Draft Benefit Coverage Standard for Genetic Testing Recommendations

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Authored by: Serenedy Smith, MS,CGC Licensed Genetic Counselor, Myriad Genetics Inc.
ssmith@myriad.com
603-724-3772

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Section 1: Eligible Providers

It is respectfully requested that Colorado Medicaid reconsider this provision for limited eligible provider types and allow all licensed provider types to offer genetic counseling and testing to patients in their own practice if desired, but also maintain the option of referral to a genetics professional (genetic counselor, geneticist, APN with genetics credentials) for patients and providers who wish to utilize this service. Multiple published guidelines[1-9] and government health plans, including CMS, advocate for a variety of licensed healthcare provider types to be able to identify, counsel, and test patients at risk of hereditary cancers within their own practices. Several of these guidelines and government plans are highlighted below:

The US Preventive Services Task Force (USPSTF)[1] states that "Genetic counseling is recommended prior to testing, and is defined as a communication process that deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. A number of approaches are in practice, including educational, decision-making, and psychosocial support. Providers of genetic counseling maybe genetic counselors, nurse educators, or other professionals."

The American Congress of Obstetrics and Gynecology (ACOG)[2] issued a practice bulletin for their membership which states "Evaluating a patient's risk for hereditary breast and ovarian cancer syndrome should be a routine part of obstetric and gynecologic practice". ACOG goes on to provide a description of specific issues that should be addressed by the gynecologist as he/she provides genetic counseling.

The Society of Gynecologic Oncologists (SGO)[3] provided similar guidance to their membership in a committee statement issued in 2007 where SGO proclaims "It is important to emphasize that hereditary cancer risk assessment is a process that includes assessment of risk, education and counseling; is conducted by a physician, genetic counselor or other provider with expertise in cancer genetics; and may include genetic testing if desired after appropriate counseling and consent has been obtained."

The National Comprehensive Cancer Network (NCCN)[4] included the following in the 2013 version of their practice guidelines in oncology: "Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome."

American Society of Clinical Oncology (ASCO)[5] issued a policy statement update in 2010 proclaiming "As providers of genetic risk assessment to patients and families affected by cancer, it is the role of oncologists and other health care providers to offer genetic tests in a manner that is safe and clinically appropriate. ASCO recommends that, outside of a research protocol, genetic testing for cancer susceptibility only be offered when the following three criteria are met: the individual being tested has a personal or family history suggestive

of genetic cancer susceptibility; the genetic test can be adequately interpreted; and the test results have accepted clinical utility."

Centers for Medicare and Medicaid Services http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=24308&ContrId=133&ver=62
"Pre-test genetic counseling must be provided by a qualified and appropriately trained practitioner"

Washington State Medicaid http://www.hca.wa.gov
"The agency covers genetic counseling for all FFS adults and children when performed by a physician"

Vermont State Medicaid http://dvha.vermont.gov
"A BRCA gene test may be covered for those beneficiaries when the BRCA gene test is prescribed by a licensed medical provider enrolled in the VT Medicaid program who is knowledgeable in the use of the BRCA gene test and who provides medical care to the beneficiary and who meet the clinical guidelines"

The main clinical benefit of hereditary cancer risk assessment and testing is the opportunity to prevent or reduce the risk of cancer, a disease with significant financial and economic burden to Colorado Medicaid, families, and society. While genetics professionals are extremely important healthcare providers and access to such providers should remain open, limiting access to genetic testing for high risk patients to ONLY those that have met with the above limited provider types will result in fewer mutation carriers identified and, ultimately, missed opportunities for the most appropriate medical management options for high-risk patients. Currently, the majority (70%) of BRCA testing for Colorado Medicaid members at high risk of a BRCA mutation is provided by specialists such as oncologists, surgeons, gynecologists, etc. [11] Several studies have demonstrated that less than half of patients at high-risk of hereditary cancer referred for genetic counseling attend a session [see Table1]. Given the published drop-out rates in Table 1, it is estimated that 23-60% of high risk patients in Colorado Medicaid would no longer have access to genetic testing if the test provider type is limited to a genetics professional. It is important to note that the studies referenced in Table 1 include data from university-based systems in which the genetic counselor directly contacted appropriate patients to attempt to schedule appointments, as well as a study in which telephone counseling was offered to appropriate patients. In both scenarios, access should have been easier (via direct contact to set up the appointment or through telephone counseling), however the referral drop-out rate was quite high. Keeping all avenues open to high-risk patients for genetic risk-assessment and testing will result in the most hereditary cancer mutation carriers being identified and avoid unnecessary cancer diagnoses in Colorado Medicaid members. As Colorado Medicaid members must meet the established medical criteria in the final version of the benefit coverage standard for genetic testing, only members at high-risk of a mutation will have coverage of testing services, thus overutilization due to allowing all provider types to perform risk assessment and genetic testing should not be of concern.

