Syndrome	Cancers	Benign or preneoplastic alterations
Hereditary paraganglioma-pheochromocytoma syndrome (HPPS)	Paragangliomas and/or Pheochromocytomas (up to 41%) Gastrointestinal stromal tumors (GISTs) (2-more than 5%; GIST are more common than paragangliomas/pheochromocytomas in SDHA pathogenetic variant) Renal clear cell carcinoma (2-5%) Papillary thyroid carcinoma **(R)** Neuroendocrine tumors **(R)**	Paragangliomas and/or Pheochromocytomas (up to 64%) Pulmonary chondromas Adrenal cortical adenoma Esophageal leiomyoma Pituitary adenomas **(R)**
Carney Complex (CNC)	Thyroid carcinoma (papillary, follicular)(typically at young age) Psammomatous melanotic schwannoma (PMS) Ovarian endometrioid carcinoma **(R)** Testicular cancer **(R)**	Skin pigment abnormalities: - Pale brown to black lentigines on skin and mucosa (typical on lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa) - Epithelioid-type blue nevi - Combined nevi - Café au lait macules - Depigmented lesions Myxomas: - Myxomas of skin, cardiac, breast, oropharynx, cervix, uterus, vagina - Osteochondromyxoma (nasal sinuses and long bones) Endocrine dysregulation: - Primary pigmented nodular adrenocortical disease (PPNAD)(causing Cushing syndrome) - Growth hormone (GH)-producing pituitary adenoma - Testicular tumors (Large-cell calcifying Sertoli cell tumors (LCCSCT), Leyding cell tumors, nodular adrenocortical rest)(may produce hormones) - Thyroid follicular adenomas (often nonfunctioning) Psammomatous melanotic schwannoma (PMS) Breast ductal adenoma Ovarian cysts, serous cystadenoma, teratomas
Neurofibromatosis type 1 (NF1)	Malignant peripheral nerve sheath tumors (MPNSTs) and/or Gliomas (optic nerve, brain/spinal cord) (33%) Gastrointestinal Stromal Tumors (GISTs) (6%) Pheochromocytoma and/or paragangliomas (0.24%) Rhabdomyosarcoma (RMS) Breast Cancer (often estrogen receptor negative and human epidermal growth factor receptor 2 (HER-2) positive) Juvenile myelomonocytic leukemia **(R)**	Cutaneous Features: - Café au lait macules - Intertriginous freckling (e.g., axillary, inguinal) - Plexiform/Nodular neurofibromas - Juvenile xanthogranuloma - Nevus anemicus Ocular findings:

	Neuroendocrine tumors **(R)** Melanoma **(R)** Ovarian cancer **(R)** Hodgkin lymphoma **(R)**	- Optic Pathway Gliomas (OPGs) - Lisch nodules (iris hamartomas) - Choroidal freckling - Retinal vasoproliferative tumors **(R)** - Neovascular glaucoma **(R)** Neurologic manifestations: - Cognitive deficits - Learning disabilities - Sleep disturbance - Autism spectrum disorders - Seizures (usually not attributable to a mass lesion in the brain) - Macrocephaly - Peripheral neuropathy - Multiple nerve root tumors - Low-grade astrocytomas - Brainstem gliomas - Cerebellar gliomas - Glomus Tumors Musculoskeletal Features: - Sphenoid wing dysplasia - Long bones dysplasia (tibia and fibula) - Pseudoarthrosis - Short stature - Scoliosis (dystrophic or nondystrophic type) - Nonossifying fibromas - Vertebral dysplasia - Reduced muscle strength - Osteopenia Vascular involvement: - Essential Hypertension - Vasculopathy (renal artery stenosis, coarctation of the aorta, Stenotic/ectatic cerebral arteries, cerebrovascular abnormalities) Cardiac Issues:

		- Valvular pulmonic stenosis - Congenital heart defects - Hypertrophic cardiomyopathy - Pulmonary Hypertension (often in association with parenchymal lung disease) Pheochromocytomas and/or paragangliomas (1.76%) Irritable bowel syndrome
Neurofibromatosis type 2 (NF2)	Ependymomas and gliomas **(R)** Malignant peripheral nerve sheath tumors (MPNSTs) **(R)**	Vestibular schwannomas (bilateral) Ependymomas Cranial, spinal, and peripheral nerves schwannomas Meningiomas (most intracranial, but also intradural, extramedullary spinal meningiomas) Neuropathies: - Mononeuropathy (facial nerve) - Polyneuropathy Ophthalmic manifestations: - Cataracts - Optic nerve meningiomas - Retinal hamartomas - Epiretinal membrane Cutaneous manifestations: - Plaque-like lesions - Subcutaneous nodules - Intracutaneous tumors (mostly schwannomas, but also neurofibromas)
Schwannomatosis (SCHW)	Schwannomas **(R)** *(malignant transformation of schwannomas remains a theoretic risk)* Malignant peripheral nerve sheath tumors (MPNSTs) **(R)** Rhabdoid tumors **(R)**	Schwannomas of the peripheral/spinal/subcutaneous nerves Schwannomas of the cranial nerves (trigeminal nerve) **(R)** Unilateral vestibular schwannomas (bilateral vestibular schwannoma is an exclusion criterion) Meningiomas (SMARCB1 variants) Pain (in the majority of patients, pain does not correlate with a discrete mass)
Multiple endocrine neoplasia type 1 (MEN1)	Neuroendocrine tumors (gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma, nonfunctioning) (90%) Breast cancer (33%) Carcinoid (thymic, bronchial, Type II gastric enterochromaffin-like carcinoid) (25%)	Parathyroid adenoma (hormone secreting) Pituitary adenomas (prolactinomas, growth hormone, TSH rare, ACTH, nonfunctioning)

