Draft Benefit Coverage Standard for Genetic Testing Recommendations

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Table of Contents

Section 1: Summary of Coverage Recommendations

Recommendation 1: Lynch Syndrome Testing (Please refer to Section 2a for evidence supporting recommendation)

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: Genetic/Familial High-Risk Assessment: Colorectal v2.2014.[1]

For individuals without a personal diagnosis of a Lynch Syndrome-related cancer

- Close relative meeting Revised Bethesda Guidelines; or
- Close relative meeting Amsterdam II Guidelines; or
- Close relative with endometrial cancer under age 50; or
- Close relative with known Lynch syndrome
- Individuals with ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict)

For individuals with a personal diagnosis of a Lynch Syndrome-related cancer

- Meets Revised Bethesda Guidelines; or
- Meets Amsterdam II Guidelines; or
- Diagnosed with endometrial cancer under age 50; or
- Close relative with known Lynch syndrome
- Individuals with ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict)

Recommendation 2: Adenomatous Polyposis Syndromes (Please refer to Section 2b for evidence supporting recommendation)

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: Genetic/Familial High-Risk: Colorectal v2.2014.[1]

***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

Recommendation 3: Next Generation Sequencing for Hereditary Cancer Syndromes (Please refer to Section 2c for evidence supporting recommendation)

It is respectfully requested that Colorado Medicaid consider coverage for Next Generation Sequencing for Hereditary Cancer syndromes for patients meeting Colorado Medicaid's criteria for *BRCA* or Lynch syndrome genetic testing.

Recommendation 4: *BRCA1* and *BRCA2* Genetic Testing (Please refer to Section 2d for evidence supporting recommendation)

It is respectfully requested that Colorado Medicaid provide clarification of coverage criteria for *BRCA1* and *BRCA2* genetic testing and implement the below criteria taken from the NCCN Practice Guidelines in Oncology Genetic/Familial High-Risk Assessment: Breast and Ovarian v.2.2014.[67]

- **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**
  - **Diagnosed ≤50y with:**
    - **An additional primary[B]**
    - **≥1 close blood relative[C] with breast cancer at any age**
    - **An unknown or limited family history**
  - **Diagnosed ≤60y with a**
    - **Triple negative breast cancer**
  - **Diagnosed at any age with:**
    - **≥1 close blood relative[C] with breast cancer diagnosed ≤50 y**
    - **≥2 close blood relatives [C] with breast cancer at any age**
    - **≥1 close blood relative [C] with epithelial ovarian cancer[D]**
    - **≥2 close blood relatives [C] with pancreatic cancer or prostate cancer (Gleason score ≥7) at any age**
    - **Close male blood relative [C] with breast cancer**
    - **For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required**
- **Personal history of epithelial ovarian cancer [D]**
- **Personal history of male breast cancer**
- **Personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives [C] with breast and/or ovarian [D] and/or pancreatic or prostate cancer (Gleason score ≥7) at any age**
  - **For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative [C] is needed.**
- **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 [D] with ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian cancer [D]**

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 – close blood relatives include first-, second-, and third-degree relatives on the same side of

the family
D – fallopian and primary peritoneal cancers are included

Recommendation 5: BRACAnalysis CDx as a companion diagnostic for Lynparza (olaparib) (Please refer to Section 3a for evidence supporting recommendation)

It is respectfully requested that Colorado Medicaid consider BRACAnalysis CDx™ as a covered service for the evaluation of *BRCA* mutation status as a companion diagnostic for Lynparza™ (olaparib).

Recommendation 6: Prolaris Prostate Cancer Genomic Assay (Please refer to Section 4a for evidence supporting recommendations)

It is respectfully requested that Colorado Medicaid consider coverage of Prolaris for patients with localized prostate cancer.

Recommendation 7: Vectra DA (Please refer to section 5a for evidence supporting recommendations)

It is respectfully requested that Colorado Medicaid consider coverage of Vectra DA for patients with rheumatoid arthritis.

