eAppendix. Genes With Full Coding Exonic Regions Included in 309-Gene Tumor Testing Panel With Known Hereditary Disorders That May Present in Adulthood[a]

Gene	Hereditary Disorder (OMIM No.)	Mode of inheritance	Clinical Features
ABL1	Congenital heart defects and skeletal malformations syndrome (617602)	AD	Atrial and ventricular septal defects, with aortic root dilation in adulthood. Skeletal defects are variable and include pectus excavatum, scoliosis, and finger contractures, and some patient exhibit joint laxity. Failure to thrive is observed during infancy and early childhood.
AKT1	Proteus syndrome (176920)	Somatic mosaicism	Mosaicism for a somatic activating mutation in the *AKT1* gene; a highly variable, severe disorder of asymmetric and disproportionate overgrowth of body parts, connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular malformations.
	Cowden syndrome, type 6 (615109)	AD	A hamartomatous disorder characterized by macrocephaly, facial trichilemmomas, acral keratoses, papillomatous papules, and an increased risk for breast, thyroid, endometrial and other cancers.
ACVRL1 *ALK*	Hereditary hemorrhagic telangiectasia type 2 (600376)	AD	Vascular dysplasia leading to telangiectases and arteriovenous malformations of skin, mucosa, and viscera. Epistaxis and gastrointestinal bleeding are frequent complications of mucosal involvement.
ALOX12B	Congenital ichthyosis-2 (242100)	AR	A heterogeneous group of disorders of keratinization characterized primarily by abnormal skin scaling over the whole body. These disorders are limited to skin, with approximately two-thirds of patients presenting severe symptoms.
AMER1	Osteopathia striata with cranial sclerosis (300373)	XLD	Osteopathia striata with cranial sclerosis is an X-linked dominant sclerosing bone dysplasia that presents in females with macrocephaly, cleft palate, mild learning disabilities, sclerosis of the long bones and skull, and longitudinal striations visible on radiographs of the long bones, pelvis, and scapulae. In males, the disorder is usually associated with fetal or neonatal lethality.

APC	Familial adenomatous polyposis-1 (175100)	AD	Predisposition to cancer. Affected individuals usually develop hundreds to thousands of adenomatous polyps of the colon and rectum, a small proportion of which will progress to colorectal carcinoma if not surgically treated. Gardner syndrome is a variant of FAP in which desmoid tumors, osteomas, and other neoplasms occur together with multiple adenomas of the colon and rectum. There is also an attenuated polyposis.
AR	Androgen insensitivity syndrome (300068)	XLR	Affected males have female external genitalia, female breast development, blind vagina, absent uterus and female adnexa, and abdominal or inguinal testes posing testicular cancer risk, despite a normal male 46,XY karyotype.
	Spinal and bulbar muscular atrophy, also known as Kennedy disease (313200)	XLR	A form of spinal muscular atrophy in men. Age at onset is usually in the third to fifth decade of life, but earlier involvement has been reported. The disorder is characterized by slowly progressive limb and bulbar muscle weakness with fasciculations, muscle atrophy, and gynecomastia. Due to expansion of CAG repeat in exon 1.
AR *BRCA2* *CHEK2* *CDH1*	Prostate cancer, susceptibility to (176807)	AD	Predisposition to prostate cancer.
ATM	Ataxia-telangiectasia (208900)	AR	Characterized by cerebellar ataxia, telangiectases, immune defects, and a predisposition to malignancy. Chromosomal breakage is a feature. Heterozygotes have increased risk for breast and pancreatic cancers.
ATR	Seckel syndrome (210600)	AR	Characterized by intrauterine growth retardation, dwarfism, microcephaly with mental retardation, and a characteristic 'bird-headed' facial appearance
	Familial cutaneous telangiectasia and cancer syndrome (614564)	AD	Cutaneous telangiectasia, mild developmental anomalies of hair, teeth, and nails, and a predisposition to cancer, predominantly oropharyngeal cancer.

ATM *BARD1* *PALB2* *BRCA2* *BRIP1* *CDH1* *CHEK2* *RAD51*	Familial breast cancer (114480)	AD	Breast cancer predisposition.
BAP1	Tumor predisposition syndrome (614327)	AD	At high-risk for the development of a variety of tumors, including benign melanocytic tumors as well as several malignant tumors, including uveal melanoma, cutaneous melanoma, malignant mesothelioma on exposure to asbestos, and other cancer types, such as lung adenocarcinoma, meningioma, and renal cell carcinoma.
BCOR	Syndromic microphthalmia-2 (300166)	XLD	Consists of (1) eye anomalies (congenital cataract, microphthalmia, or secondary glaucoma); (2) facial abnormalities (long narrow face, high nasal bridge, pointed nose with cartilages separated at the tip, cleft palate, or submucous cleft palate); (3) cardiac anomalies (atrial septal defect, ventricular septal defect, or floppy mitral valve); and (4) dental abnormalities (canine radiculomegaly, delayed dentition, oligodontia, persistent primary teeth, or variable root length). They suggested that inheritance might be X-linked dominant, lethal in the male.
BCORL1	Shukla-Vernon syndrome (SHUVER) (301029)	XLR	Neurodevelopmental disorder characterized by global developmental delay, variably impaired intellectual development, and behavioral abnormalities, including autism spectrum disorder and ADHD. Dysmorphic features are common and may include tall forehead, downslanting palpebral fissures, and tapering fingers. Some patients may have seizures and/or cerebellar atrophy on brain imaging. Carrier mothers may have mild manifestations, including learning disabilities.
BRAF	LEOPARD syndrome 3	AD	An acronym for the manifestations of this syndrome: multiple lentigines,

	(613707)		electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness.
	Noonan syndrome 7 (613706)	AD	A developmental disorder characterized by reduced postnatal growth, dysmorphic facial features, cardiac defects, and variable cognitive defects.
BRCA1, BRCA2, RAD51C	Familial breast-ovarian cancer (604370)	AD	Increased risk for early-onset breast cancer, bilateral breast cancer, male breast cancer, ovarian cancer.
BRCA1	Fanconi anemia complement group S (617883)	AR	Characterized by developmental delay apparent from infancy, short stature, microcephaly, and coarse dysmorphic features. Laboratory studies show defective DNA repair and increased chromosomal breakage during stress.
BRCA2	Fanconi anemia complement group D1 (605724)	AR	Developmental delay apparent from infancy, short stature, microcephaly, and coarse dysmorphic features. Laboratory studies show defective DNA repair and increased chromosomal breakage during stress.
BRIP1	Fanconi anemia complement group J (609054)	AR	Genetically heterogeneous disorder that causes genomic instability. Characteristic clinical features include developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer.
BTK	X-linked agammaglobulinemia (300755)	XLR	An immunodeficiency characterized by failure to produce mature B lymphocytes and associated with a failure of Ig heavy chain rearrangement.
CDC73	Familial isolated hyperparathyroidism-1 (145000)	AD	Hypercalcemic disorder caused by inappropriate over-secretion of parathyroid hormone (PTH) from parathyroid adenomas, hyperplasia, and carcinomas.
	Hyperparathyroidism-jaw tumor syndrome (145001)	AD	Synchronous or metachronous occurrence of primary hyperparathyroidism, ossifying fibroma of the maxilla and/or mandible, renal tumor, and uterine tumors. It is associated with increased risk of parathyroid cancer.