Table 1: Referral Drop-out rate for patients at high risk of hereditary cancer referred to a genetics professional

Reference	Patient Population	Referral Drop-out Rate
Pruski-Clark J et al. *National Interdisciplinary Breast Center Conference*. March 10-14, 2012	494 mammography patients identified through questionnaire and referred for telephone genetic counseling	87%
Buchanan AH, et al. *Community Oncology. 2009;*6:70-77	102 patients referred from rural oncology practices	36%
Cohen SA, et al. *J Genet Couns.* 2009 Dec;18(6):530-3	Patients referred for cancer genetic counseling in a community hospital	33%
South CD, et al. *Genet Med.* 2009;11(11):812-7	34 colon cancer patients with abnormal tumor screening results referred for genetic counseling	73%
O'Neill SM, et al. *Am J Med Genet C Semin Med Genet*. 2006 Nov 15;142(4):221-31	43 breast cancer patients referred for genetic counseling in an academic center	64%
Fowler ES, et al. *Community Oncology*. 2005;2: 253-260	1,124 patients referred from various providers to a community oncology genetic counseling program	50%

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Section 2: Covered Services and Limitations

2a: Lynch Syndrome (analyte codes and corresponding ICD-9 codes in Appendix I)

It is respectfully requested that Colorado Medicaid consider implementing the below criteria taken from the National Comprehensive Cancer Network (NCCN) Lynch Syndrome Test Criteria as outlined in the NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening v 1.2013[1]

For individuals <u>without</u> a personal diagnosis of a Lynch Syndrome-related cancer

- **Close relative meeting Revised Bethesda Guidelines[table 2]; or**
- **Close relative meeting Revised Amsterdam II Guidelines[table 2]; or**
- **Close relative with endometrial cancer under age 50; or**
- **Close relative with known Lynch syndrome**

For individuals <u>with</u> a personal diagnosis of a Lynch Syndrome-related cancer

- **Meets Revised Bethesda Guidelines; or**
- **Meets Revised Amsterdam II Guidelines; or**
- **Diagnosed with endometrial cancer under age 50; or**
- **Close relative with known Lynch syndrome**

Table 2: Revised Bethesda and Revised Amsterdam II Guidelines

Revised Bethesda Guidelines are as follows: • Colorectal cancer (CRC) diagnosed in a patient who is younger than 50 years of age; or • Presence of synchronous, or metachronous, CRC or other LS-related tumors^, regardless of age; or • CRC with MSI-H histology^^ diagnosed in a patient who is younger than 60 years of age; or • CRC diagnosed in a patient with one or more first-degree relatives with and LS-related cancer^, with one of the cancers being diagnosed under age 50 • CRC diagnosed in a patient with two or more first- or second-degree relatives diagnosed with LS-related cancers^, regardless of age

Revised Amsterdam II Guidelines are as follows:
• At least three relatives must have a cancer associated with Lynch Syndrome^; all of the following criteria should be present
  o One must be a first-degree relative of the other two; and
  o At least two successive generations must be affected; and
  o At least one relative with cancer associated with LS should be diagnosed before age 50 years; and
  o FAP (Familial Adenomatous Polyposis) should be excluded in the CRC case(s) (if any); and
  o Tumor should be verified whenever possible

^ LS-related tumors include: colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, small intestine, sebaceous gland adenomas and keratoacanthomas ^^MSI-H histology: presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern

The current draft benefit coverage standard for genetic testing suggests coverage of Lynch syndrome gene testing for patients with newly diagnosed colorectal cancer per the EGAPP evidence review published in 2009.[2] It is important to recognize that the goal of this evidence review was to evaluate population screening methodologies for Lynch syndrome (LS) among newly diagnosed colorectal cancer patients. The EGAPP Working Group (EWG) did NOT evaluate methodologies *or make recommendations* for identifying LS among patients with extra-colonic cancers known to be prevalent among LS mutation carriers, as this was beyond the scope of the evaluation. The EWG also did not evaluate methodologies *or make recommendations* for identifying LS in unaffected individuals at risk based on a family history of LS-related cancers.

There is increased prevalence of LS among patients affected with specific types of extra-colonic cancers, particularly gynecologic cancers in women with LS, making it imperative that these additional cancer types be considered when evaluating the overall risk of LS to the patient. In addition, employing a strategy to identify unaffected individuals with LS prior to a cancer diagnosis has been shown to be both cost-effective and clinically effective, with the ability to significantly reduce overall incidence of both colorectal and endometrial cancers.[12] Evidence supporting LS gene testing in individuals affected with LS-related cancers other than colorectal and in unaffected individuals based on a family history of LS-related cancers is as follows:

Endometrial Cancer: Individuals with endometrial cancer should be identified as candidates for Lynch syndrome testing, based on the same age and family history requirements used for individuals with colorectal cancer.

Several recent publications have addressed the significance of endometrial cancer in Lynch syndrome.[13-16] The prevalence of Lynch syndrome among individuals with endometrial cancer is similar to that of colorectal cancer.[13] The current NCCN guidelines support endometrial cancer diagnosed before age 50 as a testing criterion.[1] In their statement on Inherited Gynecologic Cancer Predispositions[3], the Society of Gynecologic Oncologists modified the Revised Bethesda criteria to apply to an individual with endometrial cancer (instead of only colorectal cancer), by including the following:

- Patients with endometrial cancer diagnosed prior to age 50
- Patients diagnosed with endometrial cancer ≥50 who have:
    - At least one first-degree relative with colorectal cancer diagnosed under age 50 *or*
    - At least two first- or second-degree relatives with a Lynch-associated cancer at any age
- Patients with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/HNPCC-associated tumor at any age

Other cancers associated with Lynch syndrome:

Additional Lynch syndrome-associated cancers include ovarian, gastric, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma), and small intestine cancers, as well as sebaceous gland adenomas/carcinomas and keratoacanthomas.[5] Individuals with the other Lynch syndrome-associated cancers should also be considered appropriate for testing, based on a family history meeting Amsterdam II or revised Bethesda guidelines[1].

Unaffected patients:

The current Lynch syndrome testing strategy described in the NCCN guidelines includes a statement that testing of unaffected family members should be considered, when no affected relative is available for testing.[1] An appropriate approach for testing of *unaffected* individuals who are at-risk for Lynch syndrome (based on their family history of cancer) should be clearly delineated, similar to the commonly accepted approach for Hereditary Breast and Ovarian Cancer.

