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# Hereditary Cancer

## GENES AND ASSOCIATED CANCERS/TUMORS August 2018

| GENE(S) | SYNDROME | ASSOCIATED RISKS |
|---|---|---|
| *AIP* | Familial isolated pituitary adenomas (FIPA) | Pituitary adenoma (>50%) |
| *ALK* | | Neuroblastoma, ganglioneuroblastoma, ganglioneuroma, possibly medulloblastoma |
| *APC* | Familial adenomatous polyposis (FAP) | Colorectal (up to 100%), small bowel, stomach, pancreatic, medulloblastoma, other |
| *ATM** | Biallelic mutations: Ataxia-telangiectasia | Female breast (2-4 fold), pancreatic, prostate |
| *AXIN2* | | Colorectal |
| *BAP1* | | Kidney, melanoma, mesothelioma |
| *BARD1* | | Breast, possibly ovarian |
| *BLM** | Biallelic mutations: Bloom syndrome | Breast, colorectal |
| *BMPR1A* | Juvenile polyposis syndrome (JPS) | Colorectal (40-50%), stomach (up to 21%) |
| *BRCA1* | Hereditary breast ovarian cancer (HBOC) | Female breast (57-87%), ovarian (39-40%), pancreatic, prostate, male breast |
| *BRCA2** | Hereditary breast ovarian cancer (HBOC)<br>Biallelic mutations: Fanconi anemia | Female breast (45-84%), ovarian (11-18%), pancreatic, melanoma, prostate (15%), male breast (>6%) |
| *BRIP1** | Biallelic mutations: Fanconi anemia | Ovarian (up to 9%), breast |
| *CASR, CFTR^, CPA1, CTRC, PRSS1, SPINK1* | | Pancreatitis (^monoallelic) |
| *CDC73* | Hyperparathyroidism-jaw tumor syndrome (HPT-JT) | Primary hyperparathyroidism (over 90% of individuals), parathyroid carcinoma (10-20%), fibro-osseous jaw tumors (30-40%), and renal hamartomas/tumors |
| *CDH1* | Hereditary diffuse gastric cancer (HDGC) | Diffuse gastric (67-83%), female lobular breast, (39-52%), colorectal |
| *CDK4* | | Melanoma (up to 74% by age 50) |
| *CDKN1B* | Multiple endocrine neoplasia type 4 *(MEN4)* | Hyperparathyroidism (nearly 100%), pituitary adenoma, neuroendocrine tumors |
| *CDKN2A* | Familial atypical multiple mole melanoma (FAMMM) | Melanoma (28-67%), pancreatic (17-25%), astrocytoma |
| *CHEK2* | | Female breast (2 fold), colorectal, prostate, other |
| *CTNNA1* | | Gastric cancer |
| *DICER1* | DICER1 syndrome | Pleuropulmonary blastoma (childhood), cystic nephroma, ovarian sex-cord tumors (most often Sertoli-Leydig cell tumors), brain, other |
| *EGFR* | | Non-small cell lung cancer (15% in ever smokers and 31% in never smokers) |
| *EPCAM, MLH1*, MSH2* MSH6*, PMS2** | Lynch syndrome (formerly HNPCC) Biallelic mutations: Constitutional mismatch repair deficiency (CMMRD) | Colorectal (up to 82%), uterine (up to 60%), stomach (6-13%), ovarian (4-12%), small intestine, hepatobiliary tract, upper urinary tract (5-6%), gliomas, pancreatic, sebaceous, prostate |
| *FANCC** | Biallelic mutations: Fanconi anemia | Breast, possibly pancreatic |
| *FH** | Hereditary leiomyomatosis and renal cell cancer (HLRCC)<br>Biallelic mutations: Fumarase deficiency | Papillary type II kidney (up to 20%), PGL/PCC |
| *FLCN* | Birt-Hogg-Dubé (BHD) | Kidney (20-34%) |
| *GALNT12* | | Colorectal |
| *GREM1* | Hereditary mixed polyposis syndrome (HMPS) | Colorectal |
| *HOXB13* | | Prostate |