CDH1	Blepharocheilodontic syndrome-1 (119580)	AD	Characterized by lower eyelid ectropion, upper eyelid distichiasis, euryblepharon, bilateral cleft lip and palate, and conical teeth. An additional rare manifestation is imperforate anus.
	Hereditary diffuse gastric cancer (137215)	AD	A cancer predisposition syndrome. Mutation carriers have a 70 to 80% lifetime risk of developing diffuse gastric cancer. In addition to gastric cancer, up to 60% of female mutation carriers develop lobular carcinoma of the breast, and some carriers may develop colorectal cancer. The characteristic microscopic foci of signet ring cell adenocarcinoma usually involves the submucosa and is often not readily detectable by routine upper endoscopy screening.
CDKN1B	Multiple endocrine neoplasia, type IV (610755)	AD	Combinations of tumors of parathyroids, pancreatic islets, duodenal endocrine cells, and the anterior pituitary, with 94% penetrance by age 50. Less commonly associated tumors include foregut carcinoids, lipomas, angiofibromas, thyroid adenomas, adrenocortical adenomas, angiomyolipomas, and spinal cord ependymomas.
CDKN2A	Familial atypical multiple mole melanoma-pancreatic carcinoma syndrome (606719)	AD	Inherited cancer predisposition syndrome in which mutation carriers have an increased risk of developing malignant melanoma and/or pancreatic cancer.
	Melanoma-astrocytoma syndrome (155755)	AD	Increased risk for cutaneous malignant melanoma, cerebral astrocytoma, or both.
CHEK2	Li-Fraumeni syndrome 2 (609625)	AD	Inheritance and early onset of tumors, multiple tumors within an individual, and multiple affected family members. The most common tumor types are soft tissue sarcomas and osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma.
	Susceptibility to breast and colorectal cancer (604373)	AD, AR	Predisposition to breast and colorectal cancer.
CARD11	Immunodeficiency 11A (615206)	AR	Primary immunodeficiency characterized by normal numbers of T and B lymphocytes, but defective intracellular signaling. There is a block in B-cell differentiation with increased numbers of transitional B cells and

			hypogammaglobulinemia, as well as decreased numbers of regulatory T cells and defects in T-cell function.
	Immunodeficiency 11B (617638)	AD	Immunodeficiency with atopic dermatitis.
CASP8	Caspase-8 deficiency (607271)	AR	A syndrome of lymphadenopathy and splenomegaly, marginal elevation of 'double-negative T cells' (DNT; T-cell receptor alpha/beta+, CD4-/CD8-), defective FAS-induced apoptosis, and defective T-, B-, and natural killer (NK)-cell activation, with recurrent bacterial and viral infections.
CBL	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia (615563)	AD	Resembles Noonan syndrome and characterized by facial dysmorphism, a wide spectrum of cardiac disease, reduced growth, variable cognitive deficits, and ectodermal and musculoskeletal anomalies. There is extensive phenotypic heterogeneity and variable expressivity. There is an increased risk for certain malignancies, particularly juvenile myelomonocytic leukemia.
CD70	Lymphoproliferative syndrome-3 (618261)	AR	Early-onset immunologic disorder characterized by increased susceptibility to Epstein-Barr virus (EBV) infection in B cells, resulting in abnormal B-cell proliferation and increased susceptibility to B-cell malignancies, including Hodgkin lymphoma. Patients usually have hypogammaglobulinemia without lymphopenia, although some subsets of immune cells may be low and some patients may have recurrent infections.
CD79A, *CD79B*	Agammaglobulinemia-3, 6 (613501)	AR	A primary immunodeficiency characterized by profoundly low or absent serum antibodies and low or absent circulating B cells due to an early block of B-cell development.
CDK4 *MITF*	Cutaneous malignant melanoma 3, 8, 9 (155600)	AD	Malignant melanoma is a neoplasm of pigment-producing cells called melanocytes that occurs most often in the skin, but may also occur in the eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes.
CCND1	Colorectal cancer	AD	Colorectal cancer is a heterogeneous disease that is common in both men and women. In

TP53	(114500)		addition to lifestyle and environmental risk factors, gene defects can contribute to an inherited predisposition to CRC. CRC is caused by changes in different molecular pathogenic pathways, such as chromosomal instability, CpG island methylator phenotype, and microsatellite instability. Chromosome instability is the most common alteration and is present in almost 85% of all cases.
CSF1R	Brain abnormalities, neurodegeneration, and dysosteosclerosis (BANDDOS) (618476)	AR	Characterized by brain abnormalities, progressive neurologic deterioration, and sclerotic bone dysplasia similar to dysosteosclerosis. The age at onset is highly variable: some patients may present in infancy with hydrocephalus, global developmental delay, and hypotonia, whereas others may have onset of symptoms in the late teens or early twenties after normal development.
	Hereditary diffuse leukoencephalopathy with spheroids (HDLS) (221820)	AD	Adult-onset rapidly progressive neurodegenerative disorder characterized by variable behavioral, cognitive, and motor changes.
CSF3R	Severe congenital neutropenia-1 (202700)	AD	A heterogeneous disorder of hematopoiesis characterized by a maturation arrest of granulopoiesis at the level of promyelocytes with peripheral blood absolute neutrophil counts below 0.5 x 10(9)/l and early onset of severe bacterial infections.
	Severe congenital neutropenia-7 (617014)	AR	Immunodeficiency characterized by onset of recurrent infections in infancy or early childhood. Patients have peripheral neutropenia, although bone marrow biopsy shows normal granulocyte maturation. The neutropenia is not responsive to treatment with G-CSF, but may be responsive to GM-CSF.
CTNNA1	Patterned macular dystrophy-2 (608970)	AD	Eye disease characterized by bilateral accumulation of pigment in the macular area that resembles the wings of a butterfly.
CTNNB1	Exudative vitreoretinopathy-7 (617572)	AD	Characterized by the incomplete development of the retinal vasculature. Its clinical appearance varies considerably, even within families, with severely affected patients often registered as blind during infancy, whereas

			mildly affected patients with few or no visual problems may have such a small area of avascularity in their peripheral retina that it is visible only by fluorescein angiography.
CUL3	Pseudohypoaldosteronism type IIE (PHA2E) (614496)	AD	Hyperkalemia despite normal renal glomerular filtration, hypertension, and correction of physiologic abnormalities by thiazide diuretics. Mild hyperchloremia, metabolic acidosis, and suppressed plasma renin activity are variable associated findings
CXCR4	Warts, Hypogammaglobulinemia, Infections and myelokathexis (WHIM) syndrome (193670)	AD	An immunodeficiency disease characterized by neutropenia, hypogammaglobulinemia, and extensive human papillomavirus (HPV) infection. Despite the peripheral neutropenia, bone marrow aspirates from affected individuals contain abundant mature myeloid cells, a condition termed myelokathexis.
CYP17A1	Isolated 17,20-lyase deficiency (202110)	AR	In 46,XX patients, production of excessive corticosterone and deoxycorticosterone results in hypertension, hypokalemic alkalosis, normal stature and amenorrhea. Aldosterone synthesis is almost totally absent.
DDR2	Spondylometaepiphyseal dysplasia, short limb-hand type (271665)	AR	Small stature with short limbs and short hands, a short nose with wide nasal bridge and wide nostrils, a long philtrum, ocular hypertelorism, retro/micrognathia, and a narrow chest.
EED	Cohen-Gibson syndrome (617561)	AD	An overgrowth disorder characterized by increased somatic parameters apparent from birth and associated with variable intellectual disability. Affected individuals have dysmorphic facial features, advanced bone age, and skeletal abnormalities, including flaring of the metaphyses of the long bones, large hands with long fingers and camptodactyly, and often scoliosis or cervical spine anomalies. Other features may include hypotonia, difficulty walking due to skeletal anomalies, and umbilical hernia.
EPHB4	Capillary malformation-arteriovenous malformation 2 (618196)	AD	Patients have small multifocal cutaneous capillary malformations (CMs) on the head, neck, trunk, and/or extremities, sometimes in association with arteriovenous malformations (AVMs), which are typically located in the brain, face, or extremities. Some affected individuals also exhibit Parkes Weber lesions of the

			extremities, and vein of Galen aneurysmal malformations (VGAMs) are present in some patients. Variable expressivity observed.
	Lymphatic malformation-7 (617300)	AD	Patients may develop severe nonimmune lymphatic-related hydrops fetalis (LRHF) in utero, resulting in early death, whereas others may have milder manifestations, such as atrial septal defect (ASD) or varicose veins as adults. The hydrops and/or swelling improves spontaneously in those who survive the neonatal period.
ERBB3	Lethal congenital contracture syndrome-2 (607598)	AR	Early fetal hydrops and akinesia, the Pena-Shokeir phenotype, specific neuropathology with degeneration of anterior horn neurons, and extreme skeletal muscle atrophy.
	Familial erythroleukemia (133180)	AD	A leukemic or preleukemic state in which red cell proliferation is the predominant feature. Hematologic characteristics include particularly ineffective and hyperplastic erythropoiesis with megaloblastic components accompanied by myeloblastic proliferation of varying degree. A subtype of acute myelogenous leukemia.
ERBB4	Amyotrophic lateral sclerosis-19 (615515)	AD	Classic ALS with onset between 60 and 70 years of age. Relatively slowly progressive upper and lower motor neuron involvement without cognitive impairment.
ERCC4	XFE progeroid syndrome (610965)	AR	Microcephaly, mild learning disabilities, enophthalmos, visual impairment, sun sensitivity, and a prematurely aged appearance.
	Xeroderma pigmentosum, complementation group F (278760)	AR	Sun sensitivity and increased skin sensitivity to UV light, as well as an increased risk of skin cancer associated with a defect in nucleotide excision repair (NER). The XPF form of XP is usually relatively mild compared to other forms.
	Fanconi anemia, complement group Q (FANCQ) (615272)	AR	A rare genomic instability disorder characterized by bone marrow failure, congenital malformations, hypersensitivity to DNA interstrand crosslink-inducing agents, chromosome fragility, and high susceptibility to cancer.