Section 2: Hereditary Cancer Syndromes Covered Services and Limitations

Section 2a: Lynch Syndrome

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: Genetic/Familial High-Risk Assessment: Colorectal v2.2014[1]

For individuals without a personal diagnosis of a Lynch Syndrome-related cancer

- **Close relative meeting Revised Bethesda Guidelines[table1]; or**
- **Close relative meeting Amsterdam II Guidelines[table1]; or**
- **Close relative with endometrial cancer under age 50; or**
- **Close relative with known Lynch syndrome**
- **Individuals with ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict)**

For individuals with a personal diagnosis of a Lynch Syndrome-related cancer

- **Meets Revised Bethesda Guidelines; or**
- **Meets Amsterdam II Guidelines; or**
- **Diagnosed with endometrial cancer under age 50; or**
- **Close relative with known Lynch syndrome**
- **Individuals with ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict)**

Table 1: Revised Bethesda and 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
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 per the Center for Disease Control's (CDC) Tier 1 category suggests coverage of Lynch syndrome genetic testing for patients with newly diagnosed colorectal cancer per the EGAPP evidence review published in 2009.[2] All other indications for Lynch syndrome genetic testing are considered Tier 2 and would not be covered indications per the current draft benefit coverage standard.

While newly diagnosed colorectal cancer patients are an important patient population to evaluate for Lynch syndrome (LS), it is important to recognize that the goal of the EGAPP evidence review was to evaluate population screening methodologies for LS among newly diagnosed colorectal cancer patients. The EGAPP Working Group (EWG) did NOT evaluate methodologies *or make recommendations* for identifying LS among patients previously diagnosed with colorectal cancer or 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 previously diagnosed with colorectal cancer and/or 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. Specifically, CMS has been covering LS testing in individuals who meet Revised Bethesda guidelines, or Amsterdam II guidelines, or are diagnosed with endometrial cancer <50y, for several years.[3] 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 (promoting the health and well-being of patients at-risk for LS), with the ability to significantly reduce overall incidence of both colorectal and endometrial cancers.[4]

Evidence supporting LS gene testing in individuals previously diagnosed with colorectal cancer, affected with LS-related cancers other than colorectal, and in unaffected individuals based on a family history of LS-related cancers is as follows:

Previously diagnosed Colorectal Cancer: Individuals with previously diagnosed colorectal cancer should be candidates for Lynch syndrome testing based upon Revised Bethesda Guidelines, Amsterdam II guidelines, or a ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict).

Colorectal cancer (CRC) has long been considered to be the hallmark cancer of LS. It is estimated that 1 in 30 patients with CRC have Lynch syndrome[5], and there is no data to indicate that the prevalence of Lynch syndrome differs between newly diagnosed and previously diagnosed patients with CRC. As a result, the same principles outlined by EWG apply to previously diagnosed patients with CRC: high analytic sensitivity and specificity of diagnostic tests, adequate levels of clinical sensitivity and specificity of testing approaches, and adequate levels of clinical utility. The CDC tier system indicates that testing services with CMS coverage or that are supported by evidenced based guidelines are considered Tier 1 tests[6]. CMS has long been covering LS testing for patients with colorectal cancer who

meet Revised Bethesda guidelines or Amsterdam II guidelines, regardless of when diagnosed[3]. Evidenced-based societal guidelines (American Society of Clinical Oncology [ASCO][7], NCCN[1], US Multi-Society Task Force [USMSTF][8]) also support LS testing for patients with colorectal cancer who meet Revised Bethesda Guidelines, Amsterdam II guidelines, or have a ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict). **Therefore, based upon the CDC definition of tiers, LS genetic testing should be considered covered testing for colorectal cancer patients meeting Revised Bethesda, Amsterdam II guidelines, or >5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict), regardless of timing of diagnosis, as non-coverage would significantly deviate from the standard of care for colorectal cancer patients as outlined by CMS coverage and societal guidelines.**

Endometrial Cancer: Women with endometrial cancer diagnosed <50y should be candidates for Lynch syndrome testing.

Several publications have addressed the significance of endometrial cancer in LS.[5,9-11] The prevalence of LS among individuals with endometrial cancer is similar to that of colorectal cancer.[5] The CDC tier system indicates that testing services with CMS coverage or that are supported by evidenced based guidelines are considered Tier 1 tests.[6] CMS has long been covering LS testing for women with endometrial cancer diagnosed <50y.[3] The current NCCN guidelines[1] as well as the US Multi-Society Task Force on Colorectal Cancer[8] support endometrial cancer diagnosed before age 50 as a testing criterion. **Therefore, based upon the CDC definition of tiers, LS genetic testing should be considered a covered testing service for women with endometrial cancer diagnosed <50y as non-coverage would significantly deviate from the standard of care for endometrial cancer patients as outlined by CMS coverage and societal guidelines.**

Other cancers associated with Lynch syndrome: Additional LS-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.[12] **Individuals with the other LS-associated cancers should also be considered appropriate for LS genetic testing, based on a family history meeting Amsterdam II or revised Bethesda guidelines.[1]**

Unaffected patients: Individuals with family histories concerning for LS as defined by Revised Bethesda Guidelines, Amsterdam II guidelines or a ≥5% risk of LS on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict) should be candidates for LS testing.

