Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 47 Genes

Indications for Ordering

Individuals with
- A clinical diagnosis of a cancer at an earlier age than typical
- A rare form of cancer
- A cancer occurring in an individual of the sex not typically affected
- More than one primary cancer
- Bilateral or multifocal cancer
- A personal or family history suggestive of a hereditary cancer syndrome
  - Cancer diagnosed in numerous family members at an early age

Test Description

- Targeted capture followed by parallel sequencing of all exons and intron/exon boundaries of 45 genes (excludes *EPCAM* and *PMS2*)
  - See table for list of genes
- Sanger sequencing and multiplex ligation probe amplification (MLPA) of *PMS2*
- Targeted sequencing of the *CHEK2* c.1100delC variant
- Custom comparative genomic hybridization (CGH) array to detect deletions and/or duplications of 46 genes (excludes *PMS2)*

Tests to Consider

Primary tests

Cancer Panel, Hereditary, Sequencing and Deletion/Duplication, 47 Genes 2012032
- Confirm diagnosis of a hereditary cancer syndrome with personal or family history consistent with features of more than one cancer syndrome
- Tests for specific genes or components of the hereditary cancer panel may be available individually at ARUP
  - For test availability and further information, see the test directory at www.aruplab.com/genetics

Related test

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Specific cancer syndromes associated with variants in genes in this panel
- Breast/ovarian
- Central nervous system
- Endocrine
- Endometrial
- Gastrointestinal
- Melanoma
- Pancreatic
- Renal

Incidence

5-10% of cancers are hereditary

Symptoms

Highly variable and dependent on the specific gene variant and syndrome involved

Genetics

Genes – see table

Inheritance
- Primarily autosomal dominant
  - Affected individual inherits one variant in a tumor suppressor gene and acquires a second variant in the homologous gene during his/her lifetime
  - Affected individual inherits one variant in an oncogene
- Rarely autosomal recessive

Test Interpretation

Clinical sensitivity – unknown

Results

- Positive
  - One pathogenic variant detected in a gene with autosomal dominant inheritance
    - Confirms diagnosis of hereditary cancer syndrome
    - 50% chance of passing the variant on to offspring
  - Two pathogenic variants detected on opposite chromosomes in a gene with autosomal recessive inheritance
    - Confirms diagnosis of hereditary cancer syndrome
  - One pathogenic variant detected in a gene with autosomal recessive inheritance
    - Confirms carrier status for a hereditary cancer syndrome
- Negative
  - No pathogenic variants detected
    - Reduces the likelihood of, but does not exclude, a diagnosis of a hereditary cancer syndrome
- Inconclusive
  - Variants of unknown clinical significance may be identified

Limitations

- Not determined or evaluated
  - Deep intronic and regulatory variants
  - Breakpoints of large deletions/duplications
  - Sequence changes in *EPCAM*
  - Deletions/duplications in
    - *ATM (*exon 12*)*
    - *BAP1* (exon 1)
    - *BMPR1A* (exon 9)
    - *CDH1* (exon 1)
    - *CHEK2* (exons 11-15), with the exception of the c.1100delC variant
    - *FH (*exons 1, 9)
    - *FLCN* (exon 8)
    - *MSH2* (exon 1)
    - *NF2* (exons 7, 13)
    - *PTEN* (exon 8)
    - *RET* (exon 1)
    - *RAD51D* (exon 1)
    - *SMARCB1* (exon 5)
    - *STK11* (exons 4, 6, 7)
    - *TSC2* (exons 7, 17, 23, 25, 29, 32, 41)
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations
- Only genes in the following table will be tested

Gene Symbol	Gene Name	NM #	OMIM #	Inh.[1]	Cancer/Tumor Association
ALK	Anaplastic lymphoma receptor tyrosine kinase	004304	105590	AD	Neuroblastoma, ganglioneuroblastoma, ganglioneuroma
APC	Adenomatous polyposis coli	ex1b:001127511 ex1a15:001127510	611731	AD	Colon, small bowel, medulloblastoma, hepatoblastoma, soft tissue and desmoid tumors, osteomas
ATM	Ataxia telangiectasia mutated (includes complementation groups A, C, and D)	000051	607585	AD	Breast
BAP1	BRCA1 associated protein-1	004656	603089	AD	Mesothelioma, lung adenocarcinoma, meningiomas, cutaneous melanoma, uveal melanoma
BARD1	BRCA1- associated RING domain 1	000465	601593	AD	Breast, neuroblastoma
BMPR1A	Bone morphogenic protein receptor, type 1A	004329	601299	AD	Colon, stomach, upper gastrointestinal (GI)
BRCA1	Breast cancer 1	007294	113705	AD	Breast, ovarian, fallopian, peritoneal, pancreatic, prostate
BRCA2	Breast cancer 2	000059	600185	AD	Breast, ovarian, fallopian, peritoneal, pancreatic, prostate, gallbladder, gastric, melanoma
BRIP1	BRCA1 interacting protein C-terminal, helicase 1	032043	605882	AD	Breast, ovarian
CDH1	Cadherin 1, E-cadherin (epithelial)	004360	192090	AD	Gastric, breast, prostate
CDK4	Cyclin dependent kinase 4	000075	123829	AD	Glioma, sarcoma, melanoma, breast, and colorectal
CDKN1B	Cyclin-dependent kinase inhibitor 1B	004064	600778	AD	Endocrine tumors (MEN1-like)
CDKN2A	Cyclin-dependent kinase inhibitor 2A	000077	600160	AD	Melanoma, pancreatic
CHEK2	CHK2 checkpoint homologue (S. pombe RAD53)	007194	604373	AD	Breast, colorectal, prostate