FANCA	Fanconi anemia, complementation group A (227650)	AR	Developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
FANCC	Fanconi anemia, complement group C (227645)	AR	Developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
FANCG (XRCC9)	Fanconi anemia, complement group G (614082)	AR	Developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
FANCL (PHF9)	Fanconi anemia, complement group L (614083)	AR	Developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
FAS	Autoimmune lymphoproliferative syndrome (ALPS) type IA (601859)	AD	A heritable disorder of apoptosis, resulting in the accumulation of autoreactive lymphocytes. It manifests in early childhood as nonmalignant lymphadenopathy with hepatosplenomegaly and autoimmune cytopenias.
FGF3	Congenital deafness with labyrinthine aplasia, microtia and microdonita (610706)	AR	Deafness with labyrinthine aplasia, microtia, and microdontia.
FGF10 *FGFR2* *FGFR3*	Lacrimoauriculodentodigital syndrome (149730)	AD	A multiple congenital anomaly disorder mainly affecting lacrimal glands and ducts, salivary glands and ducts, ears, teeth, and distal limb segments.
FGF10	Aplasia of lacrimal and salivary glands (180920)	AD	Irritable eyes, epiphora (constant tearing), and xerostomia (dryness of the mouth), which increases risk of dental erosion, dental caries, periodontal disease, and oral infections. ALSG has variable expressivity, and affected

			individuals may have aplasia or hypoplasia of the lacrimal, parotid, submandibular, and sublingual glands and absence of the lacrimal puncta. In affected individuals, the misdiagnosis is often made of the more prevalent disorder Sjogren syndrome.
FGFR1	Hypogonadotropic hypogonadism-2 with or without anosmia (147950)	AD	Characterized by absent or incomplete sexual maturation by the age of 18 years, in conjunction with low levels of circulating gonadotropins and testosterone and no other abnormalities of the hypothalamic-pituitary axis. Other associated non-reproductive phenotypes, such as anosmia, cleft palate, and sensorineural hearing loss, occur with variable frequency.
	Encephalocraniocutaneous lipomatosis (ECCL) (613001)	Somatic mosaicism	The malformations are patchy and asymmetric. The most characteristic skin anomaly is nevus psiloliparus, a well-demarcated, alopecic fatty tissue nevus on the scalp, seen in 80% of affected individuals. Other dermatologic features include frontotemporal or zygomatic subcutaneous fatty lipomas, nonscarring alopecia, focal dermal hypoplasia or aplasia of the scalp, periocular skin tags, and pigmentary abnormalities following the lines of Blaschko. Choristomas of the eye (epibulbar dermoids or lipodermoids) are also present in 80% of patients, and can be unilateral or bilateral. Characteristic CNS features include intracranial and intraspinal lipomas, seen in 61% of patients, and less often cerebral asymmetry, arachnoid cysts, enlarged ventricles, and leptomeningeal angiomatosis. A predisposition to low-grade gliomas has also been observed. Seizures and intellectual disability are common, but one-third of affected individuals have normal intellect. Skeletal manifestations include bone cysts and jaw tumors, such as odontomas, osteomas, and ossifying fibromas.
	Trigonocephaly-1 (190440)	AD	A keel-shaped forehead with wide biparietal diameter, resulting in a triangular shape of the head. Trigonocephaly results from premature closure of the metopic sutures and usually occurs sporadically.
FRFR1	Pfeiffer syndrome	AD	Craniosynostosis syndrome with characteristic anomalies of the hands and feet. Three clinical

FGFR2	(101600)		subtypes, which have important diagnostic and prognostic implications, have been identified. Type 1, the classic syndrome, is compatible with life and consists of craniosynostosis, midface deficiency, broad thumbs, broad great toes, brachydactyly, and variable syndactyly. Type 2 consists of cloverleaf skull with Pfeiffer hands and feet, together with ankylosis of the elbows. Type 3 is similar to type 2 but without cloverleaf skull. Ocular proptosis is severe, and the anterior cranial base is markedly short. Various visceral malformations have been found in association with type 3. Early demise is characteristic of types 2 and 3
FGFR2	Apert syndrome (101200)	AD	Craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet with a tendency to fusion of bony structures.
	Crouzon craniofacial dysostosis (123500)	AD	Craniosynostosis causing secondary alterations of the facial bones and facial structure. Common features include hypertelorism, exophthalmos and external strabismus, parrot-beaked nose, short upper lip, hypoplastic maxilla, and a relative mandibular prognathism
	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis (207410)	AD	Craniosynostosis syndrome characterized by radiohumeral synostosis present from the perinatal period. There is a wide spectrum of anomalies including midface hypoplasia, choanal stenosis or atresia, and multiple joint contractures. Mortality has been reported to be as high as 80% in the neonatal period, primarily due to airway compromise, and prognosis improves with increasing age.
	Jackson-Weiss syndrome (123150)	AD	Craniosynostosis characterized by premature fusion of the cranial sutures as well as radiographic anomalies of the feet.
	Saethre-Chotzen syndrome (101400)	AD	Craniosynostosis, facial dysmorphism, and hand and foot abnormalities. Coronal synostosis resulting in brachycephaly is the most frequent cranial abnormality observed, and the most common facial features are asymmetry, hypertelorism, and maxillary hypoplasia.
FGFR3	Crouzon syndrome with acanthosis nigricans	AD	Crouzon syndrome with acanthosis nigricans is considered a distinct disorder from classic

	(612247)		Crouzon syndrome caused by a highly specific mutation of the FGFR3 gene, A391E mutation.
FGF23	Hyperphosphatemic familial tumoral calcinosis-2 (617993)	AR	Metabolic disorder characterized by the progressive deposition of basic calcium phosphate crystals in periarticular spaces, soft tissues, and sometimes bone. The biochemical hallmark is hyperphosphatemia caused by increased renal absorption of phosphate due to loss-of-function mutations.
	Hypophosphatemic rickets (193100)	AD	Isolated renal phosphate wasting, hypophosphatemia, and inappropriately normal 1,25-dihydroxyvitamin D3 (calcitriol) levels. Patients frequently present with bone pain, rickets, and tooth abscesses.
FH	Hereditary leiomyomatosis and renal cell cancer (150800)	AD	Tumor predisposition syndrome characterized by the variable development of 3 tumors: cutaneous piloleiomyomata that develop in essentially all patients by age 40 years; leiomyomata (fibroids) of the uterus, and rarely leiomyosarcomas, at a mean age of 30 years (range, 18 to 52 years); and type 2 papillary renal cell carcinoma at a mean age of 46 years (range, 17 to 75 years), which occurs in about 20% of patients. Some patients may develop collecting duct renal cell carcinoma.
	Fumarase deficiency (606812)	AR	Metabolic disorder characterized by early-onset hypotonia, profound psychomotor retardation, and brain abnormalities, such as agenesis of the corpus callosum, gyral defects, and ventriculomegaly.
FLCN	Birt-Hogg-Dube syndrome (135150)	AD	Genodermatosis characterized by hair follicle hamartomas, kidney tumors, and spontaneous pneumothorax.
	Pneumothorax, primary spontaneous (173600)	AD	Isolated primary spontaneous pneumothorax.
FOXL2	Blepharophimosis, epicanthus inversus, and ptosis, types 1 and 2 (110100)	AD AR	Eyelid dysplasia, namely, small palpebral fissures (blepharophimosis), drooping eyelids (ptosis), and a tiny skin fold running inward and upward from the lower lid (epicanthus inversus). In type I BPES, the eyelid abnormalities are coinherited with ovarian

