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Genodermatoses – Opportunities for Early Detection and Cancer Prevention

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Abstract

Purpose of Review This review describes the clinical features of the major adult-onset genodermatosis-associated hereditary cancer predisposition syndromes. Diagnosis of these conditions can be challenging due to a wide range of clinical features, varied presentations within families and the involvement of multiple medical specialities.

Recent Findings By emphasising the cutaneous and other non-malignant features, we aim to alert clinicians from all specialities to clues in the clinical history which should prompt consideration of a genodermatosis-associated hereditary cancer predisposition syndrome. In recognition of the move towards remote (telephone or video) appointments since the Covid-19 pandemic, we propose criteria which could be used by Cancer Genetics services to triage patients for in-person consultations in order to examine for signs of genodermatosis.

Summary Although individually rare, familiarity with these conditions amongst genetic and non-genetic clinicians is important as early diagnosis provides an opportunity to implement risk-reduction measures prior to a cancer diagnosis.

Keywords Genodermatoses · Hereditary cancer · Inherited skin · Cancer susceptibility · Cancer risk

Introduction

Genodermatoses are hereditary dermatological conditions, a number of which are associated with an increased risk of internal malignancy, so-called hereditary cancer predisposition syndromes (HCPS) [1]. HCPS occur as a consequence of a constitutional pathogenic variant in a cancer susceptibility gene and are typically autosomal dominant so that first-degree relatives are at 50% risk of the same condition. Diagnosis of an HCPS is often made retrospectively following a cancer diagnosis, using indicators such as young age at cancer diagnosis, an uncommon tumour type or a strong family history of cancer in order to guide investigations. Although HCPS account for a minority of the overall cancer burden at 5–10% [2], establishing a diagnosis is important to provide patients with appropriate risk management options and identify at-risk family members.

HCPS can present with a range of dermatological and other non-malignant features and to a multitude of specialities, including the General Medical, Gynaecological and even the Dental Clinic. Recognition of these features provides a window of opportunity to establish a diagnosis and implement surveillance strategies *prior* to a cancer diagnosis. Yet, the recognition of HCPS can be challenging due to its varied clinical features and rarity amongst the general population.

In this review, we describe the presenting dermatological, non-dermatological and oncological features of the major adult-onset genodermatosis-associated HCPS (Table 1). In addition, we propose criteria to allocate in-person consultations to patients referred to Cancer Genetics services who may be at risk of a genodermatosis-associated HCPS, in recognition that remote (telephone or video-conferencing) appointments as a result of the Covid-19 pandemic are now commonplace. Genodermatosis-associated HCPS presenting predominantly in childhood (including, but not limited to xeroderma pigmentosa, tuberous sclerosis, neurofibromatosis type 1 and type 2 and chromosome breakage disorders) are outside of the scope of this paper and are reviewed by Ladd et al. [3•].

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Table 1 Summary table of genodermatosis-associated hereditary cancer predisposition syndromes

Name	Gene	Mode of inheritance	Age of onset	Dermatological features	Associated tumours	Other features
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	*FH*	AD	Usually adulthood (youngest renal cancer diagnosed at age 7)	Multiple pilar leiomyomas	HLRCC-associated renal cancer Rarely: Phaeochromocytoma Paraganglioma	Uterine leiomyomas
Birt-Hogg-Dubé syndrome (BHDS)	*FLCN*	AD	Adulthood	Fibrofolliculomas Trichodiscomas Acrochordons Perifollicular fibromas Less commonly: Angiofibromas Oral papules Cutaneous collagenomas Multiple epidermal cysts	Renal tumours: Oncocytic/chromophobe hybrid Renal oncocytoma Chromophobe, Oncocytoma Clear cell carcinoma, Hybrid clear cell-chromophobe Papillary renal cell carcinomas	Pulmonary cysts and spontaneous pneumothorax Renal cysts
Cowden syndrome/PTEN hamartoma tumour syndrome	*PTEN*	AD	Childhood or adulthood	Trichilemmomas Oral papillomas Acral keratoses Mucocutaneous neuromas Penile freckling Lipomas Vascular malformations	Breast cancer Endometrial cancer Epithelial thyroid cancer Renal cell cancer Colorectal cancer Melanoma	Cerebellar dysplastic gangliocytoma Macrocephaly Intellectual disability Fibrocystic breast disease, Benign thyroid disease, Hamartomatous gastrointestinal polyps, Genitourinary malformations Uterine fibroids Fibromas
Gorlin syndrome	*PTCH1* or *SUFU*	AD	Childhood or adulthood	Multiple basal cell carcinomas Palmar and/or plantar pits Less commonly: Eyelid meibomian cysts Sebaceous and dermoid cysts Acrochordons	Ovarian fibroma Cardiac fibroma Medulloblastoma Meningioma	Jaw keratocyst Falx calcification Macrocephaly Lympho-mesenteric or pleural cysts Cleft lip or palate Congenital rib or vertebral anomalies Polydactyly (pre/post-axial) Eye anomalies Pigmentary changes in the retinal epithelium Intellectual disability Facial gestalt (frontal bossing, pouting lower lip, coarse facial features)