	Adrenocortical carcinomas (cortisol-secreting, aldosterone-secreting) **(R)** Pheochromocytoma **(R)** Thyroid carcinomas **(R)**	Adrenocortical Tumors: - Cortical adenomas - Cortical hyperplasia - Multiple adenomas - Nodular hyperplasia - Cysts - Pheochromocytoma **(R)** Skin findings: - Facial angiofibromas - Collagenomas - Lipomas - Café au lait macules - Confetti-like hypopigmented macules - Multiple gingival papules Central nervous system tumors: - Meningioma - Ependymoma Leiomyomas Thyroid adenomas, thyroid colloid goiters
Multiple Endocrine Neoplasia type 2 (MEN2A)	Medullary carcinoma of the thyroid (MTC) (up to 90%) Pheochromocytoma **(R)**	Parathyroid adenoma/ hyperplasia C-cell hyperplasia (CCH) Pheochromocytoma (upto to 88%) Cutaneous lichen amyloidosis **(R)** Hirschsprung disease (HSCR)
Multiple Endocrine Neoplasia type 2 (MEN2B)	Medullary carcinoma of the thyroid (MTC) (up to 100%) Pheochromocytoma **(R)**	C-cell hyperplasia (CCH) Pheochromocytoma (up to 50%) Mucosal neuromas (lips, tongue, pharynx, palate) Submucosal nodules (lips) Distinctive facies with enlarged lips Ganglioneuromatosis of the gastrointestinal tract Marfanoid habitus
Familial medullary thyroid carcinoma (FMTC)	Medullary carcinoma of the thyroid (MTC)	C-cell hyperplasia (CCH) Hirschsprung disease (HSCR)
Multiple Endocrine Neoplasia type 4 (MEN4)	Neuroendocrine tumors (gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma, nonfunctioning) (25%, unknown the malignant component)	Parathyroid adenoma (hormone secreting)

	Carcinoid Adrenocortical carcinomas (cortisol-secreting, aldosterone-secreting) **(R)** Testicular cancer **(R)** Thyroid carcinomas **(R)** Pheochromocytoma **(R)**	Pituitary adenomas (prolactinomas, growth hormone, TSH rare, ACTH, nonfunctioning) (25%, unknown the malignant component) Adrenocortical Tumors: - Cortical adenomas - Cortical hyperplasia - Multiple adenomas - Nodular hyperplasia - Cysts - Pheochromocytoma **(R)**
Hyperparathyroidsm-jaw tumor syndrome (HPT-JT)	Parathyroid carcinoma (23%) Uterine tumors Wilms tumor **(R)**	Parathyroid adenoma Jaw tumors: ossifying fibromas of the maxilla and/or mandible (Cementifying fibromas / cemento-ossifying fibromas) Kidney cysts, renal hamartoma Benign uterine tumors Mixed epithelial-stromal tumors **(R)** Adult mesoblastic nephroma **(R)**
Parathyroid carcinoma syndrome (PC)	Parathyroid carcinomas (generally secreting) (23%)	None
HOXB13-hereditary cancer syndrome (HOXB13)	Prostate cancer (33%)	None
NBN-hereditary cancer syndrome (NBN)	Breast cancer Prostate cancer Melanoma Medulloblastoma Non-Hodgkin Lymphoma Colorectal cancer	None
Njimegen Breakage Syndrome (NBS)	T cell and B cell lymphomas Medulloblastoma Glioma Rhabdomyosarcoma	Disproportionate microcephaly Craniofacial features ("bird-like face"): - a sloping forehead - upward slanted palpebral fissures - prominent nose - relatively large ears - retrognathia Immunodeficiency (agammaglobulinemia) → recurrent infections Autoimmune diseases (e.g., immune thrombocytopenia and hemolytic anemia, childhood sarcoidosis, lymphocytic interstitial pneumonitis)