			failure; type II BPES consists of the eyelid defects only.
	Premature ovarian failure 3 (608996)	AD	Cessation of ovarian function under the age of 40 years and is characterized by amenorrhea, hypoestrogenism, and elevated serum gonadotropin concentrations.
GATA3	Hypoparathyroidism, sensorineural deafness, and renal dysplasia (146255)	AD	Hypoparathyroidism, sensorineural deafness, and renal disease (HDR), also known as Barakat syndrome.
GATA4	Atrioventricular septal defect 4, 5 (614474)	AD	A spectrum of congenital heart malformations characterized by a common atrioventricular junction coexisting with deficient atrioventricular septation. In ostium primum atrial septal defect (ASD) there are separate atrioventricular valvar orifices despite a common junction, whereas in complete AVSD the valve itself is also shared.
	Ventricular septal defect 1 (614429)	AD	Ventricular septal defect (VSD) is the most common form of congenital cardiovascular anomaly, occurring in nearly 50% of all infants with a congenital heart defect and accounting for 14 to 16% of cardiac defects that require invasive treatment within the first year of life.
GATA4 *GATA6*	Tetralogy of Fallot (187500)	AD	Heritability is about 54% and that in sibs the recurrence risk is about 1% for Fallot tetralogy and about 2% for any cardiac defect
GATA4 *GATA6*	Atrial septal defect 2, 9 (614475)	AD	Secundum atrial septal defect (ASD) is a common congenital heart malformation that occurs as an isolated anomaly in 10% of individuals with congenital heart disease.
GATA6	Pancreatic agenesis and congenital heart defects (600001)	AD	Congenital heart defects and other congenital anomalies.
GNA11	Hypocalcemia, autosomal dominant 2 (615361)	AD	Low or normal serum parathyroid hormone concentrations (PTH). Approximately 50% of patients have mild or asymptomatic hypocalcemia; about 50% have paresthesias, carpopedal spasm, and seizures; about 10% have hypercalciuria with nephrocalcinosis or kidney stones; and more than 35% have ectopic

			and basal ganglia calcifications. Gain-of-function missense mutations.
	Hypocalciuric hypercalcemia, type II (145981)	AD	Lifelong elevations of serum calcium concentrations with low urinary calcium excretion and normal circulating parathyroid hormone concentrations in most patients. Patients are generally asymptomatic, although pancreatitis or chondrocalcinosis may develop in some affected adults.
GNAQ	Congenital capillary malformations 1 (163000)	Somatic mosaicism	Capillary malformations are a form of vascular malformation that are present from birth, tend to grow with the individual, do not regress spontaneously, and show normal rates of endothelial cell turnover. Capillary malformations are distinct from capillary hemangiomas, which are highly proliferative lesions that appear shortly after birth and show rapid growth, slow involution, and endothelial hypercellularity.
	Sturge-Weber syndrome (185300)	Somatic mosaicism	Intracranial vascular anomaly, leptomeningeal angiomatosis, most often involving the occipital and posterior parietal lobes. The most common symptoms and signs are facial cutaneous vascular malformations (port-wine stains), seizures, and glaucoma. Stasis results in ischemia underlying the leptomeningeal angiomatosis, leading to calcification and laminar cortical necrosis. The clinical course is highly variable.
GNAS	Pseudohypoparathyroidism Ib (603233)	AD	Resistance to parathyroid hormone with isolated renal parathyroid hormone resistance manifesting as hypocalcemia, hyperphosphatemia, and increased serum parathyroid hormone.
	Pseudohypoparathyroidism Ia (103580)	AD	Resistance to parathyroid hormone with isolated renal parathyroid hormone resistance manifesting as hypocalcemia, hyperphosphatemia, and increased serum parathyroid hormone. Loss of function of the Gs-alpha isoform on the paternal allele.
	Progressive osseous heteroplasia (166350)	AD	Characterized by dermal ossification beginning in infancy, followed by increasing and extensive bone formation in deep muscle and fascia; loss

			of function of the Gs-alpha isoform on the paternal allele
	Pseudopseudohypoparathyroidism (612463)	AD	No resistance to parathyroid hormone or other hormones, but do manifest the constellation of clinical features referred to as Albright hereditary osteodystrophy, which includes short stature, obesity, round facies, subcutaneous ossifications, brachydactyly, and other skeletal anomalies. Some patients have mental retardation. Caused by a mutation resulting in loss of function of the Gs-alpha isoform on the paternal allele.
	Pseudohypoparathyroidism Ic (612462)	AD	Essentially identical to that of pseudohypoparathyroidism, except for retained erythrocyte Gs activity, which may result from the location of the mutation within the *GNAS* gene.
	McCune-Albright syndrome (174800)	Somatic mosaicism	classic triad of polyostotic fibrous dysplasia (POFD), cafe-au-lait skin pigmentation, and peripheral precocious puberty. However, the disorder is clinically heterogeneous and can include various other endocrinologic anomalies such as thyrotoxicosis, pituitary gigantism, and Cushing syndrome.
HNF1A	Maturity-onset diabetes of the young (MODY), type III (600496)	AD	Familial noninsulin-dependent diabetes mellitus characterized by an early age of onset (childhood, adolescence, or young adulthood under 25 years).
	Familial hepatic adenomas (142330)	AD	Familial hepatic adenomas can occur through biallelic inactivation.
HRAS *KRAS* *NRAS*	Schimmelpenning-Feuerstein-Mims syndrome (163200)	Somatic mosaicism	Also known as linear sebaceous nevus syndrome, is characterized by sebaceous nevi, often on the face, associated with variable ipsilateral abnormalities of the central nervous system, ocular anomalies, and skeletal defects.
IKZF1	Common variable Immunodeficiency 13 (616873)	AD	Primary immunodeficiency disorder characterized by recurrent bacterial infections, mainly affecting the respiratory tract, and associated with hypogammaglobulinemia and decreased numbers of B cells. The age at onset of clinical features can range from infancy to adulthood, and some patients may have a mild

			disorder or even remain clinically asymptomatic.
JAK2	Thrombocythemia 3 (614521)	AD	characterized by increased platelet production resulting in increased numbers of circulating platelets. Thrombocythemia can be associated with thrombotic episodes, such as cerebrovascular events or myocardial infarction.
JAK3	SCID, autosomal recessive, T-negative/B-positive type (600802)	AR	Defective cellular and humoral immune function. Patients with SCID present in infancy with recurrent, persistent infections by opportunistic organisms, including Candida albicans, Pneumocystis carinii, and cytomegalovirus, among many others. Laboratory analysis shows profound lymphopenia with diminished or absent immunoglobulins. The common characteristic of all types of SCID is absence of T cell-mediated cellular immunity due to a defect in T-cell development. Without treatment, patients usually die within the first year of life.
KDM5C	Mental retardation, X-linked, syndromic, Claes-Jensen type (300534)	XLR	Severe mental retardation, slowly progressive spastic paraplegia, facial hypotonia, and maxillary hypoplasia.
KDR	Hemangioma, capillary infantile (602089)	AD	Capillary hemangiomas are benign, highly proliferative lesions involving aberrant localized growth of capillary endothelium. Hemangiomas were defined as lesions that were present at birth or shortly thereafter, displayed a proliferative growth phase, and showed evidence of regression subsequent to infancy.
KIT *SDHB* *SDHC*	Familial gastrointestinal stromal tumor (606764)	AD	Gastrointestinal stromal tumors are mesenchymal tumors found in the gastrointestinal tract that originate from the interstitial cells of Cajal, the pacemaker cells that regulate peristalsis in the digestive tract. Approximately 70% of GISTs develop in the stomach, 20% in the small intestine, and less than 10% in the esophagus, colon, and rectum.
KIT	Cutaneous mastocytosis (154800)	AD	Characterized by the abnormal accumulation of mast cells in various tissues, especially in the skin and hematopoietic organs. Mastocytosis usually appears in infancy or early adulthood.