Table 1 (continued)

Name	Gene	Mode of inheritance	Age of onset	Dermatological features	Associated tumours	Other features
Peutz-Jegher syndrome	*STK11*	AD	Childhood or adulthood	Mucocutaneous melanocytic macules	Breast cancer Colorectal cancer Gastric cancer Small bowel cancer Pancreatic cancer Cervical adenocarcinoma (adenoma malignum) Sex cord tumours with annular tubules (SCTAT) Uterine cancer Less commonly: Lung cancer Testicular cancer	Hamartomatous intestinal polyps, especially small intestine Extra-intestinal polyps (renal pelvis, bladder, ureters, gallbladder, nostrils and lungs)
Familial atypical multiple mole melanoma syndrome (FAMMM)	*CDKN2A* or *CDK4*	AD	Adulthood	Melanoma	Pancreatic cancer	N/A
BAP1 tumour predisposition syndrome (BAP1-TPDS)	*BAP1*	AD	Adulthood	BAPoma Melanoma Basal cell carcinoma	Uveal melanoma Malignant mesothelioma (pleural or peritoneal) Renal cell carcinoma	N/A
Carney syndrome	*PRKAR1A*	AD	Childhood/adulthood	Lentigines Epithelioid-type blue naevi Cutaneous myxomas Less commonly: Freckling Cafe au lait macules Depigmented lesions Skin tags (multiple) Lipomas	Endocrine tumours: Primary pigmented nodular adrenocortical disease (PPNAD) Growth-hormone secreting adenomas Large-cell calcifying Sertoli cell tumours Thyroid follicular adenomas Thyroid cancer (papillary or follicular) Other: Myxomas – cardiac, breast, oropharynx, female genital tract and osteochondromyxomas	May present with symptoms of cardiac outflow obstruction, emboli, hypercortisolism, acromegaly, gynaecomastia, multiple thyroid nodules

Table 1 (continued)

Name	Gene	Mode of inheritance	Age of onset	Dermatological features	Associated tumours	Other features
Multiple endocrine neoplasia type 1 (MEN)	*MEN1*	AD	Childhood/adulthood	Facial angiofibromas Collagenomas Lipomas Less commonly: Café au lait macules Hypopigmented macules Gingival papules	Endocrine tumours: Parathyroid Endocrine tumours of the gastro-entero-pancreatic tract Anterior pituitary tumours Carcinoid Adrenocortical Other: Meningioma Ependymoma	May present with symptoms relating to associated tumour hormone secretion and/or mass effect
Multiple endocrine neoplasia type 2B (MEN2B)	*RET*	AD	Childhood	Mucosal neuromas (tongue, palate, pharynx) Submucosal nodules on lips Eyelid neuromas	Medullary thyroid cancer Phaeochromocytoma	Marfanoid habitus Diffuse intestinal ganglioneuromatosis
APC-associated polyposis	*APC*	AD	Childhood/adulthood	Lipomas Fibromas Epidermal cysts Multiple pilomatricomas	Colorectal cancer Small bowel (duodenal and peri-ampulla) cancer Cribriform-morular variant of papillary thyroid cancer Hepatoblastoma Medulloblastoma Pancreatic cancer Gastric cancer Desmoid tumours	Colonic polyposis Osteomas Dental anomalies Congenital hypertrophy of retinal pigment epithelium
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	AD	Adulthood	Sebaceous tumours: Adenomas Epitheliomas Carcinoma Keratoacanthomas	Colorectal cancer Endometrial cancer Depending on gene: Ovarian cancer Gastric cancer Small bowel cancer Biliary tract cancer Brain tumours Pancreatic cancer Prostate cancer	N/A

AD autosomal dominant, *N/A* not applicable

Hereditary Leiomyomatosis and Renal Cell Cancer

Hereditary leiomyomatosis and renal cell cancer (HLRCC), also known as *FH*-Tumour Predisposition Syndrome, or previously, Reed syndrome, is an autosomal dominant HCPS characterised by an increased risk of renal cancer, cutaneous and uterine leiomyomata [4]. HLRCC occurs due to heterozygous inactivating pathogenic variants of *FH*, a tumour suppressor gene which encodes the tricarboxylic acid cycle enzyme, fumarate hydratase [5]. In contrast, biallelic pathogenic *FH* variants cause the autosomal recessive condition, fumarate hydratase deficiency, a severe neurodevelopmental disorder presenting in infancy. The prevalence of HLRCC is estimated at 1 in 200,000 [6], and penetrance is unknown [4].