Current societal guidelines support the evaluation and genetic testing of unaffected women who are at-risk for Hereditary Breast and Ovarian Cancer syndrome based on family history.[6-8] The ideal scenario of initially testing an affected relative is often not feasible, as the relative(s) may be deceased, unable to pursue testing for financial reasons, disinterested in testing, or estranged from the unaffected patient who is at-risk. Despite the fact that these same challenges exist for Lynch syndrome, current published guidelines continue to focus on affected individuals, thereby limiting the identification of unaffected Lynch syndrome mutation carriers at a point when effective medical interventions can reduce or eliminate the risk of cancer.

Among unaffected individuals with mutation-proven Lynch syndrome, several studies have demonstrated a high compliance rate with the recommended colon cancer surveillance strategies and a significant clinical impact.[9-11, table 3] Published data demonstrates that genetic testing for Lynch syndrome significantly improves adherence to cancer screening recommendations, with 73-100% of mutation carriers undergoing colonoscopy.[9-11] Frequent colonoscopic surveillance results in an 86% reduction in the diagnosis of late-stage colorectal cancer, a 50% reduction in the overall risk of colon cancer, and a 65% decrease in overall mortality.[18,19] Data also confirms the efficacy of preventive surgeries for gynecologic cancer risk reduction. Among a group of mutation-positive women followed for a mean of 13 years, no endometrial or ovarian cancers developed after prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy.[20]

A recent publication by Dinh et al.[12] evaluated the health outcomes and cost effectiveness of a strategy to identify and test unaffected individuals at-risk for Lynch Syndrome. Using a robust simulation model previously described in the literature, the authors concluded that risk assessment of unaffected individuals starting at ages 25-35, followed by genetic testing for selected patients would reduce colorectal cancer incidence by 12.4% and endometrial cancer incidence by 8.8%. The strategy was determined to have a cost effectiveness ratio

of ~$26,000/QALY, well below the common benchmark of $50,000 and comparable to colorectal cancer screening, cervical cancer screening, and mammography.

Table 3: Clinical Utility of LS Gene Testing Among Patients With and Without Previous Cancer Diagnoses

Reference	Description of Results
Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. *J Clin Oncol* 2009;27(28):4793-7	Long term compliance for colorectal cancer AND endometrial cancer surveillance in LS pts exceeded 95% (follow up 11.5 years)
Hadley DW, Ashida S, Jenkins JF, et al. *Clin Genet* 2011;79(4):321-8	Lynch syndrome mutation carriers were significantly more likely to have undergone colonoscopy after receiving positive LS mutation results versus pre-genetic testing (31% pre-test versus 52% post genetic test)
Yurgelun MB, Mercado R, Rosenblatt M, et al. *Gynecol Oncol* 2012;127(3):544-51	At one year follow up, 100% of female LS mutation carriers were adherent to guidelines for endometrial cancer risk-reduction and 56% had undergone prophylactic hysterectomy; by three years follow up, 69% had undergone prophylactic hysterectomy
Ketabi Z, Mosgaard BJ, Gerdes AM, et al. *Obstet Gynecol* 2012;120(5):1005-12	Survey of 421 women from LS families, overall 67% had participated in gynecologic cancer surveillance
Collins VR et al. *Genet Med* 2007;9(5):290-10	Three years post genetic test results for 19 LS mutation carriers and 54 non-carriers, 100% of LS mutation carriers had undergone at least one colonoscopy in previous 3 years versus 7% of non-carriers. Also, 69% of the 13 female LS mutation carriers had undergone gynecologic screening in the previous 2 years
Hadley DW et al. *J Clin Oncol* 2004;22(1):39-44	Significant decrease in colonoscopy use for individuals one year post genetic test result for those who test negative for LS mutations (8% compared to 59% pre-genetic test result)
Halbert CH et al. *Arch Intern Med* 2004;164(17):1881-7	12 months following genetic test results, LS mutation carriers were significantly more likely to have undergone colonoscopy versus high-risk individuals who declined genetic testing and individuals who tested negative for LS mutations (73% LS positive vs. 22% test decliners vs. 16% LS negative)

Section 2b: BRCA1 and BRCA2 (analyte codes and corresponding ICD-9 codes in Appendix II)

It is respectfully requested that Colorado Medicaid consider implementing the below criteria taken from the NCCN Practice Guidelines in Oncology Genetic/Familial High Risk Assessment: Breast and Ovarian v4.2013.[1]

- **Individual from a family with a known deleterious BRCA1/BRCA2 mutation**
- **Personal history of breast cancer[A] plus one or more of the following:**
    - **Diagnosed age ≤45 y**
    - **Two breast primaries[B] when the first breast cancer diagnosis occurred ≤age 50 y**
    - **Diagnosed age ≤50 y with ≥1 close blood relative with breast cancer at any age or with a limited family history**
    - **Diagnosed age ≤60 y with a triple negative breast cancer**
    - **Diagnosed any age with ≥1 close blood relative with breast cancer diagnosed ≤50 y**
    - **Diagnosed any age with ≥2 close blood relatives with breast cancer at any age**
    - **Diagnosed at any age with ≥1 close blood relative with epithelial ovarian cancer[C]**
    - **Diagnosed at any age with ≥2 close blood relatives with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age**
    - **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**
- **Personal history of epithelial ovarian cancer**
- **Personal history of male breast cancer**
- **Personal history of pancreatic cancer or aggressive prostate cancer at any age with ≥2 close blood relatives with breast and/or ovarian and/or pancreatic or aggressive prostate cancer at any age**
- **Family history only**
    - **First- or second-degree blood relative meeting any of the above criteria**
    - **Third-degree relative with breast cancer and/or ovarian cancer with ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian cancer**

