

MYvantage® Hereditary Comprehensive Cancer Panel

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Background

The MYvantage® Hereditary Comprehensive Cancer Panel from Quest Diagnostics™ provides a comprehensive analysis of 34 hereditary cancer predisposition genes utilizing next-generation (NGS)/massively parallel sequencing (MPS) technologies.

NCCN overview of multigene testing

- The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.
- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost effective.
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include "indeterminate" penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain pathogenic variants in a known pathogenic/likely pathogenic variant alone to assign risk for relatives.

- In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
- Pathogenic/likely pathogenic variants in many breast cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions.
- It is for these and other reasons that multi-gene testing is ideally offered in the context of professional genetic expertise for pre-and post-test counseling. (Individuals with the recommended expertise include certified genetic counselors, as well as clinicians who have had extensive training and/or experience in identification and management of hereditary syndromes)

Related Medical Guidelines

[BRCA 1 and 2 Genetic Testing \(Sequence Analysis/Rearrangement\)](#)
[Genetic Testing for Colorectal Cancer / Lynch Syndrome](#)
[Genetic Testing for PTEN Hamartoma Tumor Syndrome](#)

Guideline (Criteria A, **B** or **C** may be applied)

- A. MYvantage® testing is considered medically necessary when results will directly impact surveillance or treatment and one or more of the following criteria are met:
- Individual from a family with a known deleterious mutation in a gene on the Myvantage panel
 - Personal history of breast cancer (includes invasive and ductal carcinoma in situ) + one or more of the following:
 - Diagnosed ≤ 45 y
 - Diagnosed 46–50 y with:
 - An additional breast cancer primary at any age (Note: Two breast cancer primaries includes bilateral [contralateral] disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously)
 - ≥ 1 close blood relative with breast cancer at any age
 - ≥ 1 relative with prostate cancer (Gleason score ≥ 7 or metastatic)
 - An unknown or limited family history
 - Diagnosed ≤ 60 y with:
 - Triple negative breast cancer
 - Diagnosed at any age with:
 - ≥ 2 close blood relatives with breast cancer at any age
 - ≥ 1 close blood relative with pancreatic cancer
 - ≥ 1 close blood relative with metastatic prostate cancer
 - ≥ 1 close blood relative with breast cancer diagnosed ≤ 50 y
 - ≥ 1 close blood relative with ovarian carcinoma
 - A close male blood relative with breast cancer
 - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required (Note: Testing for Jewish Ashkenazi founder-specific mutation[s] should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met. Founder mutations exist in other populations)
 - 3 or more diagnoses of breast cancer in patient and/or close blood relative

- Personal history of ovarian carcinoma
- Personal history of male breast cancer
- Personal history of high-grade prostate cancer (Gleason score ≥ 7) at any age with ≥ 1 close blood relative with ovarian carcinoma at any age or breast cancer ≤ 50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥ 7 or metastatic) at any age
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- Personal history of exocrine pancreatic cancer
- Personal history of pancreatic cancer or any first degree relative of an individual with pancreatic cancer
- BRCA1/2 pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis
- Pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis in any gene that would have clinical implications if found in the germline
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
 - First- or second-degree blood relative meeting any of the above criteria
 - Third-degree blood relative who has breast cancer and/or ovarian carcinoma (includes fallopian tube and primary peritoneal cancers) and who has ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian carcinoma
- Unaffected/asymptomatic member with positive family history of hereditary breast and ovarian cancer (HBOC) syndrome

Note: Members are eligible for BRCA 1 and 2 rearrangement testing if the criteria for comprehensive sequence analysis are met and the analysis is negative.

B. Applicable to microsatellite instability (MSI), LS/HNPCC (MLH1, MSH2, MSH6, PMS2, EPCAM), FAP coli and attenuated FAP coli (APC genetic testing), MYH-associated neoplasia or MAP (MYH genetic testing)

1. MYvantage® testing is also considered medically necessary when one the following (a or b) is applicable:

Diagnosis or screening, as indicated by 1 or more of the following:

- a. EPCAM, MLH1, MSH2, MSH6, or PMS2 gene or limited gene panel (i.e., EPCAM, MLH1, MSH2, MSH6, PMS2 genes) testing when personal history increases risk, as indicated by 1 or more of the following:
 - i. Personal history of colorectal cancer diagnosed before age 50 years
 - ii. Personal history of colorectal cancer and 1 or more additional positively diagnosed tumors associated with Lynch syndrome[A] regardless of age
 - iii. Personal history of colorectal or endometrial cancer, and one or more first-degree[B] or second degree[C] relatives with Lynch syndrome-related cancer diagnosed before age 50 years
 - iv. Personal history of colorectal or endometrial cancer, and 2 or more first-degree [B] or second degree[C] relatives with Lynch syndrome-related cancers, regardless of age