Gene Symbol	Gene Name	NM #	OMIM #	Inh.[1]	Cancer/Tumor Association
EPCAM Del/dup	Epithelial cell adhesion molecule	002354	185535	AD	Colorectal, stomach, small bowel, ovarian
FH	Fumarate hydratase	000143	136850	AD	Type 2 papillary renal carcinoma
FLCN	Folliculin	144997	607273	AD	Renal cell carcinoma, fibrofolliculomas
MAX	MYC associated factor X	002382	154950	AD	Pheochromocytoma
MEN1	Multiple endocrine neoplasia 1	130799	613733	AD	Glucagonomas, gastrinomas, VIPomas, thymic, bronchial, gastric, breast
MET	Multiple endocrine neoplasia 1	001127500	164860	AD	Papillary renal carcinoma
MLH1	MutL homologue 1, colon cancer, nonpolyposis type 2 (E. coli)	000249	120436	AD	Ovarian, colon, small intestine, endometrial, bladder, renal pelvis, ureter, hepatobiliary, central nervous system (CNS)
MSH2	MutS homologue 2, colon cancer, nonpolyposis type 1 (E. coli)	000251	609309	AD	Ovarian, colon, small intestine endometrial, bladder, renal pelvis, ureter, hepatobiliary, CNS
MSH6	MutS (E.coli) homologue 6	000179	6006787	AD	Ovarian, colon, small intestine, endometrial, bladder, renal pelvis, ureter, hepatobiliary, CNS
MUTYH	MutY homologue (E.coli)	001128425	604933	AR/AD	Colon (AR), gastric, breast, duodenal, endometrium (AD)
NBN	Nibrin (NBS1)	002485	602667	AD	Breast, ovarian
NF2	Neurofibromatosis 2 protein	000268	607379	AD	Bilateral vestibular schwannomas, meningiomas, ependymomas, astrocytomas
PALB2	Partner and localizer of BRCA2	024675	610335	AD	Breast, pancreatic
PHOX2B	Paired-like homeobox 2B	003924	603851	AD	Neural crest derivative tumors, neuroblastomas, gangliomas
PMS2	Postmeiotic segregation increased 2, yeast homologue	000535	600259	AD	Ovarian, colon, small intestine, endometrial, bladder, renal pelvis, ureter, hepatobiliary, CNS
PTEN	Phosphatase and tensin homolog	000314	601728	AD	Thyroid, breast, renal, endometrial, colorectal, melanoma
RAD51C	RAD51 homolog (S. cerevisiae)	058216	602774	AD	Breast, ovarian
RAD51D	RAD51D homolog D (S. cerevisiae)	002878	602954	AD	Breast, ovarian
RB1	Retinoblastoma	000321	604041	AD	Retinoblastoma, pinealoblastoma, sarcomas, melanoma
RET	Ret proto-oncogene	020975	164761	AD	Medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma
SDHAF2	Succinate dehydrogenase complex assembly factor 2	017841	613019	AD	Paraganglioma, pheochromocytoma
SDHB	Succinate dehydrogenase complex, subunit B, iron sulphur	003000	185470	AD	Paraganglioma, pheochromocytoma, papillary thyroid, renal cell carcinoma, GI stromal, neuroblastoma, renal cell carcinoma
SDHC	Succinate dehydrogenase complex, subunit C, integral membrane protein	003001	602413	AD	Paraganglioma, pheochromocytoma, GI stromal tumors
SDHD	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690	AD[2]	Paraganglioma, pheochromocytoma
SMAD4	SMAD, mothers against DPP homologue 4	005359	600993	AD	Colon, stomach, upper GI
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	003073	601607	AD	Renal, extra renal, medullary thyroid, choroid plexus, medulloblastoma, central primitive neuroectodermal, schwannomatosis, meningiomas
STK11	Serine/threonine kinase 11 (LKB1)	000455	602216	AD	Colon, pancreatic, breast, ovarian
SUFU	Suppressor of fused homologue	016169	607035	AD	Medulloblastoma, desmoplastic melanoma, meningioma
TMEM127	Transmembrane protein 127	017849	613403	AD	Paraganglioma, pheochromocytoma

Gene Symbol	Gene Name	NM #	OMIM #	Inh.[1]	Cancer/Tumor Association
TP53	Tumor protein 53	000546	191170	AD	Breast, ovarian, brain, adrenocortical, soft tissue sarcomas, leukemia, hepatocellular
TSC1	Tuberous sclerosis 1	000368	605284	AD	Renal cell carcinoma, angiomyolipoma
TSC2	Tuberous sclerosis 2	000548	191092	AD	Renal cell carcinoma, angiomyolipoma
VHL	von Hippel Lindau syndrome	000551	608537	AD	Renal cell carcinoma, hemangioblastoma, pheochromocytoma, neuroendocrine tumors

[1]Inh. = inheritance; AD = autosomal dominant; AR = autosomal recessive
[2]Parent of origin