A - invasive and ductal carcinoma in situ breast cancers should be included

B – bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously

C- fallopian and primary peritoneal cancers are included

The current draft benefit coverage standard for genetic testing suggests following the USPSTF defined family history risk factors of a BRCA1/BRCA2 gene mutation for test coverage. The USPSTF statement was published in 2005, based on a review of evidence published through October 2004.[2] As such, the USPSTF recommendations *do not* reflect advances from 2005 onward in the understanding of the risk factors for carrying a BRCA1 or BRCA2 mutation. In contrast, the NCCN Practice Guidelines in Oncology are reviewed and published on an annual basis by experts in the field of cancer screening and treatment and genetics. In addition, the 2005 USPSTF guidelines were outlined specifically for pre-symptomatic (unaffected) women from high-risk families, and NOT for women with a personal cancer history. *In contrast,* the NCCN guidelines outline specific genetic testing criteria for BOTH the high-risk affected and unaffected patient populations. Given the proven clinical utility of BRCA gene testing[table 4] in both affected and unaffected at-risk individuals, it would benefit Colorado Medicaid to provide coverage for members based on the most current peer-reviewed evidence and expert opinion. There are significant clinical shortcomings when comparing USPSTF recommendations to the NCCN Practice Guidelines in Oncology for the identification of patients at increased risk of a BRCA1/BRCA2 mutation , several of these shortcomings are outlined below:

Paternal Inheritance of BRCA1/2 Mutations:

The USPSTF recommendations will miss a significant number of BRCA mutation carriers who have inherited the mutation from their fathers by limiting family history of breast cancer to first degree relatives in the following 2 criteria:

- Two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger
- A first-degree relative with bilateral breast cancer

Hereditary Breast and Ovarian Cancer syndrome has autosomal dominant inheritance with sex-limited expression.[3] A BRCA mutation carrier is equally as likely to have inherited a mutation from her father as from her mother but male BRCA mutation carriers are much less likely to be affected with breast cancer than females (8% vs. up to 87%). [4-13] Close paternal female relatives (paternal aunts, paternal grandmothers, paternal nieces) are not first degree relatives and their cancer history is not considered in the USPSTF criteria highlighted above. The issue is illustrated in the example below:

Case Example

Patient A: 34 year old unaffected patient who has a paternal aunt with breast cancer at age 42 and a paternal grandmother with breast cancer at age 40; both of these second degree relatives are deceased.

Patient B: 34 year old unaffected patient who has a mother with breast cancer at 60 and a maternal aunt with breast cancer at 49; both of these relatives are deceased.

Patient A has a higher probability of carrying a BRCA mutation than patient B (5.6% vs 2.6%)[41]. However, only patient B qualifies for BRCA testing according to USPSTF recommendations.

Ovarian Cancer Significantly Increases Risk of a BRCA1/BRCA2 Mutation:

The USPSTF recommendations will miss a significant number of BRCA mutation carriers due to the requirement for 2 or more first- or second-degree relatives affected with ovarian cancer in order to be considered at increased risk of a mutation. Since the publication of the USPSTF recommendation statement which included a review of published data through October 2004, there have been numerous studies published in peer-reviewed journals proving the high prevalence of BRCA1/BRCA2 mutations among unselected ovarian cancer patients. Approximately 14% of patients with invasive ovarian cancer are BRCA*1/2* mutation carriers.[14-16] Pal et al. found that one third of ovarian cancer patients with identified mutations had NO history of breast or ovarian cancer in a first or second degree relative.[14] These data suggest that BRCA gene mutations account for a large proportion of ovarian cancers and hereditary cancer testing of *BRCA1* and *BRCA2* should be considered for patients with invasive, nonmucinous epithelial carcinomas, regardless of family history or age at diagnosis.[14-16] Therefore, in accordance with the NCCN practice guidelines in oncology, every Colorado Medicaid member with a personal diagnosis of, or ONE close relative (first or second degree) with, epithelial ovarian cancer should be provided BRCA1/BRCA2 test coverage.

Triple Negative Breast Cancer Significantly Increases Risk of a BRCA1/BRCA2 Mutation:

The USPSTF recommendations will miss a significant number of BRCA mutation carriers by failing to include triple negative breast cancer (TNBC) as a risk factor for BRCA mutations. Triple negative breast cancers lack three receptors: estrogen, progesterone, and human epidermal growth factor receptor2. Both *BRCA1* and *BRCA2* mutation carriers have an increased incidence of TNBC. Atchley et al. found 57% of *BRCA1*- and 23% of *BRCA2*-associated breast tumors were triple negative, compared with approximately 14% among sporadic breast cancer patients.[17] Other authors have reported that as many as 90% of breast tumors in BRCA1 carriers are triple negative.[18] Numerous published studies have concluded that patients with TNBC have a significantly increased risk to carry a BRCA gene mutation, with the prevalence of BRCA1 mutations ranging from 9-28%[19-23] and the prevalence of BRCA2 mutations ranging from 4-17%[19,20,24,25] . Two recent studies evaluated populations of patients with TNBC unselected for age at diagnosis or family history, one from MD Anderson Cancer Center[19] and the other from a community oncology practice.[20] The prevalence of germline BRCA1/BRCA2 mutations among the 77 TNBC patients evaluated at MD Anderson was 18%, while the prevalence among the 199 TNBC patients in the community setting was nearly 11%. Therefore, in accordance with the NCCN practice guidelines in oncology[1], every

Colorado Medicaid member with a personal diagnosis of, or ONE close relative (first or second degree) with, TNBC diagnosed at <60 years should be provided BRCA1/BRCA2 test coverage.

