# Hereditary Pancreatic Cancer Panel, Sequencing and Deletion/Duplication

Last Literature Review: August 2022 Last Update: June 2024

Pathogenic germline variants in multiple genes have been implicated in hereditary pancreatic cancer. Hereditary cancer syndromes are often characterized by early age of cancer onset (typically before 50 years of age) and multiple, multifocal, and/or similar cancers in a single individual or in a closely related family member(s). Refer to the Genes Tested table for more details regarding the genes and syndromes included on the Hereditary Pancreatic Cancer Panel. Genes included on this panel are also included in other ARUP hereditary cancer tests. For more information, refer to the ARUP Hereditary Cancer Panel Comparison table.

## Featured ARUP Testing

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the Hereditary Cancer Panel Comparison table.

### Hereditary Pancreatic Cancer Panel, Sequencing and Deletion/Duplication 3005708

**Method:** Massively Parallel Sequencing/Sequencing/Multiplex Ligation-Dependent Probe Amplification (MLPA)

- Recommended test to confirm a hereditary cause of pancreatic cancer in individuals with a personal or family history
- Testing minors for adult-onset conditions is not recommended. Testing will not be performed on minors without prior approval. For additional information, please contact an ARUP genetic counselor at 800-242-2787.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

# Genetics

## Genes

Refer to the Genes Tested table for genes included in the panel.

## Etiology

Approximately 10% of pancreatic cancers are associated with a hereditary cause.[1]

## Inheritance

- Autosomal dominant
- Some genes are also associated with autosomal recessive childhood cancer predisposition or other syndromes.

# Test Interpretation

## Contraindications for Ordering

- For individuals with a suspected diagnosis of Lynch syndrome, consider testing specific to Lynch syndrome as some relevant variants are not included on this panel. Refer to Lynch Syndrome - Hereditary Nonpolyposis Colorectal Cancer (HNPCC) for more information.
- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with methodology used for germline assays
- Individuals with hematological malignancy and/or a previous allogeneic bone marrow transplant should not undergo molecular genetic testing on peripheral blood specimen.
  - Testing of cultured fibroblasts is required for accurate interpretation of test results.

## Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.
- Long-range PCR followed by nested Sanger sequencing is performed on the following gene and exons:
  - *PMS2* (NM_000535) 11, 12, 13, 14, 15

- Bidirectional Sanger sequencing is performed on the following gene and exon:
  - *MSH2* (NM_000251) 5
  - *PMS2* (NM_000535) 7
- Multiplex ligation-dependent probe amplification (MLPA) is performed on the following gene to call exon-level deletions and duplications:
  - *PMS2* (NM_000535)

## Sensitivity/Specificity

### Clinical Sensitivity

Variable, dependent on phenotype

### Analytic Sensitivity/Specificity

| Variant Class | Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%) | Analytic Specificity (NPA) Estimate (%) |
|---|---|---|
| SNVs | >99 (96.9-99.4) | >99.9 |
| Deletions 1-10 bp[b] | 93.8 (84.3-98.2) | >99.9 |
| Insertions 1-10 bp[b] | 94.8 (86.8-98.5) | >99.9 |
| Exon-level[c] deletions | 97.8 (90.3-99.8) [2 exons or larger]<br>62.5 (38.3-82.6) [single exon] | >99.9 |
| Exon-level[c] duplications | 83.3 (56.4-96.4) [3 exons or larger] | >99.9 |
| Exon-level deletions/duplications (MLPA) | >99 | >99 |

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by MLPA unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; MLPA, multiplex ligation-dependent probe amplification; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

## Limitations

- A negative result does not exclude a heritable form of cancer.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted genes
  - Regulatory region and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Sequence variants in *EPCAM*
  - The following exons are not sequenced due to technical limitations of the assay:
    - *APC* (NM_001354896) 12; (NM_001354898, NM_001354904) 2; (NM_001354900) 11
    - *BRCA1* (NM_007300) 13
    - *MEN1* (NM_001370251) 8
    - *VHL* (NM_001354723) 2
- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement.
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

- Deletions/duplications in the following exons:
  - *APC* (NM_001354896) 12; (NM_001354898, NM_001354904) 2; (NM_001354900) 11
  - *BRCA1* (NM_007294, NM_007299, NM_007300) 2; (NM_007298) 1
  - *CDKN2A* (NM_000077, NM_001195132, NM_001363763, NM_058195) 2
  - *MEN1* (NM_001370251) 8
  - *VHL* (NM_001354723) 2

## Genes Tested

To compare directly to other hereditary cancer panels offered by ARUP Laboratories, refer to the Hereditary Cancer Panel Comparison table.