	Piebaldism (172800)	AD	Characterized by the congenital absence of melanocytes in affected areas of the skin and hair. A white forelock of hair, often triangular in shape, may be the only manifestation, or both the hair and the underlying forehead may be involved. The eyebrows and eyelashes may be affected. Irregularly shaped white patches may be observed on the face, trunk, and extremities, usually in a symmetrical distribution.
KRAS	Noonan syndrome 3 (609942)	AD	Characterized by short stature, facial dysmorphism, and a wide spectrum of congenital heart defects. The distinctive facial features consist of a broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears.
	RAS-associated autoimmune leukoproliferative disorder (614470)	AD	Characterized by lymphadenopathy, splenomegaly, and variable autoimmune phenomena, including autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and neutropenia.
MAF	Cataract 21, multiple types (610202)	AD	Multiple types of cataract, which have been described as cortical pulverulent, lamellar, nuclear, nuclear pulverulent, nuclear stellate, anterior polar, anterior subcapsular, posterior subcapsular, and cerulean. In some cases, the cataracts are of juvenile onset.
MAP3K1	46XY sex reversal 6 (613762)	AD	Individuals with 46,XY complete gonadal dysgenesis are phenotypically female; however, they do not develop secondary sexual characteristics at puberty and do not menstruate. They have bilateral 'streak gonads,' which typically consist of fibrous tissue and variable amounts of wavy ovarian stroma. A uterus and fallopian tube are present and external genitalia are female.
MDM2	Lessel-Kubisch syndrome (618681)	AR	Characterized by short stature and progeroid features, including prematurely gray hair, pinched facies, and scleroderma-like skin changes. Renal failure-associated hypertension and hypogonadism have also been observed.
MED12	Opitz-Kaveggia syndrome	XLR	Mental retardation syndrome characterized by dysmorphic features, including relative macrocephaly, hypertelorism, downslanted

	(305450)		palpebral fissures, prominent forehead with frontal hair upsweep, and broad thumbs and halluces. Most have hypotonia, constipation, and partial agenesis of the corpus callosum. Some patients have sensorineural hearing loss and joint laxity evolving into joint contractures.
	Lujan-Fryns-type of X-linked syndromic intellectual disorder (309520)	XLR	Marfanoid habitus and similar craniofacial changes: long, narrow face, small mandible, high-arched palate, and hypernasal voice with mild to moderate mental retardation and psychotic behavior.
	Ohdo syndrome, X-linked (300895)	XLR	Low weight, blepharophimosis, ptosis, wide depressed nasal bridge, long flat philtrum, thin vermilion, microstomia, micrognathia, cryptorchidism, scrotum hypoplasia, joint hyperextensibility, clinodactyly, overriding third toes, cafe-au-lait spots, developmental delay, deafness, and feeding problems.
MEN1	Multiple endocrine neoplasia 1 (131100)	AD	Characterized by varying combinations of tumors of parathyroids, pancreatic islets, duodenal endocrine cells, and the anterior pituitary, with 94% penetrance by age 50. Less commonly associated tumors include foregut carcinoids, lipomas, angiofibromas, thyroid adenomas, adrenocortical adenomas, angiomyolipomas, and spinal cord ependymomas. Except for gastrinomas, most of the tumors are non-metastasizing.
MERTK	Retinitis pigmentosa 38 (613862)	AR	Progressive degeneration of rod and cone photoreceptors in a rod-cone pattern of dysfunction. Night blindness, the development of tunnel vision, and slowly progressive decreased central vision starting at approximately 20 years of age.
MET	Hereditary papillary renal cancer (605074)	AD	Characterized by the development of multiple, bilateral papillary renal tumors
	Osteofibrous dysplasia (607278)	AD	A tumor-like bone lesion that usually presents as a painless swelling or anterior bowing of the tibia, although pain may occur in up to 25% of cases and presentation may follow pathologic fracture. Most reports of osteofibrous dysplasia describe isolated tibial lesions, although a significant subgroup describe isolated and

			ipsilateral fibular involvement. Cases with ulnar and radial involvement have been reported.
MITF	Waardenburg syndrome type 2A (193510)	AD	Characterized by pigmentary abnormalities of the hair, skin, and eyes; congenital sensorineural hearing loss.
	Tietz albinism-deafness syndrome (103500)	AD	Generalized pigment loss and congenital complete sensorineural hearing loss.
	COMMAD syndrome (617306)	AR	Coloboma, osteopetrosis, microphthalmia, macrocephaly, albinism, and deafness.
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Lynch syndrome (aka hereditary nonpolyposis colorectal cancer) (120435)	AD	Predisposition to colorectal, endometrial, ovarian, gastric, biliary tract, urinary tract, and prostate cancer. Epigenetic silencing of *MSH2* caused by deletion of 3-prime exons of the *EPCAM* gene and intergenic regions directly upstream of the MSH2 gene.
	Muir-Torre syndrome (158320)	AD	Cancer predisposition seen with Lynch syndrome and sebaceous adenoma/carcinoma.
MLH1 *MSH2* *MSH6* *PMS2*	Constitutional mismatch repair deficiency (276300)	AR	Childhood cancer predisposition syndrome with 4 main tumor types: hematologic malignancies, brain/central nervous system tumors, colorectal tumors and multiple intestinal polyps, and other malignancies including embryonic tumors and rhabdomyosarcoma. Many patients show signs reminiscent of neurofibromatosis type I, particularly multiple cafe-au-lait macules
MLH3	Hereditary non-polyposis colorectal cancer 7 (614385)	AR	Classical or attenuated adenomatous polyposis and possibly extracolonic tumors, including breast cancer.
MPL	Thrombocytopenia, congenital amegakaryocytic (604498)	AR	Expressed in infancy and characterized by isolated thrombocytopenia and megakaryocytopenia with no physical anomalies.
MTAP	Diaphyseal medullary stenosis with malignant fibrous histiocytoma (112250)	AD	Bone dysplasia characterized by pathologic fractures due to abnormal cortical growth and diaphyseal medullary stenosis. The fractures heal poorly, and there is progressive bowing of the lower extremities. Some with a limb-girdle myopathy, with muscle weakness and atrophy. Approximately 35% of affected individuals

			develop an aggressive form of bone sarcoma consistent with malignant fibrous histiocytoma or osteosarcoma.
MRE11A	Ataxia-telangiectasia-like disorder 1 (604391)	AR	Progressive cerebellar degeneration resulting in ataxia and oculomotor apraxia. Laboratory studies of patient cells showed increased susceptibility to radiation, consistent with a defect in DNA repair.
MSH3	Familial adenomatous polyposis 4 (617100)	AR	Multiple colonic adenomas in adulthood, often with progression to colorectal cancer. Proliferative lesions in other tissues may also occur
MST1R	Nasopharyngeal carcinoma, susceptibility to, 3 (617075)	AD	Nasopharyngeal carcinoma is a malignant tumor that emerges from the epithelium of the nasopharynx. Some patients have onset before 20 years of age.
MUTYH	Familial adenomatous polyposis 2 (608456)	AR	Adult-onset of multiple colorectal adenomas and adenomatous polyposis. Affected individuals have a significantly increased risk of colorectal cancer.
NBN	Nijmegen breakage syndrome (251260)	AR	Chromosomal instability syndromes characterized by microcephaly, growth retardation, immunodeficiency, and predisposition to cancer.
NF1	Neurofibromatosis 1 (162200)	AD	Multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, iris Lisch nodules, and choroidal freckling; less often, learning disabilities; increased susceptibility to the development of benign and malignant tumors.
	Neurofibromatosis, familial spinal (162210)	AD	High load of spinal tumors that may be asymptomatic or result in neurologic symptoms, including back pain, difficulty walking, and paresthesias. Spinal NF is a subtype of neurofibromatosis type 1.
	Neurofibromatosis-Noonan syndrome (601321)	AD	Neurofibromatosis with manifestations of Noonan syndrome, including short stature, ptosis, midface hypoplasia, webbed neck, learning disabilities, and muscle weakness.
	Leukemia, juvenile myelomonocytic	AD	Juvenile myelomonocytic leukemia is an aggressive pediatric myelodysplastic syndrome (MDS)/myeloproliferative disorder (MPD) characterized by malignant transformation in

	(607785)		the hematopoietic stem cell compartment with proliferation of differentiated progeny. 10-15% have neurofibromatosis type 1.
NF2	Neurofibromatosis 2 (101000)	AD	Multiple neoplasia syndrome characterized by tumors of the eighth cranial nerve (usually bilateral), meningiomas of the brain, and schwannomas of the dorsal roots of the spinal cord.
NFKB1A	Ectodermal dysplasia and immunodeficiency 2 (612132)	AD	Variable features of ectodermal dysplasia (e.g., hypo/anhidrosis, sparse hair, tooth anomalies) and various immunologic and infectious phenotypes of differing severity.
NFE2L2	immunodeficiency, developmental delay, and hypohomocysteinemia (617744)	AD	Immunodeficiency, mildly delayed psychomotor development, poor overall growth from infancy, and hypohomocysteinemia. Additional features, such as congenital heart defects and liver involvement, are more variable.
NKX2-1	Hereditary benign chroea (118700)	AD	Movement disorder that manifests before age 5 years and has a stationary or only slightly progressive course. Intelligence is normal or slightly below normal and mental deterioration is not seen. In some families, the choreic movements decrease during adolescence or early adulthood.
	Non-medullary thyroid cancer 1 (188550)	AD	Multinodular goiter (MNG)/papillary thyroid carcinoma with young age at onset and frequent bilateral involvement.
NOTCH1	Aortic valve disease 1 (109730)	AD	Bicuspid, or bicommissural, aortic valve. A spectrum of developmental aortic valve anomalies and severe valve calcification.
	Adams-Oliver syndrome 5 (616028)	AD	Combination of aplasia cutis congenita of the scalp vertex and terminal transverse limb defects (e.g., amputations, syndactyly, brachydactyly, or oligodactyly). In addition, vascular anomalies such as cutis marmorata telangiectatica congenita, pulmonary hypertension, portal hypertension, and retinal hypervascularization. Congenital heart defects have been estimated to be present in 20% (e.g., ventricular septal defects, anomalies of the great arteries and their valves, and tetralogy of Fallot).