Pancreatic Cancer Significantly Increases Risk of a BRCA1/BRCA2 Mutation:

The USPSTF recommendations will miss a significant number of BRCA mutation carriers by failing to include pancreatic cancer as a risk factor for BRCA mutations. Both men and women with mutations in *BRCA1* or *BRCA2* have an elevated risk of pancreatic cancer compared to the general population.[26-33, 34-40] However, *BRCA2* mutation carriers , with a risk of pancreatic cancer of up to 7% by age 80, appear to be at higher risk than *BRCA1* mutation carriers.[28] The risk of pancreatic cancer in the general population is less than 1% by age 80.[29] Because the presence of pancreatic cancer in combination with other HBOC-related risk factors raises the risk of a BRCA mutation in a family, the NCCN added pancreatic cancer to its BRCA test criteria in 2012.

Table 4: Clinical Utility of BRCA Gene Testing Among Patients With and Without Previous Cancer Diagnosis

Reference	Description of Results
Schwartz MD, et al. *Cancer*. 2012;118(2):510-7.	Long-term follow-up of 144 BRCA mutation carriers (mean 5.3 years post genetic test result) found more than 80% of mutation carriers pursued prophylactic mastectomy , prophylactic bilateral salpingo-oophorectomy , or both.
Kauff ND, et al. *J Clin Oncol*. 2008;26:1331-1337.	Prospective study of 1079 BRCA positive women aged ≥30 with intact ovaries found that 65% of BRCA1 mutation carriers pursued prophylactic bilateral salpingo-oophorectomy at a median of 5.5 months after genetic test results and 63% of BRCA2 mutation carriers pursued bilateral salpingo-oophorectomy at a median of 4.1 months after receiving genetic test results
Skytte, et al. *Clin Genet*. 2010;77(4)342-9.	Retrospective study of 306 Danish women with BRCA gene mutations and no personal history of cancer. 10 years post genetic testing, 75% of mutation carriers had undergone risk reducing salpingo-oophorectomy and 50% had undergone risk reducing mastectomy.
Evans DG, et al. *Cancer Epidemiol Biomarkers Prev*. 2009;18(8):2318-24.	Uptake of risk reducing surgeries assessed in British cohort of 211 unaffected BRCA mutation carriers and 3,515 women at >25% lifetime risk of breast cancer but without known BRCA gene mutation. Overall, 40% of the BRCA mutation carriers underwent bilateral risk reducing mastectomy (BRRM) and 45% underwent bilateral risk reducing oophorectomy (BRRO). In contrast, out of the 3,515 women at high risk of breast cancer but no known BRCA mutation only 6.4% of

	those women at 40-45% lifetime risk of breast cancer pursued BRRM; 2.5% of those at 33-39% lifetime risk of breast cancer pursued BRRM; and 1.8% of those at 25-32% lifetime risk of breast cancer pursued BRRM
Manchanda R, et al. *BJOG*. 2012;119(5):527-36.	Out of a population of 1133 women with high risk family histories of breast and ovarian cancer, women who received positive BRCA mutation results were 2.3 times more likely to undergo prophylactic oophorectomy versus high risk patients who were not offered genetic testing (55% at 5 years for BRCA mutation carriers versus 22% at 5 years for high risk untested women)
Metcalfe KA, et al. *Breast Cancer Res Treat*. 2012 Jun;133(2):735-40.	Prospective study of 19 BRCA mutation carriers identified through population screening program for unselected Ashkenazi and Sephardic Jews in Ontario Canada. 2 years post genetic testing, the uptake of prophylactic bilateral salpingo-oophorectomy was 89.5% and the uptake of prophylactic mastectomy was 11.1%. In addition, 100% of the 19 BRCA positive women had undergone breast MRI and mammogram 1 year post genetic test result versus 0% and 63% respectively prior to genetic testing
Metcalfe KA, et al. *J Clin Oncol*. 2008;26:1093-1097.	International cohort of BRCA mutation carriers who had been diagnosed with unilateral breast cancer including 927 subjects. Overall, 49% of the US cohort (302 patients) included in the study opted for contralateral prophylactic mastectomy
Beattie MS, et al. *Genet Test Mol Biomarkers* 2009;13:51-56.	Out of 272 BRCA mutation carriers followed for a median of 3.7 years post genetic test result, 51% chose prophylactic bilateral salpingo-oophorectomy and 23% chose risk reducing mastectomy

Section 2c: Adenomatous Polyposis Syndromes (analyte codes and corresponding ICD-9 codes in Appendix I)

It is respectfully requested that Colorado Medicaid consider providing coverage of genetic testing for adenomatous polyposis syndromes in at-risk members and implement the below criteria taken from the NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening v 1.2013[7]

APC Test Criteria:

- **Personal history of >10 adenomas; or**
- **Personal history of desmoid tumor; or**
- **Known deleterious APC mutation in family**

MYH Test Criteria:

- **Personal history of >10 adenomas; or**
- **Individual meets criteria for Serrated Polyposis Syndrome (SPS)* with at least some adenomas**
- **Known deleterious biallelic MYH mutations in family**

*one or more of the following[7]: at least 5 serrated polyps[±] proximal to the sigmoid colon with 2 or more of these being >10mm; or any number of serrated polyps in an individuals who has a first-degree relative with serrated polyposis; or greater than 20 serrated polyps of any size but distributed throughout the colon

±Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas

<u>Adenomatous Polyposis Syndromes Background:</u>

Hereditary adenomatous polyposis syndromes account for a small, but important, proportion of colorectal cancer (CRC). It is estimated that mutations in the *APC* gene, which cause Familial Adenomatous Polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP), account for up to 1% of all CRC.[1] An additional ~1% of colorectal cancer occurs in individuals

who have a germline mutation in both copies of their *MYH* genes (termed "biallelic mutations"), causing MHY-Associated Polyposis (MAP).[2,3] In two studies looking specifically at early onset CRC (defined as CRC diagnosed either prior to the age of 56[4] or prior to the age of 50[5]), it was estimated that up to 3% of early onset CRC is due to MAP.

