGLs) develop in extra-adrenal sympathetic and/or parasympathetic paraganglia sited from the skull base to the pelvis. Phaeochromocytomas and paragangliomas (PPGLs) are all neuroendocrine tumours of neural crest origin, many of which secrete catecholamines resulting in the classic triad of symptoms—headaches, palpitations, and sweating. Over 18 PPGL germline susceptibility genes have been identified. A germline PPGL pathogenic variant is identified in up to 40% PPGL patients, confirming PPGL's high heritability [86•]. Syndromic PPGL and non-syndromic inherited PPGL account for 16% and 24% of all PPGLs respectively. Inherited PPGL may occur at a younger age (10–20% occur in paediatric patients), or present with multifocal or metastatic disease. Referral for genetic testing should always be considered, due to high pathogenic variant detection even in apparently sporadic disease. SDHB antibody staining of tumour tissue may reveal immunonegativity and is a useful tool, indicating a high likelihood of an *SDHx* disease [87]. All patients with PPGL require tailored surveillance for a decade after diagnosis, but if the hereditary disease is confirmed, this becomes lifelong [27].

### Syndromic PPGL

**MEN2A and 2B** PCC occurs in both MEN2A and MEN2B, affecting 15–50% MEN2 patients, correlated to their specific genotype [88]. PCC in MEN2 may occur synchronously or metachronously (average interval of 9 years) and is more frequent in MEN2A due to exon 11 *RET* pathogenic variants (31–61%) [47] or in MEN2B (50%) exon 16 pathogenic variant [10•], with over 50% developing bilateral disease. Although onset at age 12 years has been described, it is more common at age > 30 years [86•]. PCC occurs after MTC in 55%, is identified synchronously with MTC in 30%, or is the first manifestation in 15% of MEN2 cases [89]. PGLs and malignant disease are rare [89].

PCCs in MEN2 secrete only epinephrine, which may alert the clinician to its underlying aetiology. Preparation for PCC surgery using alpha blockade, careful timing, and choice of procedures, e.g. cortical-sparing adrenalectomy preserving adrenocortical function, leads to better MEN2 outcomes [89]. MTC surgery is rarely an emergency, but a PCC crisis is, so if a patient presents with synchronous disease (MTC and PCC), PCC surgery should occur first.

**NF1** Five percent of NF1 patients develop PCCs (mean age 41) but this rises to 50% in hypertensive NF1 patients [86•]. PCCs occur bilaterally in 10% and become malignant in 12% [90]. Patients are recommended to have annual BP assessment, but regular plasma metanephrines are

not required, unless the patient is symptomatic or hypertensive [20].

**VHL** About 20–25% VHL patients develop PPGLs (mean age 30 years, youngest 5 years) with bilateral disease in 40%, and a malignancy rate ~5% [91]. Some patients with exon 3 missense pathogenic variants in *VHL* almost exclusively develop bilateral PPGLs with few other manifestations. Annual PPGL screening, measuring blood pressure and plasma metanephrines from age 5 years, is key to early detection [92].

### Non-syndromic PPGL

**SDHx Genes** The PPGL genes, *SDHA*, *SDHB*, *SDHC*, and *SDHD*, encode four subunits of succinate dehydrogenase to form the mitochondrial complex 1 cluster. *SDHAF2* encodes an SDH assembly factor, responsible for flavination of the SDHA protein, a crucial step in the formation of the mitochondrial complex, part of the respiratory chain. Germline pathogenic variants in any of these genes predispose to PPGLs, with frequent childhood onset, although penetrance is incomplete [86•]. *SDHAF2* and *SDHD* pathogenic variants are only active through paternal transmission [86•]. *SDHD* and *SDHAF2* patients more frequently develop multifocal head and neck PGLs, whereas SDHB patients have a higher occurrence of thoracoabdominal PGLs compared to head and neck PGLs or PCCs, and have a higher likelihood of malignant disease (up to 30%) [93]. Pathogenic variants in *SDHB* are the most frequent, accounting for 10% of PPGLs whereas *SDHD* and *SDHC* are found in 6% and 3% respectively [86•].

Germline pathogenic variants in *FH*, *MAX*, and *TMEM127* are each identified in 1–2% PPGLs [94]. Up to 40% of *FH* patients with PPGL develop malignant disease (40%) [86•]. *TMEM127* predisposes to later onset PPGLs (often age >40 years). Identification of further minor PPGL genes includes gain of function pathogenic variants in *DNMT3A* [3] *MERTK*, and *MET*, and loss of function variants in *ELGN1*, *HIF2A*, *KIF1B*, *MDH2*, and *SLC25A11* [86•].

Identification of hereditary PPGL enables at-risk families to be referred for tailored surveillance beginning age 5–10 years, e.g. annual plasma metanephrines [95] and MRI scanning every 3 years from skull base to pelvis [96]. Many head and neck PGLs are non-secretory and therefore radiological surveillance is important for early detection. Localised PPGLs can be cured by complete surgical resection but in the head and neck, this may result in considerable morbidity, such that radiotherapy or a 'watch and wait' policy may be preferable [27].

## Conclusion

In this review of inherited endocrine neoplasia, we have highlighted both syndromic and non-syndromic forms of endocrine disease. Patients with inherited endocrine syndromes may develop multiple tumours at several sites over decades; hence, we have presented a gland-to-gene approach in the text complemented by a syndrome-to-gland approach in Table 1.

Our knowledge of the inherited basis for many of these tumours is expanding, with a number of new genes described in recent years, e.g. *GCM2* pathogenic variants causing familial isolated hyperparathyroidism and parathyroid cancer or *ARMC5* pathogenic variants resulting in primary macronodular adrenal hyperplasia or the plethora of genes leading to hereditary PPGL [86•]. New mechanisms of disease are also apparent, as evidenced by the discovery that copy number variations result in disease, with duplications of *GPR101* and *PRKACA* causing Acrogigantism and PPNAD respectively.

Once an inherited cause of endocrine neoplasia is confirmed, lifelong surveillance is required, even though some conditions may have lower penetrance in non-index cases, e.g. SDHB [97]. All patients with endocrine neoplasia should be offered treatment and care in centres with relevant expertise. The evidence base for many surveillance recommendations is weak, as the number of affected patients with each inherited endocrine neoplasia is small. However, accrued data are emerging from some cohorts in diseases such as MEN1 and MEN2, providing a greater understanding of the natural history of the disease, helping to refine care [98, 99•]. Furthermore, opportunities for research and development of novel treatments are emerging [11••].

There have been some key improvements in the surgical care of endocrine neoplasia patients, particularly in MEN2. Risk reduction to avoid MTC is possible provided that early thyroidectomy is undertaken, and adrenal function can be preserved, if cortical-sparing adrenal surgery is employed when a patient has developed bilateral PCC.

Central to these developments are the patients and their families who live with these conditions. Fortunately, they can benefit from medical organisations specifically set up for endocrine neoplasia, for example the Association for Multiple Endocrine Neoplasia Disorders [AMEND] [100], who provide patient-friendly information and support via internet forums, patient update days, or telephone helplines, enabling patients to navigate the ongoing burden of lifelong surveillance and treatment of endocrine neoplasia.

## Compliance with Ethical Standards

**Conflict of Interest** Alexander T Deng and Louise Izatt each declares no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.



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- • Of importance
- •• Of major importance

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