		Growth retardation and short stature Decline in intellectual ability Hypergonadotropic hypogonadism (in female: primary ovarian insufficiency) Skin: Café-au-lait spots Depigmented skin lesions Porokeratosis Cutaneous noncaseating granulomas Clinodactyly and syndactyly Choanal atresia Cleft lip and palate Hydronephrosis Gastrointestinal tract stenosis/atresia Hip dysplasia Tracheal hypoplasia **(R)** Preaxial or postaxial polydactyly **(R)** Horseshoe kidney **(R)** Hypospadias **(R)** Anomalies of the central nervous system: **(R)** - hydrocephaly - schizencephaly - arachnoid cysts
Von Hippel Lindau Syndrome (VHLS)	Renal cell carcinoma (clear cell subtype) (80%) Pheochromocytoma **(R)** (30%, unknown the malignant percentage) Pancreatic neuroendocrine tumors (12%, unknown the malignant percentage) Endolymphatic sac tumors **(R)** (4%, unknown the malignant percentage)	CNS hemangioblastomas Retinal capillary hemangioblastomas (retinal angiomas) Multiple and bilateral renal cysts Pheochromocytoma Paragangliomas Endolymphatic sac tumors of the middle ear Pancreatic serous cystadenomas Epididymal and broad ligament cystoadenomas ***VHL type 1****. Retinal angioma, CNS hemangioblastoma, renal cell carcinoma, pancreatic cysts, and neuroendocrine tumors. VHL type 1 is characterized by a low risk for pheochromocytoma.*

		VHL type 2*. Pheochromocytoma, retinal angiomas, and CNS hemangioblastoma. VHL type 2 is characterized by a high risk for pheochromocytoma.* - *Type 2A. Pheochromocytoma, retinal angiomas, and CNS hemangioblastoma; low risk for renal cell carcinoma* - *Type 2B. Pheochromocytoma, retinal angiomas, CNS hemangioblastoma, pancreatic cysts, and neuroendocrine tumors; high risk for renal carcinoma* - *Type 2C. Risk for pheochromocytomas only*
Hereditary papillary renal carcinoma syndrome (HPRC)	Type 1 papillary renal cell cancer (multifocal, bilateral)	
Hereditary leiomyomatosis and renal cancer cell syndrome (HLRCC)	Renal cancer (type 2 papillary renal cell cancer, collecting duct renal cell carcinoma **(R)**, clear cell renal cell carcinoma **(R)**, Wilm's tumor **(R)**) (19%) Cutaneous leiomyosarcoma **(R)** Uterine leiomyosarcoma **(R)** Leydig cell tumors **(R)** Gastrointestinal stromal tumors (GIST) **(R)** Breast cancer **(R)**	Cutaneous leiomyomas Uterine leiomyomas Ovarian cystadenomas **(R)** Pheochromocytoma **(R)** Paraganglioma **(R)**
Tuberous Sclerosis Complex (TSC)	Brain cancer (malignant transformation of subependymal giant cell tumors) (up to 90%) Renal cell carcinoma, malignant angiomyolipomas (4%) Rhabdomyosarcoma **(R)**	Skin: - Hypomelanotic macules - Confetti skin lesions - Facial angiofibromas - Shagreen patches - Fibrous cephalic plaques - Ungual fibromas Central Nervous System: - Cortical glioneuronal hamartomas - Cortical dysplasias - Subependymal nodules (SENs) - Subependymal giant cell astrocytomas (SEGAs) Seizures Developmental delay Intellectual disability Neuropsychiatric Disorder:

		- Autism spectrum disorder (ASD) - Attention deficit hyperactivity disorder (ADHD) - Learning and cognitive impairment - Disruptive behaviors and emotional problems (anxiety, depression) Kidneys: - Benign angiomyolipoma - Lymphangiomas - Renal cysts - Oncocytoma (benign adenomatous hamartoma) Cardiac rhabdomyomas Lung: - Lymphangioleiomyomatosis (LAM) - Multifocal micronodular pneumonocyte hyperplasia (MMPH) Retinal lesions (hamartomas) Extrarenal angiomyolipomas (AMLs) (hepatic AMLs)
Birt-Hogg-Dubé syndrome (BHD)	Kidney cancer (19%) - Hybrid oncocytic/chromophobe tumor - Chromophobe tumor - Oncocytoma - Clear cell carcinoma - Papillary carcinoma **(R)** - Mixed-type carcinoma **(R)** Colon cancer **(R)** Cutaneous melanoma (including multiple desmoplastic melanomas) and choroidal melanoma **(R)** Parotid **(R)** Thyroid cancer **(R)** Parathyroid cancer **(R)** Basal cell carcinoma **(R)**	Cutaneous manifestations: - Fibrofolliculomas - Skin tags (acrochordons) - Angiofibromas - Oral papules - Cutaneous collagenomas - Multiple epidermal cysts - Koenen's tumor **(R)** - Trichoblastoma Soft tissues: - Angiolipoma **(R)** - Leiomyoma **(R)** - Lipoma **(R)** - Fibroadenomatosis **(R)**