Adenomatous polyposis syndromes have historically been associated with severe polyposis, with patients developing hundreds to thousands of colorectal adenomas. It is now known that individuals with *APC* or biallelic *MYH* mutations may have a less severe clinical presentation. Phenotypic analysis of a large, well-studied kindred with AFAP determined that 36.6% of the mutation-positive family members had <10 colonic adenomatous polyps and 13.3% of mutation positive individuals had <10 adenomas and no first degree relative with >10 adenomas.[6] In a multicenter, case-control study, 9 of 26 (~35%) subjects with biallelic *MYH* mutations had no additional adenomas and 7 of 26 (~27%) had a limited number (<10) of adenomas at the time of their colorectal cancer diagnosis.[49]

There is clinical overlap of the hereditary polyposis conditions. FAP is clinically defined as >100 adenomatous colon polyps, although thousands may be observed in some patients.[14] AFAP patients generally have between 10 and 100 adenomas, although some patients may have even fewer adenomas.[15] MAP usually manifests as less severe polyposis and, as a result, appears clinically similar to AFAP.[11,16,17] The presence of ten cumulative colon adenomas is often considered the threshold for when to consider genetic testing for a hereditary polyposis syndrome.[12] In many cases, genetic testing is the only way to make a definitive diagnosis of a hereditary syndrome in a patient with multiple adenomas.

Germline mutations in *APC* account for up to 85-90% of clinically diagnosed FAP and up to 30% of clinically diagnosed AFAP.[8,9] Biallelic *MYH* mutations are estimated to be responsible for ~1.4%[3] of all adenomatous polyposis and for ~15-30% of adenomatous polyposis patients who are negative upon *APC* mutation analysis.[11]

FAP and MAP may present in a single affected individual who has no other family history of colon adenomas or colon cancer. The autosomal recessive pattern of MAP allows for this clinical presentation, which may also result in a family with multiple siblings affected but no other family history in previous generations.[50] Additionally, 20-30% of all individuals with FAP or AFAP will be the first in their family to have the condition.[18] The *APC* mutation in these individuals is *de novo* or "new", meaning that it occurs spontaneously at the time of fertilization of the egg and sperm.

<u>Adenomatous Polyposis Syndromes Increase Colorectal Cancer Risk:</u>

Without medical intervention, nearly 100% of individuals with FAP will develop colorectal cancer. The risk of colorectal cancer in mutation carriers is approximately 93% by age 50 and >99% by age 70.[19] Approximately 70% of untreated individuals with AFAP will develop colorectal cancer in their lifetime.[15] Individuals with biallelic *MYH* mutations are at significantly increased risk for colorectal cancer. A recent population-based study found an 80% risk of CRC

by age 70 years (50 fold increase in risk).[20] Some studies have found a slight increase in CRC risk among carriers of one *MYH* mutation (monoallelic) while other studies have failed to demonstrate an increased risk. This remains an area of active investigation; however if there is an increased CRC risk, it is most likely no more 2 or 3 fold higher than that of the general population. [1,11,20-23]

Familial Adenomatous Polyposis Increases the Risk of Other Cancers:

Individuals with FAP also have elevated lifetime risks for extracolonic cancers. For patients with FAP, the risk of duodenal and periampullary cancer is between 4% and 12%.[24] The risks of thyroid, biliary tract, gastric, pancreatic, and adrenal gland cancers are also increased, as is the risk for cancers of the central nervous system (most often, medulloblastomas).[1,8,25-32] However, the overall lifetime risk for each of these cancers is less than 2%.

There is also a small risk of hepatoblastoma (1.6%) in children prior to age 5.[33] The general population incidence of hepatoblastoma is approximately 0.5 - 1.5 diagnoses per 1 million per year in children younger than 15 years. Hepatoblastoma is a fast growing tumor of the liver that typically occurs in early childhood and often presents with an asymptomatic abdominal mass. Hepatoblastoma is generally treatable when detected early, but fatal when not.[16,33]

Familial Adenomatous Polyposis and Extra-Colonic Features:

Fundic gland polyps of the stomach are found in 26-61% of individuals with FAP. These tumors are often numerous and may occur at young ages. In rare cases, gastric carcinoma has been associated with diffuse fundic gland polyps.[34,35]

Duodenal adenomas are very common in individuals with a polyposis syndrome, with the vast majority located in the first and second portions of the duodenum.[34-37]

Desmoid tumors occur in approximately 15% of individuals with FAP. They can be a major cause of morbidity because of compression and obstruction of inter abdominal structure, and due to challenges in effective treatment. The majority of these tumors occur in the abdomen, most commonly (80%) developing post colectomy.[1,36]

Various additional non-malignant extracolonic features may occur among individuals with FAP, including osteomas, soft tissue tumors, dental abnormalities, and congenital hypertrophy of the retinal pigmented epithelium.[1,38-42]

Most of the available data on extra-colonic cancer risks and other manifestations are based on individuals with FAP. Among individuals with attenuated FAP, findings in the upper gastrointestinal tract (fundic gland polyps, duodenal adenomas and their attendant cancer risks) are not common. Other extra-colonic features are also less commonly observed.