HLRCC presents dermatologically with non-malignant smooth muscle tumours surrounding hair follicles, called multiple pilar leiomyomas or piloleiomyomas [7]. Piloleiomyomas appear as reddish-brown or flesh-coloured, tender or non-tender firm papules or nodules which may be sensitive to pressure or cold [7]. They predominantly occur on the trunk and limbs, along the lines of Blaschko, or adopting linear, segmental or zosteriform patterns [7]. The age-related prevalence of cutaneous leiomyomas in HLRCC is 78% to age 75, occurring at a mean age of 45.9 years [6]. Around 73% of patients with multiple piloleiomyomas harbour a detectable pathogenic variant in FH, whilst single, vascular (angioleiomyomas) and genital leiomyomas are not usually associated with HLRCC [7]. Cutaneous leiomyosarcoma has been reported in five individuals with HLRCC to date [8, 9].

Uterine leiomyomas (fibroids) develop in approximately 31–77% of individuals [6, 9] and are more likely to be multiple, to occur at a younger age (mean 33.8 versus 45.4 years) and to require surgical intervention with myomectomy or hysterectomy, than their sporadic counterparts [10]. Phaeochromocytomas and paragangliomas represent a rare association with HLRCC [9].

Renal tumours in HLRCC are typically unilateral and aggressive in nature, tending to present with advanced disease and early metastases [6]. Although historically described as type 2 papillary renal cell carcinomas, a range of morphologies is now recognised, including unspecified papillary, tubulo-papillary, tubular, tubulocystic and collecting duct tumours [6, 9, 11], and the WHO criteria 2016 recognise HRLCC-associated renal cancer as its own pathological entity [12]. The lifetime risk of HLRCC-associated renal cancer is 15–21% [6], with a mean age of diagnosis of 44 years, although the youngest reported case to date is age 7 [13].

Birt-Hogg-Dubé Syndrome

Birt-Hogg-Dubé syndrome (BHDS) occurs due to heterozygous pathogenic variants in the tumour suppressor gene *folliculin* (*FLCN*) [14]. BHDS is characterised by cutaneous manifestations, lung cysts, spontaneous pneumothoraces, renal cysts and renal tumours [15]. Penetrance is estimated at 90–95%, although the expression may be variable even within families [15, 16].

Dermatological features consist of fibrofolliculomas, trichodiscomas, acrochordons (skin tags) and perifollicular fibromas [17]. These benign skin lesions occur in 48% of individuals [18], arising between the second and fourth decades [15]. The most common skin feature, fibrofolliculomas, occur in 90% and appear as multiple pale or flesh-coloured papules predominantly on the nasal and paranasal areas, neck and trunk [15, 16]. Fibrofolliculomas are benign tumours of the hair follicle and may form part of the same histological spectrum as trichodiscomas and perifollicular fibromas [19]. Less commonly, angiofibromas, oral papules, cutaneous collagenomas and multiple epidermal cysts may be seen [15].

Non-dermatological features include lung cysts in 92% with lower lung predominance and a disproportionate number of paramediastinal cysts [15, 18, 20]. BHDS is a common cause of familial spontaneous pneumothorax, with this complication occurring in 51% of individuals with BHDS, at a mean age of 34 years (range 10–78 years), and sometimes multiple times [18, 21].

Renal tumours in BHDS may be unilateral, multifocal or bilateral and occur in around 34% of individuals [16]. These represent a range of histological subtypes, including oncocytic/chromophobe hybrid tumours, renal oncocytoma, chromophobe, oncocytoma, clear cell carcinoma, hybrid clear cell-chromophobe or papillary renal cell carcinomas [18]. Estimates of the prevalence of renal tumours in BHD vary and may be subject to ascertainment bias, but a recent systematic review found a malignant renal tumour prevalence of 22.5% in 929 patients with BHDS who underwent abdominal imaging with a median age of onset of 47 years (range 14–83 years) [18].

Cowden Syndrome

Cowden syndrome (CS) occurs due to pathogenic variants in the *PTEN* tumour suppressor gene [22] and forms part of a spectrum of related disorders collectively known as *PTEN* hamartoma tumour syndromes, which include Bannayan-Riley-Ruvalcaba syndrome (BRRS), *PTEN*-related proteus and proteus-like syndromes [23]. The phenotype in CS is

broad and variable and includes cutaneous, neurological, gastrointestinal and genitourinary manifestations in addition to increased cancer risk [24]. Clinical diagnostic criteria are divided into pathognomonic, major and minor features, and a clinical scoring system, available at http://www.lerner.ccf.org/gmi/ccscore/, has been proposed to indicate patients suitable for Clinical Genetics referral [23, 24]. Estimates of the prevalence of 1 in 200,000 likely underestimate the true prevalence due to the variable phenotype [23].