While the ideal scenario for genetic evaluation revolves around initially testing an affected relative, this 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. As a result, this testing approach often leaves patients with significant family histories concerning for LS unable to be adequately assessed for their risk of LS. In addition, there has been growing evidence that testing patients for LS based upon their family history leads to improved adherence to surveillance and management guidelines which promotes the health and well-being of at-risk patients and is a cost-effective strategy that reduces the colorectal and endometrial cancer incidence in these high-risk individuals.

Improved adherence to surveillance management guidelines and improved outcomes: Individuals with LS have up to an 80% risk of colorectal cancer and up to a 71% risk of endometrial cancer.[1,8] Among unaffected individuals with mutation-proven LS, several studies have demonstrated a high compliance rate with the recommended colorectal cancer surveillance strategies and a significant clinical impact.[13-15,table 2] Published data demonstrates that genetic testing for LS significantly improves adherence to cancer screening recommendations, with 73-100% of mutation carriers undergoing colonoscopy.[13-15] This improved surveillance has been demonstrated to improve outcomes for patients by significantly reducing cancer risk and mortality of LS-associated cancers. Specifically, 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.[16-17] 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.[18]

Cost-effectiveness: A publication by Dinh et al.[4] evaluated the health outcomes and cost effectiveness of a strategy to identify and test unaffected individuals at-risk for LS. 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.

Given the cost-effectiveness of LS genetic testing in unaffected patients as well as strong evidence that identification of LS mutation carriers results in high compliance rates with guideline recommended surveillance and management strategies which have been shown to significantly reduce cancer risk and improve outcomes, evidenced based societal guidelines (NCCN, USMSTF) support testing of unaffected patients who have family histories that meet Revised Bethesda Guidelines, Amsterdam II guidelines or in patients who have a ≥5% risk of Lynch syndrome on one of the following risk prediction models (MMRpro, PREMM[1,2,6], or MMRpredict).[1,8] **Therefore, LS testing should be considered a covered testing service for unaffected patients with family histories concerning for LS (as outlined in the proposed criteria above) as non-coverage would significantly deviate from the standard of care as put forth by societal guidelines.**

Table 2: 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: Adenomatous Polyposis Syndromes

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: Genetic/Familial High-Risk: Colorectal v2.2014.[1]

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: 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

The CDC does not address genetic testing for the adenomatous polyposis syndromes, and therefore this testing would not be covered under the draft coverage benefit standard in its

current form.[6] The below comments address why genetic testing for adenomatous polyposis syndromes should be considered a covered service.

Adenomatous Polyposis Syndromes Background:

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.[19] 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 *MYH*-Associated Polyposis.[20,21] In two studies looking specifically at early onset CRC (defined as CRC diagnosed either prior to the age of 56[22] or prior to the age of 50[23]), it was estimated that up to 3% of early onset CRC is due to *MYH*-Associated Polyposis.

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 (MAP) 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.[24] In a multicenter, case-control study, 9 of 26 (~35%) subjects with MAP had no additional adenomas and 7 of 26 (~27%) had a limited number (<10) of adenomas at the time of their colorectal cancer diagnosis.[25]

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.[26] AFAP patients generally have between 10 and 100 adenomas, although some patients may have even fewer adenomas.[27] MAP usually manifests as less severe polyposis and, as a result, appears clinically similar to AFAP.[28-30] The presence of >10 cumulative colorectal adenomas is often considered the threshold for when to consider genetic testing for a hereditary polyposis syndrome.[31] 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.[32,33] MAP is estimated to be responsible for~1.4%[21]of all adenomatous polyposis and for ~15-30% of adenomatous polyposis patients who are negative upon *APC* mutation analysis.[33]

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.[34] Additionally, 20-30% of all individuals with FAP or AFAP will be the first in their family to have the condition.[35] 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.