	Squamous cell carcinoma **(R)** Dermatofibrosarcoma protuberans **(R)** Sarcomas **(R)** Gastric cancer **(R)** Peritoneal mesothelioma **(R)** Head & neck cancer **(R)** Oncocytic adrenal tumor **(R)** Lymphoma & leukemia **(R)** Lung cancer **(R)** Neuroendrocine tumors **(R)** Prostate cancer **(R)** Breast cancer **(R)** Uterine cancer **(R)**	Muscoskeletal: - Cardiac rhabdomyoma **(R)** - Osteoma **(R)** - Rhabdomyoma **(R)** Lungs: - Lung cysts - Spontaneous pneumothorax - Clear cell sugar tumor **(R)** Multifocal renal oncocytosis Renal angiomyolipoma **(R)** Colon polyps **(R)** Warthin parotid tumor Thyroid nodules/cysts Parathyroid adenoma **(R)** Adrenal adenoma **(R)** Pheochromocytoma **(R)** Hepatic cysts or angioma **(R)** Nervous system: - Astrocytoma **(R)** - Cerebral hemangioma **(R)** - Meningioma **(R)** - Neurothekeoma **(R)** - Oncocytic pituitary adenoma **(R)** - Schwannoma **(R)**
Li-Fraumeni syndrome (LF)	Adrenocortical carcinomas (ACC) (.7%) Breast cancer (ductal, ER+, PR+, HER2+, malignant phyllodes tumors of the breast) (85% in female) Nervous system cancer (glioblastoma, astrocytoma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, choroid plexus carcinomas) (30%)) Sarcomas (osteosarcoma, soft-tissue sarcoma (e.g., rhabdomyosarcoma)) (60%)	Colorectal polyps

	Hematologic cancer (leukemia (ALL, AML), myelodysplastic syndrome (MDS), Hodgkin and non-Hodgkin lymphomas) Gastrointestinal cancer (colorectal cancer up to 24%, gastric cancer up to 16%) Cancers of the head and neck Kidney cancers Lung cancers Skin cancers Ovary cancers Pancreas cancers Testis cancers Thyroid cancers Gestational choriocarcinoma (The pregnant mother of a fetus heterozygous for a paternally inherited TP53 pathogenic variant is at risk for choriocarcinoma or another gestational trophoblastic disease)	
Bloom syndrome (BSyn)	Leukemia (AML, ALL) Non-Hodgkin lymphoma Myelodysplasia Oropharyngeal tumors Upper GI tumors Colorectal carcinoma Genitourinary tumors Skin carcinomas Breast carcinoma Wilms tumor Lung tumors	Habitus: - Proportionate small stature - Mild microcephaly - Keel-shaped face - Malar hypoplasia - Nasal prominence - Small mandible - Protuberant ears - Absence of upper lateral incisors Skin: - Sparse, subcutaneous adipose tissue - Erythematous rash on the nose and cheeks (sun-sensitive facial erythema) - Café-au-lait spots - Hypopigmented skin lesions - Cheilitis - Blistering and fissuring of the lips - Eyebrow and eyelash hair loss - Alopecia areata - Vesicular and bullous lesions Infertility in men (hypogonadism) Premature menopause in women (premature menopause)

		Immunodeficiency Variable intellectual impairment Diabetes mellitus Gastroesophageal reflux Chronic obstructive pulmonary disease
Familial GIST (fGIST)	GISTs	Hyperpigmentation (KIT) Urticaria pigmentosa (KIT) Dysphagia (KIT) Gastrointestinal autonomic nerve tumors (paragangliomas) (KIT) Intestinal fibromatosis (PDGFRA) Inflammatory fibroid polyps (PDGFRA) Large hands (PDGFRA)
BRCA1- and BRCA2-associated hereditary cancer syndrome (BRCA1/2)	Breast cancer (in females: 72% BRCA1, 69% BRCA2, in males: 1.2% BRCA1, 7% BRCA2) Ovarian cancer (44% BRCA1, 17% BRCA2) Fallopian tube and primary peritoneal cancers **(R)** (2% BRCA1, 1% BRCA2) Prostate cancer (29% BRCA1, 60% BRCA2) Pancreatic cancer (16% BRCA1, 13.7% BRCA2) Gastric cancer (21.3% BRCA1, 19.3% BRCA2) Biliary tract (11.2% BRCA1) Esophageal (5.2% BRCA2) **(R)** Cutaneous and ocular melanoma (BRCA2) **(R)** Colon cancer **(R)** Lung cancer **(R)**	Ovarian cysts
CHEK2-associated hereditary cancer syndrome (CHEK2)	Breast cancer (30%) Colon cancer **(R)** Prostate cancer **(R)** Gastric cancer **(R)** Renal cancer **(R)** Thyroid cancer **(R)** Sarcoma **(R)** Leukemia and plasma cell neoplasm **(R)**	
PALB2-associated hereditary cancer syndrome (PALB2)	Breast cancer (53%) Pancreatic cancer (3%) Ovarian cancer **(R)** (5%)	
RAD51c-associated hereditary cancer syndrome (RAD51c)	Ovarian cancer (11%) Breast cancer (21%)	