- v. Personal history of colorectal cancer or endometrial cancer with high microsatellite instability or pathologic immunohistochemistry on cancer tissue testing[D]
 - vi. Personal history of endometrial cancer diagnosed before age 50 years
 - vii. Personal history of synchronous (simultaneous) or metachronous (diagnosed at different times) colorectal cancer or Lynch syndrome-related tumors[A] regardless of age
 - viii. Member with a LS-related cancer [A] or unaffected member with a ≥5% risk of having an MMR gene mutation based on predictive models (PREMM5, MMRpro, MMRpredict)
- b. EPCAM, MLH1, MSH2, MSH6, or PMS2 gene testing when family history increases risk, as indicated by 1 or more of the following:
- i. First-degree relative[B] of person with known EPCAM, MLH1, MSH2, MSH6, or PMS2 gene mutation by DNA sequence testing
 - ii. One or more first-degree relatives[B] diagnosed with colorectal cancer or Lynch syndrome related tumor[A] before age 50 years
 - iii. One or more first-degree relatives[B] with colorectal or endometrial cancer, and another synchronous or metachronous Lynch syndrome-related cancer
 - iv. Two or more first-degree[B] or second-degree[C] relatives diagnosed with colorectal cancer or Lynch syndrome-related tumor, [A] with at least 1 diagnosed before age 50 years
 - v. Three or more first-degree[B] or second-degree[C] relatives with Lynch syndrome-related cancers, regardless of age

Footnotes

[A] Lynch syndrome-related tumors include colorectal, endometrial, stomach, small bowel, ovarian, pancreas, prostate, ureter and renal pelvis, biliary tract, brain/CNS, and skin (eg, sebaceous gland adenomas, keratoacanthomas) tumors

[B] First-degree relatives consist of male or female parents, siblings, or children

[C] Second-degree relatives consist of male or female grandparents, grandchildren, aunts, uncles, nieces, nephews, or half-siblings.

[D] Loss of protein expression of the MLH1 gene on immunohistochemistry and subsequent positive BRAF mutation virtually excludes Lynch syndrome and obviates the need for germline mismatch repair gene testing; the added step of BRAF mutation testing is thought to avoid nearly half of mismatch repair gene mutation testing. Histology that is suggestive of the need to perform microsatellite instability testing includes tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous or signet ring differentiation, or medullary growth pattern

2. Familial adenomatous polyposis (FAP) coli or attenuated FAP; 1 of the following:
- a. Member has > 10 colorectal adenomatous polyps
 - b. Member has a 1st degree relative(s) with a known APC mutation
 - c. The individual has a personal history of a desmoid tumor

Note: APC negative members should be tested for MUTYH. Members with Serrated Polyposis Syndrome with associated adenomas should also be tested for MUTYH.

Limitations/Exclusions

For detection of APC1307K, an APC missense mutation of unclear clinical significance found in Ashkenazi Jewish population.

C. In addition, MYvantage® testing is considered medically necessary for members with a personal history of one of the following 4 cancer diagnoses:

- Endocrine (multiple endocrine neoplasia [MEN] types 1 or 2)
- Gastric
- Melanoma
- Pancreatic

A letter of medical necessity must accompany the request.

Limitations/Exclusions

- Testing with MYvantage is not considered medically necessary for any indication other than those listed in A, B or C above.
- Testing with MYvantage is not considered medically necessary for general population screening.

Revision History

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| May 13, 2022 | Clarified personal history of pancreatic cancer RE 1st degree relative with pancreatic cancer and ovarian carcinoma Removed personal history of pancreatic and Ashkenazi Jewish ancestry prerequisite (as having pancreatic cancer, irrespective of ethnicity, is supported for testing) |
| Dec. 13, 2019 | Imported criteria from BRCA 1 and 2 Genetic Testing (Sequence Analysis/Rearrangement) and Genetic Testing for Colorectal Cancer / Lynch Syndrome policies to denote applicability to MYvantage and added coverage for members with certain personal cancers |

Applicable Procedure Codes

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|-------|---|
| 81432 | Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53 |
| 81433 | Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11 |
| 81435 | Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11 |
| 81436 | Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11 |

Applicable Diagnosis Codes

Note: As per coding guidelines, the following codes may not be reported as the principal/first-listed diagnosis.

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| Z85.028 | Personal history of other malignant neoplasm of stomach |
| Z85.038 | Personal history of other malignant neoplasm of large intestine |
| Z85.07 | Personal history of malignant neoplasm of pancreas |
| Z85.3 | Personal history of malignant neoplasm of breast |
| Z85.41 | Personal history of malignant neoplasm of cervix uteri |
| Z85.43 | Personal history of malignant neoplasm of ovary |

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| Z85.46 | Personal history of malignant neoplasm of prostate |
| Z85.820 | Personal history of malignant melanoma of skin |
| Z85.858 | Personal history of malignant neoplasm of other endocrine glands |

References

1. GTR: Genetic Testing Registry. MyVantage™ Hereditary Comprehensive Cancer Panel. <https://www.ncbi.nlm.nih.gov/gtr/tests/552183/>. Accessed January 8, 2021.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Genetic/familial high-risk assessment: colorectal. V1.2020. Rockledge, PA: National Comprehensive Cancer Network, 2016. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf. Accessed January 8, 2021.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Genetic/familial high-risk assessment: breast and ovarian. V2.2021. Rockledge, PA: National Comprehensive Cancer Network, 2017. https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed January 8, 2021.
4. Specialty matched clinical peer review.