Cutaneous features are common, overall occurring in 98% of individuals [25], and identifiable in 90% of individuals by the second decade [26]. Four cutaneous features predominate: trichilemmomas, oral papillomas, acral keratoses and mucocutaneous neuromas [23]. Trichilemmomas are benign hamartomas which originate in the outer root sheath of the hair follicle and occur in 6–38% of patients [25, 27]. They occur as multiple flesh-coloured papules of up to 5 mm diameter, predominantly on the face and neck [28]. Oral papillomas are asymptomatic 1–3 mm papules which arise on the lips, buccal mucosa, gingivae and tongue and occur in up to 15–85% of patients. Lesions that coalesce may adopt a 'cobblestone' appearance [28]. Acral keratoses are flesh-coloured, hyperkeratotic 'wart-like' papules that tend to occur on the dorsum and palmo-plantar surfaces of the hands and feet and affect up to 10–82% of individuals with CS [24, 25, 27]. Mucocutaneous neuromas represent hamartomas of the peripheral nerve sheath and appear as painful flesh-coloured or pink papules on the face, hands, trunk and shins [28]. Penile freckling occurs in 19–46% of males with PTHS [24, 25], although this may be seen in 15% in the general population and in other genetic conditions, such as Carney, LEOPARD and Peutz-Jegher syndromes [28]. Lipomas and vascular malformations may also be seen.

Non-dermatological features include cerebellar dysplastic gangliocytoma (also known as adult Lhermitte-Duclos disease), macrocephaly (occipito-frontal circumference (OFC) ≥ 97th centile), intellectual disability, fibrocystic breast disease, benign thyroid disease (particularly multinodular goitre and adenoma), hamartomatous gastrointestinal polyps, genitourinary malformations, uterine fibroids and fibromas [23, 29].

Individuals with CS have an increased risk of a range of cancers, including breast, endometrial, epithelial thyroid, renal cell carcinoma (RCC), colorectal cancer and melanoma [30]. Female breast cancer risk is the highest, at 50% by age 50 years and 85% lifetime risk. Epithelial thyroid cancer lifetime risk is around 35% and typically of follicular histology [30], and lifetime endometrial cancer risk is around 28% [30]. Lifetime risks of RCC, colorectal cancer and melanoma are 35%, 9% and 6%, respectively [30].

Gorlin Syndrome

Gorlin syndrome (GS), also known as nevoid basal cell carcinoma syndrome or basal cell nevus syndrome, is caused by pathogenic variants in the *PTCH1*, or less commonly, the *SUFU* gene. Clinical features are broad, and clinical diagnosis rests on the presence of combinations of major and minor diagnostic criteria [31].

Prevalence has been estimated at just under 1 in 31,000, although actual prevalence may be higher due to the underdiagnosis of individuals with mild phenotypes [32]. In a study of 72 families in which individuals met clinical diagnostic criteria for GS, the pathogenic variant detection rates were 60% and 4% for *PTCH1* and *SUFU*, respectively, whilst in 36% of families, no causative variant was identified [33]. GS occurring due to *PTCH1* is highly penetrant, although it may be less so when caused by *SUFU* pathogenic variants [34], and expression of clinical features varies both within and between affected families.

Around 90% of individuals with GS develop BCCs, which originate from basal cell nevi or on otherwise normal skin [31, 34]. Common sites include the face, nape of the neck, back and chest [35]. Over a lifetime, some individuals develop hundreds to thousands of BCCs whilst others have relatively few. Risk factors include type 1 skin, excessive sun exposure or prior radiation therapy, and the presence of other genetic risk modifiers, such as the p.(Arg151Cys) *MCR1* risk allele and *TERT-CLPTM1L* (rs401681) risk alleles, both of which increase the risk of sporadic BCC [36]. The median age of onset is 33 years (range 4–76 years) [36], and the cumulative incidence is 13.7% and 12% by age 20 in males and females, respectively, and 80% and 76.5% by age 80 [35]. Histologically, they appear as typical BCCs, and metastasis is rare [35]. The other major cutaneous feature is the presence of two or more pits on the palms or soles of the feet, which appear as pin-prick or punched-out lesions [34]. Other skin findings can include eyelid meibomian cysts, sebaceous and dermoid cysts and skin tags [34].