RAD51d-associated hereditary cancer syndrome RAD51d)	Ovarian cancer (13%) Breast cancer (20%)	
ATM-associated hereditary cancer syndrome (ATM) Ataxia telangiectasia (AT)	**Heterozygosis** Pancreatic cancer (9.5%) Prostate cancer Gastric cancer Breast cancer (30%, c.7271T>G variant 52%) Male breast cancer Ovarian cancer Melanoma Lymphoma/leukemia **Homozygosis – classical Ataxia-teleangectasia** Lymphoma/leukemia (32%) Ovarian cancer **(R)** Breast cancer **(R)** Liver cancer **(R)** Gastric cancer **(R)** Esophageal cancer **(R)** Sarcomas **(R)**	**Heterozygosis** Coronary heart disease **Homozygosis – classical Ataxia-teleangectasia** • Serum and cellular immunodeficiency with frequent infections (recurrent sinopulmonary infections) Neurological deficits: • Progressive cerebellar ataxia with onset between ages one and four years, oculomotor apraxia, choreoathetosis • Progressively slurred speech • Extrapyramidal movement disorders • Peripheral neuropathy Telangiectasias and skin abnormalities • Oculocutaneous telangiectasias • Skin telangiectasias (pinnae, nose, face, neck) • Other (cafè-au-lait macules, hypopigmented macules, melanocytic nevi, facial papulosquamous rash) • Premature aging with strands of gray hair • Pulmonary disease (bronchiectasis, interstitial lung disease/pulmonary fibrosis) • Endocrine alterations (gonadal dysgenesis, type 2 diabetes mellitus) • Laboratory abnormalities (increase AFP, T cell lymphopenia, immunoglobulin deficiency **Non classic form of AT** Attenuated phenotype
STK11-associated hereditary cancer syndrome (STK11)	Colorectal cancer (39%) Gastric cancer (29%) Small bowel cancer (13%) Pancreatic cancer (26%) Breast cancer (32-54%) Ovarian cancer (mostly sex cord tumor with annular tubules) (21%)	Multiple gastrointestinal hamartomatous polyps and in extraintestinal sites (bronchus, nasal passages, gall bladder, renal pelvis, urinary bladder, and ureters). Multiple melanocytic macules in lips, buccal mucosa, and digits.

	Adenoma malignum of the cervix (10%) Uterus cancer (9%) Sertoli cell tumors (9%) Lung (7-17%)	Men: occasionally large calcifying Sertoli cell tumors (LCST) of the testes, with consequent gynecomastia, advanced skeletal age, and ultimately short stature, due estrogen secretion
BARD1-associated hereditary cancer syndrome (BARD1)	Breast cancer (15-40%) Colon cancer **(R)** Ovarian cancer **(R)**	
BRIP1- associated hereditary cancer syndrome (BRIP1)	Ovarian cancer (4-13%) Breast cancer **(R)**	
Fanconi Anemia	Myelodysplastic syndrome/leukemia (80%) Lymphoid malignancies (acute lymphoid leukemia, Burkitt lymphoma) **(R)** Skin cancer (squamous cell carcinoma, basal cell carcinoma) Head & neck cancer (squamous cell carcinoma) Esophageal cancer Vulvar cancer Anal cancer (squamous cell carcinoma) Liver cancer Kidney cancer Brain cancer Breast cancer Testis/ovarian cancer (germ cell tumors) **(R)** Sarcomas **(R)** PALB2/BRCA2 Medulloblastoma Wilms tumor	Classical congenital abnormalities the VACTERL-H (Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal atresia, Renal, upper Limb and Hydrocephalus) association. Physical Findings: • Endocrine disorders: hypothyroidism, hyperglycemia/ impaired glucose tolerance, diabetes, and insulin resistance • Skin pigmentation alterations: café au lait macules, generalized hyperpigmentation, hypopigmentation • Growth deficiency: prenatal and/or postnatal short stature, low birth weight • Skeletal malformations of upper limbs, unilateral or bilateral: o Thumbs: absent, triphalangeal, proximally placed, bifid, duplicated, long, hypoplastic o Radii: absent or weak pulse, absent or hypoplastic (only with abnormal thumbs) o Hands: absent first metacarpal, flat thenar eminence, polydactyly, clinodactyly o Ulnae: short, dysplastic o Lower limbs: congenital hip dislocation, syndactyly, abnormal toes, club feet o Facial features: mid-face hypoplasia, triangular face shape, micrognathia o Spine anomalies: spina bifida, scoliosis, hemivertebrae, rib anomalies, coccygeal aplasia o Neck anomalies: sprengel deformity, Klippel-Feil anomaly, short or webbed neck, low hairline • Microcephaly