NOTCH2	Hajdu-Cheney syndrome (102500)	AD	Short stature, coarse and dysmorphic facies, bowing of the long bones, and vertebral anomalies. Facial features include hypertelorism, bushy eyebrows, micrognathia, small mouth with dental anomalies, low-set ears, and short neck. There is progressive focal bone destruction, including acroosteolysis and generalized osteoporosis. Additional and variable features include hearing loss, renal cysts, and cardiovascular anomalies.
	Alagille syndrome 2 (610205)	AD	Hepatic bile duct paucity and cholestasis in association with cardiac, skeletal, and ophthalmologic manifestations. There are characteristic facial features and less frequent clinical involvement of the renal and vascular systems.
NOTCH3	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) 1 (125310)	AD	Progressive disorder of the small arterial vessels of the brain manifest by migraine, strokes, and white matter lesions, with resultant cognitive impairment in some patients.
	Lateral meningocele syndrome (130720)	AD	Dysmorphic features (dolichocephaly, hypertelorism, ptosis, microretrognathia, high-arched palate, long, flat philtrum, and low-set ears), hyperextensibility, hypotonia, and characteristic lateral meningoceles, which can result in neurologic complications such as bladder dysfunction and neuropathy.
NRAS	Noonan syndrome 6 (613224)	AD	Short stature, facial dysmorphism (broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears), and a wide spectrum of congenital heart defects. Relatively frequent features include multiple skeletal defects (chest and spine deformities), webbed neck, mental retardation, cryptorchidism, and bleeding diathesis.
NT5C2	Spastic paraplegia 45 (613162)	AR	Progressive, usually severe, lower extremity spasticity.
NTRK1	Congenital insensitivity to pain with anhidrosis (256800)	AR	Sensory neuropathy with variable autonomic and motor involvement. Congenital insensitivity to pain and anhidrosis, despite normal-appearing sweat glands on skin biopsy.

PARK2	Parkinson disease, juvenile, type 2 (600116)	AR	Resting tremor, muscular rigidity, bradykinesia, and postural instability. Additional features are characteristic postural abnormalities, dysautonomia, dystonic cramps, and dementia. The disease is progressive and usually has an insidious onset in mid to late adulthood.
PDGFRA	Gastrointestinal stromal tumor/GIST-plus syndrome, somatic or familial (175510)	AD	Incomplete penetrance of multiple mesenchymal tumors of the gastrointestinal tract, including gastrointestinal stromal tumor, inflammatory fibroid polyps, and fibroid tumors. Some patients have been reported with coarse facies and skin, broad hands and feet, and premature tooth loss.
PDGFRB	Myofibromatosis, infantile, 1 (228550)	AD	Mesenchymal disorder characterized by the onset of nodules in the skin, striated muscles, bones, and, more rarely, visceral organs. Subcutaneous or soft tissue nodules commonly involve the skin of the head, neck, and trunk. Skeletal and muscular lesions occur in about 50% of patients. Lesions may be solitary or multicentric, and they may be present at birth or become apparent in early infancy or occasionally in adult life.
	Premature aging syndrome, Penttinen type (601812)	AD	Prematurely aged appearance involving lipoatrophy and epidermal and dermal atrophy, as well as hypertrophic lesions that resemble scars, thin hair, proptosis, underdeveloped cheekbones, and marked acroosteolysis.
	Kosaki overgrowth syndrome (616592)	AD	Prominent forehead, proptosis, downslanting palpebral fissures, wide nasal bridge, thin upper lip, and pointed chin. Affected individuals are tall, with an elongated lower segment, hands, and feet. Skin is hyperelastic and fragile, and there is progressive neurologic deterioration with white matter lesions on brain imaging.
PIK3CA	Congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE) syndrome (612918)	Somatic mosaicism	Progressive, complex, and mixed primarily truncal vascular malformations, dysregulated adipose tissue, varying degrees of scoliosis, and enlarged, but not severely distorted, bony structures without progressive overgrowth.
	Megalencephaly-capillary malformation-polymicrogyria syndrome	Somatic mosaicism	Primary megalencephaly, prenatal overgrowth, brain and body asymmetry, cutaneous vascular malformations, digital anomalies consisting of syndactyly with or without postaxial

	(602501)		polydactyly, connective tissue dysplasia involving the skin, subcutaneous tissue, and joints, and cortical brain malformations, most distinctively polymicrogyria.
	CLAPO syndrome (613089)	Somatic mosaicism	Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of the face and limbs, and partial/generalized overgrowth. No internal or visceral abnormalities. Normal development and mental status.
	Macrodactyly (155500)	Somatic mosaicism	Fibrofatty tissue enlargement and bony overgrowth in affected digits with resultant loss of function.
	Cowden syndrome 5 (615108)	AD	A hamartomatous disorder characterized by macrocephaly, facial trichilemmomas, acral keratoses, papillomatous papules, hamartomatous gastrointestinal polyps, and an increased risk for the development of breast, thyroid, and endometrial carcinoma
PIK3R1	Immunodeficiency 36 (616005)	AD	a primary immunodeficiency with a highly heterogeneous clinical phenotype, characterized primarily by recurrent respiratory tract infections, lymphoproliferation, and antibody deficiency. The major complication is B-cell lymphoma.
	SHORT syndrome (269880)	AD	Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay. Also triangular facies, lack of facial fat, and hypoplastic nasal alae with overhanging columella, as well as near-universal partial lipodystrophy, insulin resistance, nephrocalcinosis, and hearing deficits. Normal developmental milestones and cognition.
POLD1	Colorectal cancer, susceptibility to, 10 (612591)	AD	Multiple colorectal adenomas and carcinomas between the ages of 26 and 68 years, endometrial carcinoma, and primary brain tumors. All tumors show microsatellite stability.
	Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (615381)	AD	Prominent loss of subcutaneous fat, a characteristic facial appearance, and metabolic abnormalities including insulin resistance and diabetes mellitus. Sensorineural deafness occurs late in the first or second decades of life

POLE	Colorectal cancer, susceptibility to, 12 (615083)	AD	High-penetrance predisposition to the development of colorectal adenomas and carcinomas, with a variable tendency to develop multiple and large tumors. Onset usually occurs before age 40 years. The histologic features of the tumors may be unremarkable or show microsatellite instability.
	FILS syndrome (615139)	AR	Mild facial dysmorphism, mainly malar hypoplasia, livedo on the skin since birth, immunodeficiency resulting in recurrent infections, and short stature.
	IMAGE-I syndrome (618336)	AR	Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies, and immunodeficiency. Patients exhibit distinctive facial features and variable immune dysfunction with evidence of lymphocyte deficiency.
PPARG	Insulin resistance, severe, digenic, Lipodystrophy, familial partial, type 3 (604367)	AD	Abnormal subcutaneous adipose tissue distribution beginning in late childhood or early adult life; adipose tissue accumulates on the face and neck. Metabolic abnormalities: insulin-resistant diabetes mellitus with acanthosis nigricans and hypertriglyceridemia; hirsutism and menstrual abnormalities occur infrequently.
PRKAR1A	Carney complex, type 1 (160980)	AD	Multiple neoplasia syndrome characterized by cardiac, endocrine, cutaneous, and neural myxomatous tumors, as well as a variety of pigmented lesions of the skin and mucosae. Carney complex may simultaneously involve multiple endocrine glands. Associated with the unusual large-cell calcifying Sertoli cell tumor and psammomatous melanotic schwannomas.
	Pigmented nodular adrenocortical disease, primary, 1 (610489)	AD	Primary pigmented micronodular adrenocortical disease, a form of ACTH-independent adrenal hyperplasia resulting in Cushing syndrome.
	Myxoma, intracardiac (255960)	AD	Isolated intracardiac myxoma.
PTCH1 *SUFU*	Basal cell nevus syndrome (109400)	AD	Numerous basal cell cancers and epidermal cysts of the skin, calcified dural folds, keatocysts of the jaws, palmar and plantar pits, ovarian fibromas, medulloblastomas,