Adenomatous Polyposis Syndromes Increase Colorectal Cancer Risk:

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.[36] Approximately 70% of untreated individuals with AFAP will develop colorectal cancer in their lifetime.[27] Individuals with MAP are at significantly increased risk for colorectal cancer. A population-based study found an 80%risk of CRC by age 70 years (50 fold increase in risk).[37]

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%.[38] 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).[19,32,39-46]

There is also a small risk of hepatoblastoma (1.6%) in children prior to age 5.[47] The general population incidence of hepatoblastoma is approximately 0.5-1.5 diagnoses per 1 million per year in children younger than 15years. 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.[28,47]

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.[48,49]

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.[48-51]

Desmoid tumors occur in approximately 15% of individuals with FAP. They can be a major cause of morbidity because of compression and obstruction of interabdominal structure, and due to challenges in effective treatment. The majority of these tumors occur in the abdomen, most commonly (80%) developing post colectomy.[19,51]

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.[19,52-56]

Most of the available data on extra-colonic cancer risks and other manifestations are based on individuals with FAP. Among individuals with AFAP, findings in the upper gastrointestinal tract (fundic gland polyps, duodenal adenomas and their attendant cancer risks) are seen. Other extra-colonic features are less commonly observed.

Adenomatous Polyposis Syndromes Medical Management:

The clinical utility of genetic testing for the adenomatous 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.[56,57] 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.[26]

Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis Management:

To detect colorectal cancer or polyps in individuals at risk of FAP, the 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.[1,19]

Without intervention, individuals clinically diagnosed with FAP have nearly a 100% chance to develop CRC; preventive surgery is the standard of care to prevent colorectal cancer once adenomas are identified. The American Society of Colon and Rectal Surgeons (ASCRS) recommends colectomy or proctocolectomy, the timing of which is individualized depending on the severity of polyposis and patient-specific factors.[58]

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.[59]

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

Surveillance for individuals diagnosed with MAP should include colonoscopy beginning at age 25-30 and repeated every 3-5 years if negative. 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 1-5 years, depending on adenoma burden. Patients with duodenal adenomas are treated as FAP patients, although the incidence of duodenal polyps is less common in MAP compared to FAP and AFAP.[1]

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.[1,29,59]

CMS Coverage and Societal Guideline Support

The CDC tier system indicates that testing services with CMS coverage or that are supported by evidenced based guidelines are considered Tier 1 tests.[6] CMS has long been covering *APC* and *MYH* testing for individuals with multiple colorectal adenomas.[3] Evidenced-based guidelines including NCCN, American Gastroenterological Association (AGA), and ASCRS guidelines support *APC* and *MYH* testing for individuals with multiple colorectal adenomas.[1,26,60]
Therefore, based upon the CDC definition of tiers, *APC* and *MYH* testing should be considered a covered testing service for individuals with concerning histories (as outlined above) as non-coverage would significantly deviate from the standard of care for patients as outlined by CMS coverage and societal guidelines.

Section 2c: Next Generation Sequencing for Hereditary Cancer Syndromes

It is respectfully requested that Colorado Medicaid consider coverage for Next Generation Sequencing for Hereditary Cancer syndromes for patients meeting Colorado Medicaid's criteria for *BRCA* or Lynch syndrome genetic testing.

The CDC currently classifies all next generation sequencing tests as Tier 3,[6] and therefore would not be covered under the draft coverage benefit. There are a wide variety of next generation sequencing tests which have been developed to assess for the risk of many different disease states which have varying levels of evidence supporting their use in clinical care. The below comments are specific to next generation sequencing tests for hereditary cancer risk assessment.

Multi-Gene Testing for Hereditary Cancer Evaluation: Background

The testing approach for hereditary cancer has been based on the analysis of one or a small number of genes (such as *BRCA1/2*) for a single syndrome, with the test choice determined by evaluation of a patient's personal and family history of cancer. However, a shift has occurred towards a new model, which involves the simultaneous analysis of multiple genes combined into one test, to better target likely causative genes and improve the clinical sensitivity of the testing approach.

The transition from single syndrome to panel genetic testing is being driven by:

- improved understanding of the genetic heterogeneity underlying many cancers involved with hereditary cancer syndromes (i.e. mutations in different genes leading to the same cancers)
- similar clinical presentations of different hereditary cancer syndromes, making it difficult to select one single syndrome test over another
- advances in laboratory techniques, enabling the simultaneous analysis of multiple genes, providing greater efficiency at a cost similar to single syndrome testing.