		• Ophthalmic alterations: strabismus, microphthalmia, hypertelorism, ptosis, cataracts, astigmatism, epicanthal folds, hypotelorism
		• Developmental Delay / Intellectual Disability
		• Genitourinary tract anomalies:
		  ○ Rena: hypoplastic, dysplastic, horseshoe, ectopic, pelvic, or absent kidney; hydronephrosis or hydroureter
		  ○ Males: hypospadias, cryptorchidism, anorchia, micropenis, hypo- or azoospermia, reduced fertility
		  ○ Females: small ovaries, bicornuate or uterus malposition
		• Hearing loss. Usually conductive secondary to middle-ear bony anomalies with or without additional ear anomalies (e.g., dysplastic auricle, narrow ear canal, abnormal pinna)
		• Congenital heart defect: atrial septal defect, patent ductus arteriosus, coarctation of the aorta, ventricular septal defect, truncus arteriosus, situs inversus
		• Gastrointestinal: imperforate anus, tracheoesophageal fistula, esophageal, duodenal, or jejunal atresia, annular pancreas, malrotation
		• Central nervous system: cerebellar hypoplasia, hydrocephalus, dilated ventricles, small pituitary, pituitary stalk interruption syndrome, absent corpus callosum
		
		<u>Bone Marrow Failure</u>:
		• Thrombocytopenia or leukopenia usually precede anemia, commonly associated with macrocytosis and elevated fetal hemoglobin
		• Pancytopenia
		• Sweet syndrome (neutrophilic skin infiltration)
		• Bone marrow failure

Familial atypical multiple mole melanoma (FAMMM)	<u>Melanoma (28-67%)</u> Pancreatic cancer (adenocarcinoma) (17%) Astrocytoma (loss of both p14 and p16) Breast cancer **(R)** Lung, head & neck, gastroesophageal cancer (in smokers) **(R)**	Total body nevi count > 50 Multiple atypical nevi
Nevoid basal cell carcinoma (NBCC)	<u>Basal cell carcinomas (90%)</u> Medulloblastoma (SUFU 33% - PTCH1 <2%) Rhabdomyosarcoma **(R)**	Jaw odontogenic keratocyst Palmar and plantar pits Intracranial ectopic calcification Meningiomas

		Craniofacial anomalies (macrocephaly, frontal bossing, hypertelorism) Vertebral/rib anomalies Cleft lip/palate Polydactyly Cardiac or ovarian fibromas Lymphomesenteric or pleural cysts Ocular anomalies (congenital cataracts, coloboma, strabismus, hyperthelorim, telecanthus) Fetal rhabdomyoma
Xenoderma pigmentosus (XP)	Skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma) (65%) Oral cancer Sarcoma (angiosarcoma, fibrosarcoma, and pyogenic granuloma of oral cavity) Myelodysplastic syndrome, acute myeloid leukemia, and acute lymphoblastic leukemia **(R)** Colorectal cancer **(R)** Non-small cell lung cancer **(R)** Glioma **(R)** Uterine cancer **(R)** Breast cancer **(R)** Pancreatic cancer **(R)** Stomach cancer **(R)** Kidney cancer **(R)** Testicle cancer **(R)** Thyroid cancer **(R)**	Sun sensitivity (severe sunburn with blistering, persistent erythema, xerosis, and poikiloderma on minimal sun exposure, Sunlight-induced ocular involvement such as photophobia, keratitis, atrophy of the skin of the lids) Eye anomalies (ectropion, lagophtalmos, conjunctival melanosis, corneal neovascularization, corneal scarring, prerygium) Marked freckle-like pigmentation of the face Neurologic manifestations (progressive sensorineural hearing loss, acquired microcephaly, progressive cognitive impairment, and diminished or absent deep tendon stretch reflexes) Premature menopause
BAP1 tumor predisposition syndrome (BAP1)	Uveal melanoma (36%) Cutaneous melanoma (12-45%) Malignant mesothelioma (25%) Renal cell carcinoma (10%) Basal cell carcinoma Cholangiocarcinoma **(R)** (1.4%) Hepatocellular carcinoma **(R)** (0.7%) Breast cancer **(R)** Lung cancer **(R)** Sarcoma **(R)** Neuroendocrine tumors **(R)**	Multiple cutaneous melanocytic neoplasms called "BAP1-inactivated melanocytic tumors" (BIMTs; melanocytomas) Meningioma