Adenomatous PolyposisSyndromes Medical Management:

The clinical utility of genetic testing for the hereditary polyposis syndromes is based on the availability of medical management options that reduce cancer risk or increase the likelihood of detecting cancer at an earlier stage in identified mutation carriers. These risk management strategies fall into two general categories: surveillance and prophylactic surgery. Published data have demonstrated the efficacy of prophylactic surgery in increasing life expectancy and decreasing mortality from colorectal cancer among individuals with FAP. [42,43] Furthermore, genetic testing of unaffected relatives of a known mutation carrier eliminates the need for invasive and costly surveillance procedures in those family members who have not inherited the family mutation.[45]

Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis Management:

To detect colorectal cancer or polyps in individuals at risk of FAP, the National Comprehensive Cancer Network (NCCN) recommends sigmoidoscopic surveillance annually, beginning between the ages of 10 to 15. Colonoscopy may be preferable due to visualization of the entire colon and the safer and deeper sedation. For individuals at risk of AFAP, the NCCN recommends colonoscopy every 1 to 3 years, depending on adenoma burden, beginning in the late teens or early 20s. Colonoscopy is the method of choice for these patients since polyps often form in the right colon.[1,7]

Without intervention, individuals clinically diagnosed with FAP have nearly a 100% chance to develop CRC; preventive surgery is the standard of care to prevent colon cancer once adenomas are identified. The American Society of Colon and Rectal Surgeons recommends colectomy or proctocolectomy, the timing of which is individualized depending on the severity of polyposis and patient-specific factors.[46]

For those individuals with AFAP, colectomy is eventually needed in about two-thirds of individuals, and depends on the polyp burden and ability to manage polyps endoscopically. Proctectomy is almost never needed in AFAP.[47]

***MYH* –Associated Polyposis Management:**

Surveillance for individuals diagnosed with MAP (biallelic *MYH* mutation carriers) should include colonoscopy beginning at age 25-30 and repeated every 3-5 years if negative.[7] If polyps are detected, the frequency of colonoscopy should increase to every 1-2 years. Upper endoscopy and side viewing duodenoscopy should be considered, beginning at age 30-35 years and repeated every 3-5 years. Patients with duodenal adenomas are treated as FAP patients, although the incidence of duodenal polyps is much less common in MAP compared to FAP and AFAP.[7]

Surgical options for individuals with MAP should be determined based upon the number of adenomas. Those with a large number of adenomas may be offered a colectomy, while those with fewer adenomas may be managed by endoscopic polypectomy.[17,47]

Appendix I : Analyte Codes for Hereditary Colorectal Cancers

Service	2012 CPT Code
	81292
	81294-59
Full sequence and deletion/duplication	81295
analysis of MLH1, MSH2, MSH6, PMS2,	81297-59
and large rearrangement analysis of EPCAM	81298
	81300-59
	81317
	81319-59
Full sequence analysis of MLH1	81292-59
Deletion/duplication analysis of MLH1	81294-59
Known familial variant analysis of MLH1	81293
Full sequence analysis of MSH2	81295-59
Deletion/duplication analysis of MSH2	81297-59
Known familial variant analysis of MSH2	81296
Full sequence analysis of MSH6	81298-59
Deletion/duplication analysis of MSH6	81300-59
Known familial variant analysis of MSH6	81299
Full sequence analysis of PMS2	81317-59
Deletion/duplication analysis of PMS2	81319-59
Known familial variant analysis of *PMS2*	81318
Full Sequence and large rearrangement	81201
analysis of APC and mutation panel of MYH.	81203-59

Mutation-specific analysis for individuals	81202
with a known APC mutation(s) in the family.	
Full sequence and large arrangement	81406
analysis of MYH	
Mutation-specific analysis for individuals	81403
with a known MYH mutation in the family	
Analysis of the two most common MYH	81401
mutations in individuals of European	
ancestry	

ICD-9 Codes for Hereditary Colorectal Cancers[51,52]

ICD-9 Code[49,50]	Description
153.0	malignant neoplasm of hepatic flexure
153.1	malignant neoplasm of transverse colon
153.2	malignant neoplasm of descending colon
153.3	malignant neoplasm of sigmoid colon
153.4	malignant neoplasm of cecum
153.5	malignant neoplasm of appendix vermiformis
153.6	malignant neoplasm of ascending colon
153.7	malignant neoplasm of splenic flexure
153.8	malignant neoplasm of other specified sites of large intestine
153.9	malignant neoplasm of colon unspecified site
154.0	malignant neoplasm of rectosigmoid junction
154.1	malignant neoplasm of rectum
154.2	malignant neoplasm of anal canal
154.3	malignant neoplasm of anus unspecified site
154.8	malignant neoplasm of other sites of rectum rectosigmoid junction and anus
179.0	malignant neoplasm of uterus-part unspecified
182.8	malignant neoplasm of other specified sites of body of uterus
183.0	malignant neoplasm of ovary
183.2	malignant neoplasm of fallopian tube
197.5	secondary malignant neoplasm of large intestine and rectum
v10.05	personal history of malignant neoplasm of large intestine
v10.06	personal history of malignant neoplasm of rectum rectosigmoid junction and anus
v10.42	personal history of malignant neoplasm of other parts of uterus
v12.72	personal history of colonic polyps
182.0	malignant neoplasm of corpus uteri, except isthmus
182.1	malignant neoplasm of isthmus
189.1	malignant neoplasm of renal pelvis