Clinical Rationale:

The first key study highlighting the importance of a new approach for diagnosing hereditary cancer was published in 2011 when Walsh et al. investigated the prevalence of inherited gene mutations in an unselected ovarian cancer population.[61] Out of 360 women with primary ovarian cancer, 24% carried germline mutations in 12 different genes. While *BRCA1* and *BRCA2* represented the majority of the mutations, one-quarter of mutation carriers would have been missed without the analysis of the other genes in the study. The authors concluded that the panel approach is warranted in this population of patients meeting criteria for *BRCA1/2* testing, and that massively parallel sequencing (also known as next generation sequencing, or NGS) allows testing for many genes simultaneously in a cost effective manner.

Subsequent studies from multiple key opinion leaders in the field of cancer genetics have added to the knowledge base supporting the panel approach to hereditary cancer testing. Three studies of patients meeting testing criteria for Hereditary Breast and Ovarian Cancer (HBOC) syndrome or Lynch syndrome (LS) have shown an approximate 40- 60% increase in clinical sensitivity when using a multi-gene testing approach compared to the single syndrome approach (these specific studies were based upon utilization of a 25-gene hereditary cancer test).

Increased Mutation Detection: Studies of patients appropriate for HBOC or LS testing have shown a 40-60% relative increase in clinical sensitivity using multi-gene (25 gene) hereditary cancer testing compared to the single syndrome test approach for HBOC or LS. In a population of patients suspected of having HBOC, using a multi-gene test, 32% of carriers were found to have a mutation in clinically actionable genes other than *BRCA1/2*. Overall, 46% more clinically actionable mutations were detected with the multi-gene test versus what would have been identified with *BRCA*1/2 testing alone.[62] A follow-up study by Sharma et al. presented at the San Antonio Breast Cancer Symposium (2014) evaluated the mutation detection of multi-gene (25-gene) testing as compared to single syndrome testing in 17,152 breast cancer patients meeting NCCN hereditary cancer testing guidelines. This study found that 48.9% of mutation carriers had a *BRCA1/2* mutation while 51.1% of mutation carriers had a mutation in one of the other 23 genes, representing a 104.5% increase in mutation detection.[63] In addition, Sharma et al. also found that 45 of 1,640 mutation carriers had a mutation detected in more than one gene, which would alter management per NCCN guidelines.[67] In a population of patients suspected of having LS, using multi-gene (25-gene) testing, 28% of carriers were found to have a mutation in clinically actionable genes other than the 5 known LS genes (*MLH1*, *MSH2*, *MSH6*, PMS2, *EPCAM*).[64] Notably, 35% of the non-LS mutations were in the *BRCA1* or *BRCA2* genes, and of these only 33% would have been identified as *BRCA1* and *BRCA2* testing candidates based upon current *BRCA* testing guidelines. Overall, 41% more clinically actionable mutations were detected with multi-gene testing versus what would have been identified with LS genetic testing alone. Data has also demonstrated significant clinical overlap in polyposis syndromes which results in difficulty in clinical classification, which can be addressed by multi-gene given its ability to assess multiple polyposis associated genes simultaneously.[65,66]

Tailored Medical Management: Currently, approximately 90% of patients undergoing single syndrome (*BRCA1/2* or Lynch) testing receive a negative result and must be managed based upon their personal and family history. NCCN guidelines state that, with a panel approach, "the higher mutation detection rate may reduce the number of high-risk families with uninformative (negative) tests.[67]" With multi-gene (25-gene) testing, 40-60% more patients would be identified to have a clinically actionable genetic test result with clearly-defined gene-associated cancer risks. These cancer risks would be more accurate than those estimated by personal and family history alone. The genes on the multi-gene tests are associated with a level of cancer risk that would be considered actionable by professional society guidelines such as NCCN. The NCCN states that the higher mutation detection rate seen with a multi-gene approach "…may increase the number of patients who are provided with tailored surveillance, risk reduction options, and testing of at-risk family members.[67]"

Clinical Utility: The clinical utility of a multi-gene (25-gene) test was evaluated through a study of 1,111 patients undergoing testing.[68] Providers were surveyed pre- and post-test regarding their management recommendations for breast, ovarian, endometrial and colorectal cancers for each patient being tested. Over 74% of providers used both the genetic test result and a management tool to make management decisions. Patients with positive genetic test results had management changes 78% of the time and patients with negative test results had management changes in approximately 25% of cases based on

information gained from the management tool. Clinicians appreciate the clinical value of multi-gene testing's more comprehensive approach and the effect on improved patient care. The increased clinical sensitivity of multi-gene (25-gene) and the impact of tailored medical management resulting from improved risk stratification of the member population will result in improved outcomes for Colorado Medicaid recipients and a net cost savings for the program. Specifically, modeling would indicate that utilization of a multi-gene testing for Colorado Medicaid's membership would result in 10 cancers avoided and 4 cancers detected earlier, as compared with the single syndrome approach (just *BRCA1/2* or LS) thereby allowing for better health and well-being of Colorado Medicaid members. **Economic modeling would estimate that this would translate into nearly $2.6 million in savings for the Colorado Medicaid program over the next 15 years due to additional cancers avoided or detected earlier.**