Non-dermatological features include the development of jaw keratocysts in around 90%, which can arise in childhood, although occurrence peaks in the teenage years and is uncommon after age 30. They may be identified as translucency on routine orthopantograms, painless swellings or with complications such as dental disruption or jaw fracture [34]. Rarely, these can transform into malignant ameloblastomas [37]. Falx calcification occurs in 90% of affected individuals by 20 years of age and may also adopt a lamellar distribution [34]. Other features include macrocephaly (OFC ≥ 97th centile), lympho-mesenteric or pleural cysts, cleft lip or palate, radiographic evidence of

congenital rib (bifid, splayed, extra) or vertebral anomalies, polydactyly (pre- or post-axial), eye anomalies including cataracts, other developmental anomalies or pigmentary changes of the retinal epithelium [34]. Other frequently noted features include developmental delay and a recognisable facial gestalt with frontal bossing, pouting lower lip, coarse facial features and facial milia around the eyes, nose and malar regions [34, 38].

Tumour risks in GS include childhood medulloblastoma (also known as primitive neuroectodermal tumours or PNET), ovarian and cardiac fibromas and meningiomas. *SUFU*-related medulloblastoma and meningioma risks are 33% and 22%, respectively, both higher than the *PTCH1*-related risks of < 2% and 1.6%, respectively [33, 39]. Medulloblastoma risk peaks in early childhood (one to two years) and has a favourable prognosis [34]. Ovarian fibromas also occur more commonly in *SUFU*-related GS (43% compared to 6% in *PTCH1*-related GS) and may be bilateral, presenting as an incidental finding or with ovarian torsion [33, 34]. Cardiac fibromas occur in 2–3% and are usually present in infancy as an asymptomatic incidental finding, or as a cause of cardiac outflow obstruction or arrhythmia [31, 34].

Peutz-Jegher Syndrome

Peutz-Jegher syndrome (PJS) occurs due to heterozygous pathogenic variants in the *STK11* gene. The pathogenic variant detection rate is 60–100% in patients meeting clinical diagnostic criteria which have been proposed by Beggs et al. [40, 41]. Clinical features include intestinal polyps, characteristic mucocutaneous pigmentation and a high lifetime risk of cancer [42]. Prevalence estimates of PJS are broad, ranging from 1 in 25,000–280,000, and although PJS displays complete penetrance, variable expression of clinical features can be seen [42].

Dermatological findings consist of benign melanocytic macules arising in early childhood, initially dark blue-brown in colour and which fade as the individual approaches puberty and adulthood [42]. Macules occur in up to 95% of individuals and arise on the lips, mouth (including the buccal mucosa), nostrils, peri-anal region, fingers, toes and the dorsal and plantar surfaces of the hands and feet [40].

Individuals with PJS have an increased risk of predominantly hamartomatous small intestine polyps occurring (in order of frequency) in the jejunum, ileum and duodenum. Polyps may also occur in the stomach and large intestine and at extra-intestinal sites including the renal pelvis, bladder, ureters, gallbladder, nostrils and lungs [42]. Intussusception secondary to polyps is common and occurs in around 69% at a median age of 16 years [43]. Other presentations of polyps can include anaemia, GI bleeding, rectal prolapse and bowel obstruction [42].

The overall cancer risk in PJS is 85% by age 70 years [44], although this may be an overestimate due to ascertainment bias and the rarity of PJS [41]. Cancer risk includes both intestinal and non-intestinal malignancies. Amongst the highest risk is female breast cancer, affecting 19–54% [44, 45]. Colorectal, gastric and small bowel cancers occur in 39%, 29%, and 13%, respectively [45], whilst pancreatic cancer occurs in 11–55% [46, 47]. Overall gynaecological cancer risk is 18–50% by age 50, the most common of which is cervical adenocarcinoma (principally adenoma malignum), followed by ovarian (typically sex cord tumours with annular tubules, SCTAT) and uterine cancers [41]. Lung and testicular cancers may also occur [42].

Familial Atypical Multiple Mole Melanoma Syndrome

Familial atypical multiple mole melanoma syndrome (FAMMM) occurs due to pathogenic variants in either the *CDKN2A* or *CDK4* gene and describes the association of multiple melanocytic naevi (typically > 50 with multiple atypical nevi) with the presence of specific histological features and a family history of cutaneous malignant melanoma [48]. Overall, *CDKN2A*-associated-FAMMM accounts for 39% of cases in families with at least 3 melanoma, and melanoma risk is 60–90% by age 80 [49]. However, internationally, pathogenic variant detection rates are lower in areas of high sun exposure, demonstrating that the majority of familial risk in melanoma-prone families is accounted for by shared skin type and similar sun exposure patterns [49]. Intermediate genetic risk modifiers, such as variants in *MCR1* and *MITF*, have also been implicated [50]. Pathogenic variants in *CDK4* occur in a hotspot within codon 24 and, although highly penetrant with a 74% melanoma risk by age 50, account for a minority of families with FAMMM [51]. Superficial spreading and nodular melanomas are the most common melanoma subtypes seen in FAMMM, but histology is otherwise similar to sporadic melanoma cases [52].