*PGL/PCC: paraganglioma/pheochromocytoma*
** Biallelic mutations are associated with recessive syndromes listed under "Syndrome." Monoallelic mutations are associated with the cancer/tumor risks listed under "Associated Risks."*

# Hereditary Cancer Genes and Associated Cancer/Tumor Risks

| GENE(S) | SYNDROME | ASSOCIATED RISKS |
|---|---|---|
| *KIT* | | Gastrointestinal stromal tumors |
| *MAX* | Hereditary PGL/PCC | Malignant PCC (paternal inheritance), possibly extra-adrenal PGLs |
| *MEN1* | Multiple endocrine neoplasia type 1 (MEN1) | Parathyroid (>90%), GEP tumors (30-70%), pituitary (30-60%), adrenal (15-50%), carcinoid (up to 10%), PCC |
| *MET* | Hereditary papillary renal carcinoma (HPRC) | Papillary type I kidney (nearly 100%) |
| *MITF* | | Kidney (up to 5 fold), melanoma (2-8 fold) |
| *MRE11A** | Biallelic mutations: Ataxia-telangiectasia-like disorder | Breast, possibly ovarian |
| *MSH3* | | Biallelic mutations: colorectal |
| *MUTYH* | MUTYH-associated polyposis (MAP) | Biallelic mutations: colorectal (up to 80%), stomach, duodenal, uterine, breast<br>Monoallelic mutations: female breast (up to 1.5 fold), colorectal (up to 2 fold) |
| *NBN** | Biallelic mutations: Nijmegen breakage syndrome | Breast, possibly ovarian, medulloblastoma, ganglioglioma, prostate |
| *NF1* | Neurofibromatosis type I | Female breast (3-5 fold), malignant nerve sheath tumors (8-13%), optic glioma, astrocytoma, GIST, leukemia, PGL/PCC (up to 7%) |
| *NF2* | Neurofibromatosis type 2 (NF2) | Vestibular schwannomas (>90%), other cranial nerve schwannomas (24-51%), intracranial meningiomas (45-58%), spinal tumors (63-90%) |
| *NTHL1* | | Biallelic mutations: colorectal |
| *PALB2** | Biallelic mutations: Fanconi anemia | Female breast (33-58%), pancreatic, ovarian, possibly prostate, male breast |
| *PDGFRA* | | Gastrointestinal stromal tumors |
| *PHOX2B* | Central congenital hypoventilation syndrome | Neuroblastoma, ganglioneuroblastoma, ganglioneuroma, other |
| *POLD1, POLE* | Polymerase proofreading-associated polyposis (PPAP) | Colorectal |
| *POT1* | | Gliomas |
| *PRKAR1A* | Carney complex | Primary pigmented nodular adrenocortical disease (26-60%), pituitary adenoma (10-12%), myxomas (up to 53%), thyroid nodules (25%), large cell calcifying Sertoli cell tumor (33-41%), psammomatous melanotic schwannomas (8-10%), other |
| *PTCH1* | Gorlin syndrome | Basal cell carcinoma, medulloblastoma, sarcoma, other |
| *PTEN* | PTEN hamartoma tumor syndrome (PTHS)/Cowden syndrome | Breast (25-85%), thyroid (10-35%), uterine (5-28%), colorectal (9%), kidney (34%), melanoma (up to 6%) |
| *RAD50** | Biallelic mutations: Nijmegen breakage syndrome-like disorder | Breast, possibly ovarian |
| *RAD51C** | Biallelic mutations: Fanconi anemia | Ovarian (5-9%), female breast |
| *RAD51D* | | Ovarian (10-12%), female breast, prostate |
| *RB1* | Hereditary retinoblastoma | Retinoblastoma (childhood), melanoma, sarcoma |
| *RET* | Multiple endocrine neoplasia type 2 (MEN2) | Medullary thyroid (95-100%), PCC (up to 50%), hyperparathyroidism (up to 30%) |
| *SDHA* | Hereditary PGL/PCC type 5 | PGL/PCC (low malignant potential), kidney, GIST |
| *SDHAF2* | Hereditary PGL/PCC type 2 | PGL/PCC (up to 100%, paternal inheritance, low malignant potential) |
| *SDHB* | Hereditary PGL/PCC type 4 | PGL/PCC (both 77-100%), kidney (up to 14%), GIST |
| *SDHC* | Hereditary PGL/PCC type 3 | PGL/PCC (low malignant potential) |
| *SDHD* | Hereditary PGL/PCC type 1 | PGL/PCC (86-90%, paternal inheritance), kidney, GIST |
| *SMAD4* | Juvenile polyposis syndrome and hereditary hemorrhagic telangiectasia | Colorectal (40-50%), stomach (up to 21%) |
| *SMARCA4* | | Ovarian (small cell carcinoma, hypercalcemic type), brain, other |
| *SMARCB1** | Biallelic mutations: Coffin-Siris syndrome | Atypical teratoid/rhabdoid tumors, schwannomatosis, possibly medulloblastoma, meningioma, other |