	Thyroid cancer **(R)**	
Shelterin complex genes hereditary cancer syndrome (Shelterin)	Chronic lymphocytic leukemia Glioma Melanoma Angiosarcoma (cardiac angiosarcoma) Colorectal cancer **(R)** Thyroid cancer **(R)**	None
TERT hereditary cancer syndrome (TERT)	Acute myeloid leukemia/chronic lymphocytic leukemia Cutaneous melanoma Pancreatic cancer Lung cancer Basal cell carcinoma Head & neck cancer Anogenital cancer Bladder cancer **(R)** Prostate cancer **(R)** Cervical cancer **(R)** Glioma **(R)**	Dyskeratosis congenita: Developmental delay, short stature, microcephaly, osteoporosis, avascular necrosis of femur/humerus Blepharitis, epiphora Periodontal disease, taurodontism, decreased teeth/root ratio Esophageal stenosis, urethral stenosis Premature hair greying/alopecia, abnormal eyelashes Pulmonary fibrosis, pulmonary arteriovenous malformations Gastrointestinal teleangiectasias Liver disease
MC1R polymorphism (MC1R)	Cutaneous melanoma Squamous cell carcinoma **(R)** Basal cell carcinoma **(R)**	Red hair/fair skin
MITF (E318K) polymorphism	Cutaneous melanoma Uterine carcinosarcoma **(R)** Renal cancer **(R)** Pheochromocytoma/paraganglioma **(R)** Pancreatic cancer **(R)**	None
DICER1	Pleuropulmonary blastoma (up to 50%) Ovarian sex cord-stromal tumor (10%) Medulloepithelioma (3%) Differentiated thyroid carcinoma **(R)** Eembryonal rhabdomyosarcoma of the cervix **(R)** Centran nervous system cancers (pituitary blastoma, pineoblastoma, sarcomas, presacral malignant teratoid tumor, other embryonal tumors) **(R)**	Macrocephaly Retinal abnormalities Multinodular goiter Cystic nephroma Abnormal of the collecting system of the kidney Nasal chondromesenchymal hamartoma Dental anomalies
Lynch syndrome (LS),	Colorectal cancer (CRC) (MLH1 44-53%, MSH2 42-46%, MSH6 12-20%, PMS2 3%, EPCAM 75%)	Skin tumors (sebaceous neoplasms, keratoacanthomas)

Hereditary nonpolyposis colorectal cancer (HNPCC)	Endometrial cancer (EC) (MLH1 35%, MSH2 46%, MSH6 41%, PMS2 13%, EPCAM 12%) Ovarian cancer (endometrioid) (MLH1 11%, MSH2 17%, MSH6 11%, PMS2 3%) Gastric cancer (GC) (mostly intestinal-type adenocarcinoma, rarely diffuse type) and small bowel cancer (duodenum and jejunum adenocarcinomas) (MLH1 8-16%, MSH2 10-16%, MSH6 2-4%, PMS2 4%) Urinary tract cancer (transitional carcinomas of the ureter, renal pelvis, kidney, and bladder cancer) (MLH1 5%, MSH2 16%, MSH6 6%) Skin cancers (sebaceous carcinomas)(<9%) Pancreatic cancer Prostate cancer (MLH1 7%, MSH2 16%, MSH6 5%, PMS2 5%) Brain (usually glioblastoma; astrocytoma, oligodendroglioma)(1-4%) Breast cancer **(R)** Adrenocortical carcinomas **(R)** Laryngeal cancer **(R)** Hematologic malignancies **(R)** Sarcomas **(R)**	Adenomas of the colon (mostly with high grade dysplasia and/or villous histology)
RPS20-associated hereditary nonpolyposis colorectal cancer syndrome (RPS20)	Colorectal cancer	
Familial adenomatous polyposis (FAP)	Colorectal cancer (often <40) (>95%) Duodenal and periampullary cancer (<12%) Brain tumors (Turcot syndrome): medulloblastoma, ependymomas and high-grade astrocytoma (1%) Thyroid papillary carcinoma (<12%) Hepatoblastoma (<1%) Pancreatic cancer (1%) Gastric cancer (1%) Desmoid tumors (30%)	Adenomatous polyposis (>100 colon and rectum polyps) Extracolonic manifestations (Gardner syndrome): - Gastric fundic gland polyps - Duodenal adenomas - Congenital hypertrophy of the retinal pigment epithelium (CHRPE) - Juvenile nasopharyngeal angiofibromas - Osteomas, fibromas - Dental abnormalities: supernumerary teeth, odontomas - Epidermoid or sebaceous cysts - Benign thyroid nodules
Attenuated familial adenomatous polyposis (AFAP)	Colorectal cancer (> 40 years) Thyroid cancer Duodenal cancer	Adenomatous polyposis (10-100 polyps, frequently right sided) Upper GI findings similar to FAP Other extraintestinal manifestations are unusual:

		- Congenital hypertrophy of the retinal pigment epithelium (CHRPE) **(R)** - Juvenile nasopharyngeal angiofibromas **(R)** - Osteomas, fibromas **(R)** - Dental abnormalities: supernumerary teeth, odontomas **(R)** - Desmoid tumors **(R)** - Epidermoid or sebaceous cysts **(R)** - Benign thyroid nodules **(R)**
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	Gastric cancer (intestinal gastric type adenocarcinoma)	Gastric fundic gland polyps (restricted to body and fundus of the stomach)
Polymerase proofreading-associated polyposis (PPAP)	Colorectal cancer (mostly MSS) (30-60%) Duodenal cancer Endometrial cancer Ovarian cancer Brain cancer Breast cancer	Colonic adenomas (0-100 cumulative polyps) Duodenal adenomas MDPL syndrome (mandibular hypoplasia, deafness, progeroid features & lipodystrophy) (POLD1)
MUTYH associated polyposis (MAP)	Colorectal cancer (mostly MSS) (86%) Duodenal cancer (4%) Ovarian cancer (14%) Bladder cancer (6-25%) Endometrial cancer (3%) Gastric cancer (R) (1%) Kyndey cancer **(R)** Breast cancer **(R)** (<25%) Skin cancer **(R)** Thyroid cancer **(R)** Pancreatic cancer **(R)**	Colonic adenomas (10->100 cumulative polyps) Colonic hyperplastic and/or serrated polyps Gastro-duodenal adenomas Benign adrenal lesions Thyroid nodules Jawbone cysts Osteomas Congenital hypertrophy of the retinal pigment epithelium (CHRPE) Desmoid tumors Epidermoid or sebaceous cysts
NTHL1 tumor syndrome (NTHL1)	Colorectal cancer Breast cancer Duodenal cancer Endometrial cancer Cervical cancer Urothelial carcinoma of the bladder Brain cancer Basal cell carcinoma Head and neck squamous cell carcinomas Hematologic malignancies	Colonic adenomas (1-100 cumulative polyps) Hyperplastic and/or serrated polyps Duodenal adenomas Meningiomas Skin hemangiomas **(R)** Seborrheic keratosis **(R)**, intradermal nevi **(R)** Ovarian and hepatic cysts **(R)** Breast papillomas **(R)**

MSH3-associated polyposis (MSH3)	Colorectal cancer Gastric cancer Astrocytoma	Colonic adenomas (10->100 cumulative polyps) Duodenal adenomas Thyroid adenomas Mammary intraductal papillomas and cysts
MLH3-associated polyposis (MLH3)	Colorectal cancer Breast cancer	Colonic adenomas (10->100 cumulative polyps)
Juvenile polyposis syndrome (JPS)	Colorectal cancer (40%) Gastric cancer (21%) Small bowel cancer **(R)** Pancreatic cancer **(R)**	Hamartomatous gastrointestinal polyps Hereditary hemorrhagic telangiectasia or vascular abnormalities Cardiac abnormalities Skeletal and cranial abnormalities
Hereditary mixed polyposis syndrome (HMPS)	Colorectal cancer Duodenal adenocarcinoma **(R)** Prostate cancer **(R)**	Adenomatous polyps, juvenile polyps, hyperplastic polyps, and polyps containing mixed histology Desmoid tumor **(R)**
RNF43-associated serrated polyposis (RNF43), Sessile serrated polyposis cancer syndrome (SSPCS)	Colorectal cancer	Colonic serrated polyposis (0->100 cumulative polyps)
Cowden Syndrome (CS)	Breast cancer (30%) Epithelial thyroid cancer (usually follicular, rarely papillary, never medullary) (>10%) Genitourinary cancer (especially renal cell carcinoma) (10%) Endometrial cancer (10%) Colorectal cancer **(R)** (9%) Melanoma **(R)** (6%)	Cerebellar dysplastic gangliocytoma (Adult Lhermitte-Duclos disease) Intracranial vascular malformations Macrocephaly, intellectual disabilities, autism Mucocutaneous lesions: trichilemmomas (facial), acral keratoses, papillomatous lesions, mucocutaneous neuromas Benign lesions of thyroid (adenoma, multinodular goiter) Colorectal and gastrointestinal polyps (often hamartomas) Esophageal glycogen acanthosis Fibrocystic disease of the breast Lipomas, fibromas, macular pigmentation of the glans penis Genitourinary malformation Ttesticular lipomatosis Uterine fibroids
Hereditary diffuse gastric cancer syndrome (HDGC)	Gastric cancer (signet ring cancer/diffuse gastric cancer) (33-70%) Breast cancer (lobular histology) (42%) Colorectal cancer **(R)**	Cleft lip/palate **(R)**

Hereditary pancreatitis (HP)	Pancreatic cancer	Acute and chronic pancreatitis Sinusitis, respiratory symptoms, male infertility, constipation (CFTR)
Howel-Evans syndrome (HE)	Esophageal cancer (squamous cell carcinoma)	Palmoplantar keratoderma (tylosis) Leukoplakia
EGFR-associated genetic susceptibility	Lung cancer	

Supplementary Table S1. Detailed list of features associated with hereditary cancer syndromes. Underlined = a typical feature; (R) = rarely associated or weakly supported by scientific literature; (xxx%) = lifetime risk. Sources: Pubmed, Web of Science, GeneReview, UptoDate, Omim, EviQ Genetics.