Individuals with *CDKN2A*-related FAMMM are also at increased risk of pancreatic cancer, with a 17% risk to age 75 [53], although significant genotype–phenotype correlations have been identified in association with common *CDKN2A* pathogenic variants, such that the risk ranges from < 11 to > 60% [52].

BAP1 Tumour Predisposition Syndrome

BAP1 tumour predisposition syndrome (BAP1-TPDS) occurs due to pathogenic variants in *BAP1* and comprises a tumour spectrum which includes uveal melanoma, malignant

mesothelioma (pleural or peritoneal), cutaneous melanoma, RCC and basal cell carcinoma, with other tumours also implicated [54, 55]. First reported in 2011, the prevalence and penetrance of related cancers is not yet well defined.

Dermatological findings include multiple *BAP1*-inactivated melanocytic tumours (also known as atypical Spitz tumours or BAPomas). These are pinkish-brown, dome-shaped papules of around 5 mm diameter, typically occurring on the head and neck, followed by the trunk, upper and lower limbs [56]. Histologically, the lesions share features of both Spitz naevi and melanoma; however, they show biallelic *BAP1* inactivation and somatic *BRAF* p.Val600Glu [55]. Cutaneous melanoma occur as the third most frequent tumour, with a median onset of 39 years compared to 58 years in the general population, and may be multiple [55].

Carney Syndrome

Carney syndrome, or Carney complex as it can also be known, is an autosomal dominant HCPS occurring due to pathogenic variants in the *PRKAR1A* gene and consists of skin pigmentary changes and tumour predisposition, particularly endocrine tumours. Diagnostic criteria have been proposed by Mateus et al. [57]. Carney syndrome is rare, and penetrance is estimated at over 95% by age 50, although two lower penetrance variants associated with a milder phenotype have been identified [58, 59]. Other genotype–phenotype correlations have also been described [60].

Cutaneous features are often the first presentation of Carney syndrome; brown-black lentigines can be present from birth and are usually present by age 20, increasing over time before fading in early middle age [57]. Lentigines occur in around 75% of individuals and can appear anywhere on the body, particularly the face (lips, conjunctiva, inner and outer canthi) and genital regions (including the vaginal and penile mucosa), varying in number from a handful to profuse pigmentation [57, 58]. Around 43% of patients have epithelioid-type blue nevi, which appear as bluish-domed papules and cutaneous myxomas (pale, pink or flesh-coloured papules or nodules) occur in around 31% of individuals [57, 58]. Typical sites for cutaneous myxoma include the eyelids, nipples and external ear canal. Whilst they tend not to occur on the hands and feet, they may appear on any other part of the body [58]. Other cutaneous features in Carney syndrome include intense freckling, café au lait macules, depigmented lesions, multiple skin tags and lipomas [57, 58].

Myxomas may arise in other sites of the body, notably the heart, breast, oropharynx, female genital tract, bony nasal sinuses and long bones (osteochondromyxomas) [58]. Cardiac myxomas can obstruct cardiac blood flow, causing chest pain, breathlessness and palpitations, systemic emboli, heart failure and sudden death, and can occur in childhood [58, 61]. Other non-endocrine tumours include breast ductal adenomas and the nerve sheath tumour, psammomatous melanotic schwannoma, which occurs in around 10% and can arise at any site in the central or peripheral nervous system [58].

Endocrine tumours include primary pigmented nodular adrenocortical disease (PPNAD), which occurs in around 25%, usually presenting in the 20 s or 30 s and causes symptoms of ACTH-independent hypercortisolism [58]. Around 10% of adults develop acromegaly secondary to growth-hormone secreting adenomas [58]. Large-cell calcifying Sertoli cell tumours (LCCSCT) may develop before the age of 10 and are common in adult men, where they may be bilateral and multicentric. Although non-malignant, they may cause symptoms secondary to hormone secretion such as gynaecomastia in pre-pubertal boys [58]. Around three-quarters of individuals with Carney syndrome will have multiple thyroid nodules, particularly non-functioning thyroid follicular adenomas. Papillary and follicular thyroid carcinomas may also be seen [58].

Multiple Endocrine Neoplasia Type 1

Multiple endocrine neoplasia type 1 (MEN1) occurs due to pathogenic variants in the *MEN1* gene and increases susceptibility to a range of endocrine and non-endocrine tumours. Prevalence is 1 in 10,000–100,000, and penetrance is high [62, 63].