| Gene | MIM Number | Disorder/Associated Cancer(s)/Tumor(s) | Inheritance |
|---|---|---|---|
| *APC* | 611731 | FAP<br>AFAP<br>GAPPS<br>Colorectal adenomas and cancer, duodenal adenomas and cancer, gastric fundic gland polyps, medulloblastoma, osteomas, pancreatic, thyroid, and others | AD |
| *ATM* | 607585 | Breast, colorectal,[a] ovarian, pancreatic, prostate | AD |
| | | Ataxia-telangiectasia | AR |
| *BRCA1* | 113705 | HBOC syndrome<br>Breast, fallopian tube, ovarian, pancreatic, peritoneal, prostate | AD |
| | | Fanconi anemia, complementation group S | AR |
| *BRCA2* | 600185 | HBOC syndrome<br>Breast, fallopian tube, melanoma, ovarian, pancreatic, peritoneal, prostate | AD |
| | | Fanconi anemia, complementation group D1 | AR |
| *CDK4* | 123829 | Cutaneous melanoma, pancreatic[a] | AD |
| *CDKN2A* | 600160 | FAMMM-PC syndrome (also known as melanoma-pancreatic cancer syndrome)<br>Cutaneous melanoma, pancreatic | AD |
| *EPCAM*<br>(Exon 9 deletion/duplications only) | 185535 | Lynch syndrome/HNPCC<br>Brain, colorectal, endometrial, ovarian, pancreatic, prostate, renal pelvis and/or ureter, stomach, and others | AD |
| *MEN1* | 613733 | MEN type 1<br>Adrenocortical, carcinoid, GEP neuroendocrine tumors, meningioma, parathyroid, pituitary, thyroid | AD |
| *MLH1* | 120436 | Lynch syndrome/HNPCC<br>Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others | AD |
| | | CMMRD | AR |

[a]Association is suggested but not well-established at this time.

AD, autosomal dominant; AFAP, attenuated familial adenomatous polyposis; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; FAMMM-PC, familial atypical multiple mole melanoma-pancreatic carcinoma; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GEP, gastro-entero-pancreatic; GIST, gastrointestinal stromal tumor; HBOC, hereditary breast and ovarian cancer; HNPCC, hereditary nonpolyposis colorectal cancer; JPS, juvenile polyposis syndrome; LFS, Li-Fraumeni syndrome; MAP, MUTYH-associated polyposis; MEN, multiple endocrine neoplasia; PJS, Peutz-Jeghers syndrome; VHL, von Hippel-Lindau

| Gene | MIM Number | Disorder/Associated Cancer(s)/Tumor(s) | Inheritance |
|---|---|---|---|
| *MSH2* | 609309 | Lynch syndrome/HNPCC<br>Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others | AD |
| | | CMMRD | AR |
| *MSH6* | 600678 | Lynch syndrome/HNPCC<br>Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others | AD |
| | | CMMRD | AR |
| *PALB2* | 610355 | Breast, ovarian, pancreas, prostate | AD |
| | | Fanconi anemia, complementation group N | AR |
| *PMS2* | 600259 | Lynch syndrome/HNPCC<br>Brain, colorectal, endometrial, ovarian, pancreas, prostate, renal pelvis and/or ureter, stomach, and others | AD |
| | | CMMRD | AR |
| *STK11* | 602216 | PJS<br>Breast, cervix, colorectal, endometrial, lung, ovarian (sex cord with annular tubules), pancreas, Peutz-Jeghers-type hamartomatous polyps, small intestine, stomach, testes | AD |
| *TP53* | 191170 | LFS<br>Adrenocortical carcinoma, breast, choroid plexus carcinoma, CNS, colorectal, melanoma, osteosarcoma, pancreas, prostate, renal, rhabdomyosarcoma, soft tissue sarcoma, stomach, thyroid, and others | AD |
| *VHL* | 608537 | VHL syndrome<br>Endolymphatic sac tumors, epididymal and broad ligament cystadenomas, hemangioblastoma, neuroendocrine tumors, pheochromocytoma, renal cell carcinoma, retinal angioma | AD |

[a]Association is suggested but not well-established at this time.

AD, autosomal dominant; AFAP, attenuated familial adenomatous polyposis; AR, autosomal recessive; CMMRD, constitutional mismatch repair deficiency; CNS, central nervous system; FAMMM-PC, familial atypical multiple mole melanoma-pancreatic carcinoma; FAP, familial adenomatous polyposis; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; GEP, gastro-entero-pancreatic; GIST, gastrointestinal stromal tumor; HBOC, hereditary breast and ovarian cancer; HNPCC, hereditary nonpolyposis colorectal cancer; JPS, juvenile polyposis syndrome; LFS, Li-Fraumeni syndrome; MAP, MUTYH-associated polyposis; MEN, multiple endocrine neoplasia; PJS, Peutz-Jeghers syndrome; VHL, von Hippel-Lindau

## References

1. American Cancer Society. Pancreatic cancer risk factors. Accessed Feb 2022.

## Related Information

Hereditary Cancer Germline Genetic Testing