*GIST: gastrointestinal stromal tumor*

*GEP tumors: gastro-entero-pancreatic tumors. These include gastrinomas, insulinomas, vasoactive intestinal peptide-secreting tumors (VIPomas), and glucagonomas.*

*PGL/PCC: paraganglioma/pheochromocytoma*

** Biallelic mutations are associated with recessive syndromes listed under "Syndrome." Monoallelic mutations are associated with the cancer/tumor risks listed under "Associated Risks."*

| GENE(S) | SYNDROME | ASSOCIATED RISKS |
|---|---|---|
| *SMARCE1* | | Meningioma |
| *STK11* | Peutz-Jeghers syndrome (PJS) | GI cancers (up to 57%), breast (up to 45%), pancreatic, other |
| *SUFU* | | Basal cell carcinomas, jaw keratocysts, medulloblastoma, possibly meningioma, other |
| *TMEM127* | Hereditary PGL/PCC | PGL/PCC (<5% malignant potential) |
| *TP53* | Li-Fraumeni syndrome (LFS) | Breast, sarcoma, brain, adrenocortical, leukemia, other |
| *TSC1,TSC2* | Tuberous sclerosis complex (TSC) | Kidney (2-5%), brain and spine, skin, liver, lung, heart |
| *VHL** | von Hippel-Lindau disease (VHL) Biallelic mutations: Familial erythrocytosis-2 | Kidney (25-70%), PCCs (10-26%, <5% malignant potential), hemangioblastomas (brain and spine) |
| *XRCC2* | | Female breast, male breast |

*PGL/PCC: paraganglioma/pheochromocytoma*
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## Oncology Test Menu

### BrainTumorNext (27 genes)
*AIP, ALK, APC, CDKN1B, CDKN2A, DICER1, MEN1, MLH1, MSH2, MSH6, NBN, NF1, NF2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, SMARCA4, SMARCB1, SMARCE1, SUFU, TP53, TSC1, TSC2, VHL*

### BRCAplus (8 genes)
*ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, TP53*

### BreastNext (17 genes)
*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53*

### CancerNext (34 genes)
*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CHEK2, CDK4, CDKN2A, DICER1, EPCAM, GREM1, HOXB13, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMAD4, SMARCA4, STK11, TP53*

### CancerNext-*Expanded* (67 genes)
*AIP, ALK, APC, ATM, BAP1, BLM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, DICER1, EPCAM, FANCC, FH, FLCN, GALNT12, GREM1, HOXB13, MAX, MEN1, MET, MITF, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, XRCC2*

### ColoNext (17 genes)
*APC, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53*

### CustomNext-*Cancer* (up to 81 genes)
Choose any number of genes from the following: *AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, BMPR1A, CASR, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CFTR, CHEK2, CPA1, CTNNA1, CTRC, DICER1, EGFR, EPCAM, FANCC, FH, FLCN, GALNT12, GREM1, HOXB13, KIT, MAX, MEN1, MET, MITF, MLH1, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, POT1, PMS2, POLD1, POLE, PRKAR1A, PRSS1, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, SPINK1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, XRCC2*