			lymphomesentreic cysts, fetal rhabdomyomas, and various stigmata of maldevelopment (e.g., rib and vertebral abnormalities, cleft lip or cleft palate, and cortical defects of bones).
PTEN	Cowden syndrome 1, Lhermitte-Duclos syndrome (158350)	AD	A hamartomatous disorder characterized by macrocephaly, facial trichilemmomas, acral keratoses, papillomatous papules, and an increased risk for the development of breast, thyroid, and endometrial carcinoma.
PTPN11	Noonan syndrome 1 (163950)	AD	Short stature, facial dysmorphism (broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears), and a wide spectrum of congenital heart defects.
	LEOPARD syndrome 1 (151100)	AD	Lentigines, Electrocardiogram abnormalities, Ocular hypertelorism, Pulmonary stenosis; Abnormal genitalia, Retardation of growth, Deafness.
	Metachondromatosis (156250)	AD	Exostoses (osteochondromas), commonly of the hands and feet, and enchondromas of long bone metaphyses and iliac crests.
PTPRO	Nephrotic syndrome, type 6 (614196)	AR	Proteinuria, hypoalbuminemia, and edema, resulting in end-stage kidney disease if untreated.
RAD51	Mirror movements-2 (614508)	AD	Involuntary movements of a side of the body that mirror intentional movements on the opposite side.
RAD51	Fanconi anemia, complement group R (617244)	AD	Developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
RAD51C	Fanconi anemia, complement group O (613390)	AR	Developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. The cellular hallmark of FA is hypersensitivity to DNA crosslinking agents and high frequency of chromosomal aberrations pointing to a defect in DNA repair.
RAF1	Noonan syndrome 5	AD	Short stature, facial dysmorphism, and a wide spectrum of congenital heart defects. The

	(611553)		distinctive facial features consist of a broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate, and low-set, posteriorly rotated ears.
	Cardiomyopathy, dilated, 1NN (615916)	AD	Nonsyndromic dilated cardiomyopathy.
RB1	Retinoblastoma (180200)	AD	An embryonic malignant neoplasm of retinal origin. It almost always presents in early childhood and is often bilateral. Spontaneous regression ('cure') occurs in some cases.
RBM10	TARP syndrome (311900)	XLR	Talipes equinovarus, atrial septal defect, Robin sequence (micrognathia, cleft palate, and glossoptosis), and persistent left superior vena cava. Not all patients have all classic features. Some patients have the additional features of central nervous system dysfunction, renal abnormalities, variable cardiac anomalies including hypertrophic obstructive cardiomyopathy, and variable distal limb defects including syndactyly. Most patients die in late prenatal or early postnatal stages.
RET	Hirschsprung disease (142623)	AD	Aganglionic megacolon is characterized by congenital absence of intrinsic ganglion cells in the myenteric (Auerbach) and submucosal (Meissner) plexuses of the gastrointestinal tract.
	Multiple endocrine neoplasia IIA (171400)	AD	Multiple endocrine neoplasms, including medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid adenomas.
	Multiple endocrine neoplasia IIB (162300)	AD	Hamartoneoplastic syndrome characterized by aggressive medullary thyroid carcinoma (MTC), pheochromocytoma, mucosal neuromas, and thickened corneal nerves. Most affected individuals have characteristic physical features, including full lips, thickened eyelids, high-arched palate, and marfanoid habitus. Other more variable features include skeletal anomalies and gastrointestinal problems.
	Central hypoventilation syndrome, congenital (209880)	AD	Idiopathic congenital central hypoventilation syndrome, also known as 'Ondine's curse', is a rare disorder characterized by abnormal control of respiration in the absence of

			neuromuscular, lung or cardiac disease, or an identifiable brainstem lesion. Patients breathe normally while awake, but hypoventilate with normal respiratory rates and shallow breathing during sleep; more severely affected patients hypoventilate both awake and asleep.
	Familial medullary thyroid cancer (155240)	AD	Medullary thyroid carcinoma (MTC) is a malignant tumor of the calcitonin-secreting parafollicular C cells of the thyroid.
RET *SDHB* *SDHD* *VHL*	Pheochromocytoma (171300)	AD	Susceptibility to the development of isolated pheochromocytoma.
RNF43	Sessile serrated polyposis cancer syndrome (SSPCS) (617108)	AD	Multiple serrated polyps in the colon and an increased personal and familial risk of colorectal cancer. Defined by the World Health Organization as the presence of at least 5 sessile serrated polyps (also known as 'sessile serrated adenomas,' or SSAs) proximal to the sigmoid colon, with 2 or more that are greater than 10 mm in diameter; or any number of serrated polyps in a person with a first-degree relative with SSPCS; or more than 20 serrated polyps of any size, distributed throughout the colon.
SDHA	Paragangliomas 5 (614165)	AD	Also referred to as 'glomus body tumors,' are tumors derived from paraganglia located throughout the body. Nonchromaffin types primarily serve as chemoreceptors (hence, the tumor name 'chemodectomas') and are located in the head and neck region (i.e., carotid body, jugular, vagal, and tympanic regions), whereas chromaffin types have endocrine activity, conventionally referred to as 'pheochromocytomas,' and are usually located below the head and neck (i.e., adrenal medulla and pre- and paravertebral thoracoabdominal regions).
	Leigh syndrome (256000)	AR	Defective mitochondrial energy generation. It most commonly presents as a progressive and severe neurodegenerative disorder with onset within the first months or years of life, and may result in early death. Affected individuals

			usually show global developmental delay or developmental regression, hypotonia, ataxia, dystonia, and ophthalmologic abnormalities, such as nystagmus or optic atrophy.
SDHA *SDAD*	Mitochondrial respiratory chain complex II deficiency (252011)	AR	A highly variable phenotype. Some patients have multisystem involvement of the brain, heart, muscle, liver, and kidneys resulting in death in infancy, whereas others have only isolated cardiac or muscle involvement with onset in adulthood and normal cognition. In some cases, treatment with riboflavin may have clinical benefit.
SDHB	Paragangliomas 4 (115310)	AD	Also referred to as 'glomus body tumors,' are tumors derived from paraganglia located throughout the body. Nonchromaffin types primarily serve as chemoreceptors (hence, the tumor name 'chemodectomas') and are located in the head and neck region (i.e., carotid body, jugular, vagal, and tympanic regions), whereas chromaffin types have endocrine activity, conventionally referred to as 'pheochromocytomas,' and are usually located below the head and neck (i.e., adrenal medulla and pre- and paravertebral thoracoabdominal regions).
SDHC	Paragangliomas 3 (605373)	AD	Also referred to as 'glomus body tumors,' are tumors derived from paraganglia located throughout the body. Nonchromaffin types primarily serve as chemoreceptors (hence, the tumor name 'chemodectomas') and are located in the head and neck region (i.e., carotid body, jugular, vagal, and tympanic regions), whereas chromaffin types have endocrine activity, conventionally referred to as 'pheochromocytomas,' and are usually located below the head and neck (i.e., adrenal medulla and pre- and paravertebral thoracoabdominal regions).
SDHD	Paragangliomas 1 (168000)	AD	Also referred to as 'glomus body tumors,' are tumors derived from paraganglia located throughout the body. Nonchromaffin types primarily serve as chemoreceptors (hence, the tumor name 'chemodectomas') and are located in the head and neck region (i.e., carotid body, jugular, vagal, and tympanic regions), whereas chromaffin types have endocrine activity,