Cutaneous tumours include facial angiofibromas (in up to 85%), collagenomas (up to 70%) and lipomas (up to 30%) [62, 63]. The presence of three or more angiofibromas with any collagenomas gives a diagnostic sensitivity of 75% and specificity of 95% [64]. Café au lait macules, hypopigmented macules and gingival papules are also described [63].

Endocrine tumours may present with multi-systemic signs and symptoms depending on the underlying histology and associated hormone secretion. Parathyroid tumours, for example, which occur in 90–100% of affected individuals, typically present with hypercalcaemia secondary to primary hyperparathyroidism and are multi-glandular in nature [62, 63]. Endocrine tumours of the gastro-entero-pancreatic tract occur in 40–70% and include gastrinoma (in up to 40% of affected individuals), insulinoma, non-functioning and pancreatic polypeptide-secreting tumours, and rarely, glucagonomas and vasoactive intestinal polypeptidomas [62]. Anterior pituitary tumours occur in 30–40% and are most commonly prolactinoma or growth-hormone secreting, although other hormone secreting and non-functioning tumour types are recognised. Carcinoid and adrenocortical tumours also occur [63]. Meningioma and ependymoma are amongst the non-endocrine tumours described [63].

Multiple Endocrine Neoplasia Type 2B

Multiple endocrine neoplasia type 2B (MEN2B) occurs as part of a spectrum of endocrine tumour predisposition syndromes caused by pathogenic variants in the *RET* gene and which also include multiple endocrine neoplasia type 2A (MEN2A) and familial medullary thyroid carcinoma (FMTC).

Cutaneous features of MEN2B consist of mucosal neuromas on the tongue, palate, pharynx, and lips and neuromas of the eyelids [65].

The major risk in MEN2B is of medullary thyroid cancer, which occurs in up to 100% of affected individuals, often in early childhood, and is associated with aggressive disease and early mortality without prophylactic thyroidectomy in infancy [66]. Around one-half of individuals develop phaeochromocytoma, which may be multiple and bilateral [66]. Other features include a Marfanoid appearance, prominent corneal nerve fibres, tearless crying (alacrima) and diffuse intestinal ganglioneuromatosis [67]. A significant genotype–phenotype correlation has been identified in MEN2B [65].

APC-associated Polyposis

APC-associated polyposis syndromes occur due to pathogenic variants in the *APC* gene and comprise familial adenomatous polyposis (FAP), attenuated FAP and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [68].

Cutaneous features include lipomas (55%), fibromas (48%) and epidermal cysts (26%), and multiple pilomatricomas have also been described [68, 69]. Cutaneous manifestations have a low diagnostic sensitivity such that their significance should be interpreted in the context of other APC-associated features [69]. Non-cutaneous extra-intestinal features consist of osteomas (especially of the skull and mandible), dental anomalies (supernumerary or congenitally absent teeth, odontomas, dentigerous cysts and odontomas), desmoid tumours and multiple or bilateral regions of congenital hypertrophy of the retinal pigment epithelium [68].

The most prominent feature of FAP (and attenuated FAP to a lesser degree) is the presence of multiple colonic polyps which predispose to a high risk of colorectal cancer. Extra-colonic malignancy risks include small bowel cancer (duodenal and peri-ampulla), papillary thyroid carcinoma (typically cribriform-morular variant) and hepatoblastoma, with increased relative risks of medulloblastoma, pancreatic and gastric cancer [68].

Lynch Syndrome

Lynch syndrome (LS) is an autosomal dominant HCPS caused by pathogenic variants in the genes *MLH1*, *MSH2*, *MSH6* or *PMS2*, or deletions in the *EPCAM* gene. LS is relatively common, with an overall prevalence estimate of 1 in 279 [70]. Individuals with biallelic pathogenic variants in *MLH1*, *MSH2*, *MSH6* or *PMS2* develop constitutional mismatch repair deficiency (CMMRD), which has a very high risk of childhood-onset malignancy (largely haematological, central nervous system and gastrointestinal-type cancers) and a range of non-malignant features, notably multiple hyperpigmented and hypopigmented macules [71].

Individuals with LS have significantly increased risks of colorectal and endometrial cancer compared to the general population and increased risks of other cancers to varying degrees (depending on the implicated gene) including ovarian, gastric, small intestine, biliary tract, brain, skin, pancreatic and prostate cancer [72].

Skin features consist of sebaceous tumours including sebaceous adenomas, epitheliomas, carcinomas and keratoacanthomas and are found in 1–9% of affected individuals [72]. The combination of sebaceous tumours and Lynch-related cancers is also known as Muir Torre syndrome (MTS). Immunohistochemistry of mismatch repair proteins is poorly diagnostic of LS when performed in sebaceous tumours due to its high false positive rate; therefore, the Mayo MTS risk score has been proposed to indicate those patients requiring further evaluation [73].