### GYNplus (13 genes)
*BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, TP53*

### MelanomaNext (8 genes)
*BAP1, BRCA2, CDK4, CDKN2A, MITF, PTEN, RB1, TP53*

### OvaNext (25 genes)
*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, DICER1, EPCAM, MRE11A, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TP53*

### PancNext (13 genes)
*APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53*

### PGLNext (12 genes)
*FH, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL*

### ProstateNext (14 genes)
*ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53*

### RenalNext (19 genes)
*BAP1, EPCAM, FH, FLCN, MET, MITF, MLH1, MSH2, MSH6, PMS2, PTEN, SDHA, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL*

# Hereditary Cancer Genes

## BY PRIMARY CANCER TYPE

### BREAST

Highest risk: *BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53*

Elevated risk: *ATM, BARD1, BLM, BRIP1, CHEK2, FANCC, MRE11A, MUTYH, NBN, NF1, RAD50, RAD51C, RAD51D, STK11, XRCC2*

### PARAGANGLIOMA/ PHEOCHROMOCYTOMA

Highest risk: *RET, SDHAF2, SDHB, SDHD, VHL*

Elevated risk: *FH, MAX, MEN1, NF1, SDHA, SDHC, TMEM127*

### BRAIN

Highest risk: *MEN1, MLH1, MSH2, MSH6, NF1, NF2, PTCH1, PMS2, TP53, TSC1, TSC2, VHL*

Elevated risk: *AIP, ALK, APC, CDKN1B, CDKN2A, DICER1, NBN, PHOX2B, POT1, PRKAR1A, PTEN, SMARCA4, SMARCB1, SMARCE1, SUFU*

### PANCREATIC

Highest risk: *ATM, BRCA1, BRCA2, CDKN2A, STK11*

Elevated risk: *APC, EPCAM, FANCC, MEN1, MLH1, MSH2, MSH6, PALB2, PMS2, TP53*

Pancreatitis: *CASR, CFTR, CPA1, CTRC, PRSS1, SPINK1*

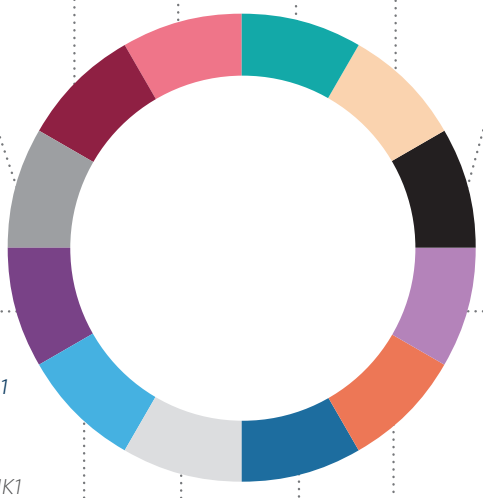
### PROSTATE

Highest risk: *ATM, BRCA1, BRCA2, CHEK2, HOXB13*

Elevated risk: *EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53*

### OTHER

Elevated risk: *CDC73, EGFR, KIT, PDGFRA*



### OVARIAN

Highest risk: *BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D*

Elevated risk: *BARD1, CHEK2, DICER1, MRE11A, NBN, RAD50, SMARCA4, STK11, TP53*

### UTERINE

Highest risk: *EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN*

Elevated risk: *MUTYH, TP53*

### MELANOMA

Highest risk: *CDK4, CDKN2A*

Elevated risk: *BAP1, BRCA2, MITF, PTEN, RB1, TP53*

### STOMACH

Highest risk: *BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2, SMAD4*

Elevated risk: *APC, CTNNA1, MEN1, MUTYH, NF1, STK11, TP53*

### KIDNEY

Highest risk: *FH, FLCN, MET, PTEN, SDHB, VHL*

Elevated risk: *BAP1, EPCAM, MITF, MLH1, MSH2, MSH6, PMS2, SDHA, SDHC, SDHD, TP53, TSC1, TSC2*

### COLORECTAL

Highest risk: *APC, BMPR1A, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, SMAD4, STK11*

Elevated risk: *AXIN2, BLM, CDH1, CHEK2, GALNT12, GREM1, MSH3, NTHL1, PTEN, POLD1, POLE, TP53*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