			conventionally referred to as 'pheochromocytomas,' and are usually located below the head and neck (i.e., adrenal medulla and pre- and paravertebral thoracoabdominal regions).
SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (175050)	AD	Hamartomatous polyps occurring throughout the gastrointestinal tract, resulting in an increased risk of gastrointestinal cancer, and telangiectases of the skin, and oral and nasal mucosa, epistaxis, and arteriovenous malformations (AVMs) of the lungs, liver, brain, and gastrointestinal tract.
	Juvenile polyposis syndrome (174900)	AD	Predisposes to various types of tumors. The diagnosis is based on the occurrence of hamartomatous gastrointestinal polyps that turn into malignant lesions in approximately 20% of cases.
SMARC4A	Rhabdoid tumor predisposition syndrome-2 (613325)	AD	Cancer predisposition syndrome characterized by the onset in infancy, childhood, or young adulthood of various poorly differentiated tumors. Classically, tumors that arise in the central nervous system are referred to as atypical teratoid/rhabdoid tumors, whereas those arising in the kidney or other extracranial sites are referred to as malignant rhabdoid tumors. Tumors may also present as small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), also known as malignant rhabdoid tumor of the ovary (MRTO). All of these tumors are highly aggressive and often fatal.
SMARCB1	Schwannomatosis 1 (162091)	AD	Multiple cutaneous neurilemmomas and spinal schwannomas, without acoustic tumors or other signs of neurofibromatosis I or neurofibromatosis II. Some patients may develop meningiomas.
	Rhabdoid tumor predisposition syndrome 1 (609322)	AD	Predisposing to renal or extrarenal malignant rhabdoid tumors and to a variety of tumors of the central nervous system, including choroid plexus carcinoma, medulloblastoma, and central primitive neuroectodermal tumors.
SRC	Thrombocytopenia 6 (616937)	AD	Hematologic disorder characterized by increased bleeding episodes due to reduced platelet count and abnormal platelet morphology resulting from defective megakaryopoiesis. Patients may also have bone

			abnormalities, including osteoporosis or tooth loss, as well as an increased risk for myelofibrosis.
STAG2	Holoprosencephaly 13, X-linked (301043)	XLR XLD	A neurologic disorder characterized by midline developmental defects that mainly affect the brain and craniofacial structure. The severity and manifestations are variable: some patients may have full alobar HPE with cyclopia, whereas other have semilobar HPE or septooptic dysplasia. Dysmorphic features include microcephaly, hypotelorism, low-set ears, micrognathia, and cleft lip/palate.
STAT3	Autoimmune disease, multisystem, infantile-onset, 1 (615952)	AD	Early childhood onset of a spectrum of autoimmune disorders affecting multiple organs. Common manifestations include insulin-dependent diabetes mellitus and autoimmune enteropathy, or celiac disease, and autoimmune hematologic disorders.
	Hyper-IgE recurrent infection syndrome (147060)	AD	Primary immunodeficiency disorder characterized by chronic eczema, recurrent Staphylococcal infections, increased serum IgE, and eosinophilia. Patients have a distinctive coarse facial appearance, abnormal dentition, hyperextensibility of the joints, and bone fractures.
STK11	Peutz-Jeghers syndrome (175200)	AD	Melanocytic macules of the lips, buccal mucosa, and digits; multiple gastrointestinal hamartomatous polyps; and an increased risk of various neoplasms (gastrointestinal, pancreas, cervix, ovary and breast are most common).
SUFU	Joubert syndrome 32 (617757)	AR	Delayed psychomotor development, intellectual disability, dysmorphic facial features, and postaxial polydactyly. Brain imaging shows cerebellar abnormalities consistent with the molar tooth sign.
TBX3	Ulnar-mammary syndrome (181450)	AD	Posterior limb deficiencies or duplications, apocrine/mammary gland hypoplasia and/or dysfunction, abnormal dentition, delayed puberty in males, and genital anomalies.
TEK	Glaucoma 3, primary congenital, E (617272)	AD	Increased corneal diameter greater than 10 mm, accompanied by corneal edema and/or Haab striae; and had intraocular pressures (IOPs) greater than 21 mm Hg and/or optic

			nerve cupping greater than 0.4 typically before age 3; can be unilateral or bilateral.
	Venous malformations, multiple cutaneous and mucosal (600195)	AD	Multiple cutaneous and mucosal venous malformations.
TGFBR2	Loeys-Dietz syndrome 2 (610168)	AD	Aortic aneurysm syndrome with widespread systemic involvement; triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.
TNFAIP3	Autoinflammatory syndrome, familial, Behcet-like (616744)	AD	Ulceration of mucosal surfaces, particularly in the oral and genital areas. Additional more variable features include skin rash, uveitis, and polyarthritis. Symptoms become apparent in the first or second decades.
TP53	Li-Fraumeni syndrome (151623)	AD	Early onset of tumors, multiple tumors within an individual, and multiple affected family members. In contrast to other inherited cancer syndromes, which are predominantly characterized by site-specific cancers, LFS presents with a variety of tumor types. The most common types are soft tissue sarcomas and osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma. Classic LFS is defined as a proband with a sarcoma before the age of 45 years and a first-degree relative with any cancer before the age of 45 years and 1 additional first- or second-degree relative in the same lineage with any cancer before the age of 45 years or a sarcoma at any age.
	Glioma susceptibility 1 (137800)	AD Somatic mosaicism	Gliomas are central nervous system neoplasms derived from glial cells and comprise astrocytomas, glioblastoma multiforme, oligodendrogliomas, ependymomas, and subependymomas. Glial cells can show various degrees of differentiation even within the same tumor. Ependymomas are rare glial tumors of the brain and spinal cord.
	Hereditary adrenocortical carcinoma (202300)	AD	Aggressive childhood tumor, representing about 0.4% of childhood tumors, with a high incidence of associated tumors.

TSC1	Tuberous sclerosis complex 1 (191100)	AD	Multisystem disorder characterized by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, and lung. Central nervous system manifestations include epilepsy, learning difficulties, behavioral problems, and autism. Renal lesions, usually angiomyolipomas, can cause clinical problems secondary to hemorrhage or by compression and replacement of healthy renal tissue, which can cause renal failure. Patients can also develop renal cysts and renal-cell carcinomas. Pulmonary lymphangioleiomyomatosis can develop in the lungs. Skin lesions include melanotic macules, facial angiofibromas, and patches of connective tissue nevi. There is a wide clinical spectrum, and some patients may have minimal symptoms with no neurologic disability.
TSC2	Tuberous sclerosis 2 (613254)	AD	Multisystem disorder characterized by hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, and lung. These changes can result in epilepsy, learning difficulties, behavioral problems, and renal failure, among other complications.
VHL	von Hippel-Lindau syndrome (193300)	AD	Hemangioblastomas of the brain, spinal cord, and retina; renal cysts and clear cell renal cell carcinoma; pheochromocytoma, pancreatic cysts, and neuroendocrine tumors; endolymphatic sac tumors; and epididymal and broad ligament cysts.
	Familial erythrocytosis-2 (263400)	AR	Increased red blood cell mass, increased serum levels of erythropoietin, and normal oxygen affinity. High risk for peripheral thrombosis and cerebrovascular events.
WT1	Wilms tumor, type 1 (194070)	AD	Wilms tumor is the most common renal tumor of childhood, occurring with an incidence of 1 in 10,000 and with a median age of diagnosis between 3 and 4 years of age. Wilms tumors are thought to develop from abnormally persistent embryonal cells within nephrogenic rests.
	Denys-Drash syndrome (194080)	AD	Pseudohermaphroditism, Wilms tumor, hypertension and degenerative renal disease.

	Frasier syndrome (136680)	AD	Pseudohermaphroditism and progressive glomerulopathy. Patients present with normal female external genitalia, streak gonads, and XY karyotype, and frequently develop gonadoblastoma.
	Nephrotic syndrome, type 4 (256370)	AD	Nephrotic syndrome, a malfunction of the glomerular filter, leads to proteinuria, edema, and, in steroid-resistant nephrotic syndrome, end-stage renal disease.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; OMIM, Online Mendelian Inheritance in Man; XLD, X-linked dominant; XLR, X-linked recessive.

[a]The Online Mendelian Inheritance in Man database was searched using the clinical synopsis tool for each of the gene to identify genetic disorders that could have clinical relevance for adult patients. We excluded autosomal dominant syndromes that feature major congenital malformations, highly penetrant intellectual disability or developmental delay, death in infancy or childhood, and susceptibility to common diseases other than common cancers/tumors, and somatic mutations only. We included genetic disorders typically having somatic mosaicism inheritance, as this could be particularly salient in cancer patients. We included all autosomal and X-linked recessive conditions regardless of severity of the associated phenotype, as heterozygosity for these conditions could have reproductive implications for the patient and their family members.