189.2	malignant neoplasm of ureter
189.8	malignant neoplasm of other specified sites of urinary organs
189.9	malignant neoplasm of urinary organ, site unspecified
183.3	malignant neoplasm of broad ligament of uterus
183.5	malignant neoplasm of round ligament of uterus
152.0	malignant neoplasm of duodenum
152.1	malignant neoplasm of jejunum
152.2	malignant neoplasm of ileum
152.3	malignant neoplasm of meckel's diverticulum
152.8	malignant neoplasm of other specified sites of small intestine
152.9	malignant neoplasm of small intestine, unspecified site
230.3	carcinoma in situ of colon
230.4	carcinoma in situ of rectum
230.5	carcinoma in situ of anal canal
230.6	carcinoma in situ of anus, unspecified
230.7	carcinoma in situ of other and unspecified parts of intestine
230.8	carcinoma in situ of liver and biliary system
151.0-151.6, 151.8, 151.9	malignant neoplasm of stomach
157.0	malignant neoplasm of head of pancreas
157.1	malignant neoplasm of body of pancreas
157.2	malignant neoplasm of tail of pancreas
157.3	malignant neoplasm of pancreatic duct
157.4	malignant neoplasm of islets of langerhans
157.8	malignant neoplasm of other specified sites of pancreas
157.9	malignant neoplasm of pancreas part unspecified
191.8	malignant neoplasm of other parts of brain
191.9	malignant neoplasm of brain, unspecified
706.8	other specified diseases of sebaceous glands
706.9	unspecified disease of sebaceous glands
238.2	neoplasm of uncertain behavior of skin
v10.0	personal history of malignant neoplasm of gastrointestinal tract
v10.04	personal history of malignant neoplasm of stomach
v10.03	personal history of malignant neoplasm of ovary
v10.5	personal history of malignant neoplasm of urinary organs
v10.50	personal history of malignant neoplasm of urinary organ, unspecified
v10.53	personal history of malignant neoplasm of renal pelvis
v10.83	personal history of other malignant neoplasm of skin
v10.85	personal history of malignant neoplasm of brain
v10.89	personal history of malignant neoplasm of other sites
v10.9	unspecified personal history of malignant neoplasm
v16.0	family history of malignant neoplasm of gastrointestinal tract

v16.41	family history of malignant neoplasm of ovary
v16.5	family history of malignant neoplasm of urinary organs
v16.51	family history of malignant neoplasm of kidney
v16.59	family history of malignant neoplasm of other urinary organs
v16.8	family history of other specified malignant neoplasm
v16.9	family history of unspecified malignant neoplasm
v18.51	family history of colonic polyps
v84.0	genetic susceptibility to malignant neoplasm
v84.02	genetic susceptibility to malignant neoplasm of ovary
v84.09	genetic susceptibility to other malignant neoplasm
v18.9	family history of genetic disease carrier
v84.04	genetic susceptibility to malignant neoplasm of endometrium
v84.09	genetic susceptibility to other malignant neoplasm
v84.89	genetic susceptibility to other disease
795.4	other nonspecific abnormal histological findings
796.9	other nonspecific abnormal findings

Appendix II: Analyte Codes for Hereditary Breast and Ovarian Cancer Syndrome

Service	2012 CPT Code
Full sequence analysis of BRCA1 and BRCA2	81211
Comprehensive analysis for	81213-59
deletion/duplications in BRCA1 and BRCA2	
Full sequence analysis and common	81211
deletion/duplication panel of BRCA1	
and BRCA2	
Analysis of the three most common BRCA1	81212
or BRCA2 mutation in individual of	
Ashkenazi Jewish ancestry	
Full sequence analysis and common	
deletion/duplication panel for individuals	81211-59
whose results from the three most common BRCA1 or	
BRCA2 mutation testing are negative	
Comprehensive analysis for	81213-59
deletions/duplications in BRCA1 and	
BRCA2	
Full sequence and common	81214
deletion/duplication analysis of BRCA1	
Known familial variant analysis of BRCA1	81215

Full sequence analysis of BRCA2	81216
Known familial variant analysis of BRCA2	81217

ICD-9 Codes for Hereditary Breast and Ovarian Cancer[51,52]

ICD-9 code	Description
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of central portion of female breast
174.2	Malignant neoplasm of upper-inner quadrant of female breast
174.3	Malignant neoplasm of lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female), unspecified
175.0	Malignant neoplasm of nipple and areola of male breast
175.9	Malignant neoplasm of other and unspecified sites of male breast
157.0	Malignant neoplasm of head of pancreas
157.1	Malignant neoplasm of body of pancreas
157.2	Malignant neoplasm of tail of pancreas
157.3	Malignant neoplasm of pancreatic duct
157.4	Malignant neoplasm of islets of langerhans
157.8	Malignant neoplasm of other specified sites of pancreas
157.9	Malignant neoplasm of pancreas part unspecified
158.0	Malignant Neoplasm of Retroperitoneum
158.8	Malignant Neoplasm of Specified Parts of Peritoneum
158.9	Malignant neoplasm of peritoneum, unspecified
183.0	Malignant Neoplasm of Ovary
183.2	Malignant Neoplasm of Fallopian Tube
185.0	Malignant neoplasm of prostate
233.0	Carcinoma In Situ of Breast
V10.3	Personal history of malignant neoplasm of breast

V10.43	Personal history of malignant neoplasm of ovary
V10.46	Personal history of malignant neoplasm of prostate
V16.0	Family history of malignant neoplasm
V16.3	Family history of malignant neoplasm of breast
V16.41	Family history of malignant neoplasm of ovary
V16.8	Family history of other specified malignant neoplasm
V16.9	Family history of unspecified malignant neoplasm
V16.42	Family history of malignant neoplasm of prostate
V86.1	Estrogen receptor negative status [ER-]
V84.0	Genetic susceptibility to malignant neoplasm
V84.01	Genetic susceptibility to malignant neoplasm of breast
V84.02	Genetic susceptibility to malignant neoplasm of ovary
V84.09	Genetic susceptibility to other malignant neoplasm
V84.03	Genetic susceptibility to malignant neoplasm of prostate
V18.9	Family history of genetic disease carrier

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