In-person Consultations for Suspected Genodermatosis-associated HCPS

Where there is suspicion of an HCPS, patients should be referred to their local Clinical Genetics department for further assessment. The Covid-19 pandemic has necessarily seen a shift towards remote (telephone or video) appointments across medical specialities to minimise face-to-face contact. In some respects, Cancer Genetics lends itself well to remote consultations as many assessments can be completed without a physical examination, with high reported patient satisfaction levels and the advantages of reduced travel time and costs [74]. However, the inability to perform a physical examination in genodermatoses is a source of clinician dissatisfaction [75] and may represent a lost opportunity to identify subtle cutaneous or other physical cues indicative of a genodermatosis-associated HCPS.

Based on our clinical experience, we propose criteria (Box 1), which could be used at the point of triage for patients newly referred to Cancer Genetics services to identify those

with possible genodermatosis-associated HCPS who would benefit from a physical examination. We recommend that these patients, where possible, are offered an in-person consultation.

Conclusions

We have described the presenting malignant and non-malignant features of the major adult-onset genodermatosis-associated HCPS, with a focus on cutaneous features, to highlight to genetic and non-genetic clinicians the important diagnostic clues indicative of an HCPS. We acknowledge that these are a varied and diagnostically challenging group, yet early diagnosis can provide opportunities for tumour prevention for the patient and the wider family. In recognition of the challenges of the Covid-19 pandemic in limiting face-to-face patient contact, we have proposed criteria for offering in-person Cancer Genetics consultations for patients with suspected genodermatosis-associated HCPS. These criteria aim to maximise the diagnostic potential of clinical services whilst maintaining the benefits of remote appointments where appropriate.

Box 1 Proposed Criteria for In-Person Consultations in Possible Genodermatosis-Associated Hereditary Cancer Predisposition Syndromes (HCPS)

Criteria adapted from the National Genomic Test Directory (October 2021) [76].

- Patients with suspected or confirmed dermatological features of HCPS
- Personal history of cancer and intellectual disability (IQ ≤ 75)/macrocephaly (OFC ≥ 97th centile)/facial dysmorphism/congenital anomaly/consanguinity
- Personal history of
  - young onset renal cancer (diagnosed < 40 years)
  - type 2 papillary, HLRCC-associated renal cell carcinoma, tubulo-papillary renal cancer, bilateral or multifocal renal cancer (any age)
  - renal cancer and spontaneous pneumothorax or phaeochromocytoma /paraganglioma
  - uterine leiomyomata < 40 years with classic histological features of hereditary leiomyomatosis and renal cell carcinoma
  - multiple spontaneous pneumothoraces or characteristic radiological features of Birt-Hogg-Dube syndrome on chest imaging
  - cerebellar dysplastic gangliocytoma
  - thyroid goitre < 18 years
  - jaw keratocyst
  - lamellar calcification of the falx, or falx calcification < 20 years
  - SHH (sonic hedgehog)-associated medulloblastoma
  - cardiac or ovarian fibroma
  - Peutz-Jegher-type hamartomatous intestinal polyps
  - adenoma malignum of cervix or sex cord tumours with annular tubules
  - uveal melanoma
  - personal history of malignant mesothelioma and a first-degree relative with malignant mesothelioma, uveal melanoma or BAPoma
  - myxoma (including cutaneous, mucosal, cardiac, breast myxomatosis or osteochrondromyxoma)
  - primary pigmented nodular adrenocortical disease (PPNAD)
  - large-cell calcifying Sertoli cell tumours
  - psammomatous melanotic schwannoma
  - pituitary adenoma (< 20 years) or macroadenoma (< 30 years), or family history of pituitary adenoma (< 35 years)
  - primary hyperparathyroidism (< 35 years or < 45 with positive family history)
  - endocrine tumour of the gastro-entero-pancreatic tract
  - thymic or bronchial carcinoid
  - diffuse intestinal ganglioneuromatosis
  - alacrima (absent tears)
  - lip and/or tongue neuromas
  - desmoid tumour
  - multiple osteomas
  - children/young adults with multiple dental abnormalities, e.g. unerupted teeth, supernumerary teeth with dentigerous cysts or odontomas
  - multiple or bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
  - cribriform-morular variant papillary thyroid cancer
  - hepatoblastoma
- Personal history of renal cancer and a first/second degree relative with renal cancer
- Personal and family history of spontaneous pneumothorax

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Declarations

Conflict of Interest The authors declare no competing interests.

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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