Current Clinical Use:

Given the above evidence which has shown that multi-gene hereditary cancer testing can more comprehensively evaluate a patient's hereditary cancer risk, currently approximately 50-60% of all requests for hereditary cancer testing in Colorado are for multi-gene rather than single syndrome tests such as *BRCA1/2* or LS with approximately 150 Colorado clinicians utilizing multi-gene testing results to inform the clinical care of their patients. A study was conducted to assess the utilization of hereditary cancer testing multi-gene (25-gene) testing as compared to single-syndrome testing (*BRCA1/2*) based upon patient preference.[69] The majority of patients (73%) chose to pursue multi-gene testing and 12.2% were identified to have a disease-causing mutation. Of the gene mutations identified, 33.3% were in genes other than *BRCA1/2* which influenced clinical management.

Professional Societal Guidelines Support of Multi-Gene Hereditary Cancer Testing:

The NCCN guidelines provide the option of either a targeted (single syndrome) approach, or a multi-gene approach as a first-line test, in the algorithm to evaluate a patient at high risk of breast and/or ovarian cancer.[67] NCCN states that because multiple genes may contribute to breast/ovarian cancer, and there is often overlap in the cancers associated with different genes, an advantage of the multi-gene test is the ability of a "broad and unbiased" testing approach to detect mutations that might otherwise have gone undetected. The higher mutation detection rate is expected to reduce the number of uninformative negative results and increase the number of patients who can be provided with tailored medical management recommendations. NCCN points out that multi-gene testing is more cost- and time-effective than sequentially testing more than 2-3 single genes.

The Society of Gynecologic Oncology (SGO) published a practice statement in March, 2014, entitled "Next Generation Cancer Gene Panels versus Gene by Gene Testing".[70] SGO states that the "a(A)dvantages of cancer gene panels include decreased cost and improved efficiency of cancer genetic testing by decreasing the time involved, number of patient visits, and number of tests sent. A negative genetic test is more reassuring at eliminating the likelihood of inherited risk when all known genes for that phenotype have been assayed". SGO discusses the importance of accurate understanding of results and appropriate management of patients that test positive.

Conclusion:

The above data demonstrate that the multi-gene hereditary cancer testing approach significantly improves patient care by providing a more comprehensive approach to hereditary cancer testing. The data indicates that the multi-gene (25-gene) approach will identify disease causing mutations in 40-60% more high-risk individuals. These individuals will now have specific cancer risk information that can be utilized to more appropriately manage their risks according to societal guidelines. Given that it is known that there is significant genetic heterogeneity underlying many cancers involved with hereditary cancer syndromes (i.e. mutations in different genes leading to the same cancers) and that similar clinical presentations of different hereditary cancer syndromes make it difficult to select one single syndrome test over another, multi-gene hereditary cancer testing will allow for a more cost-effective approach providing greater efficiency at a cost similar to single syndrome testing. In addition, by more comprehensively understanding patients' hereditary cancer risks, economic modeling would estimate nearly $2.6 million in savings for the Colorado Medicaid program over the next 15 years due to additional cancers avoided or detected earlier, compared to the current approach. This approach represents a significant advance in hereditary cancer risk assessment which will promote the health and well-being of Colorado Medicaid members. **Therefore, based upon the significant evidence and guideline support of multi-gene hereditary cancer testing, it is respectfully requested that Colorado Medicaid consider coverage for Next Generation Sequencing for Hereditary Cancer syndromes for patients meeting Colorado Medicaid's criteria for *BRCA* or LS genetic testing.**

Section 2d: BRCA1 and BRCA2

It is respectfully requested that Colorado Medicaid provide clarification regarding the coverage criteria for *BRCA1* and *BRCA2* genetic testing and implement the most current NCCN Practice Guidelines in Oncology Genetic/Familial High-Risk Assessment: Breast and Ovarian, which is currently version v.2.2014 (current criteria outlined below).[67]

- **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**
  - **Diagnosed ≤50y with:**
    - **An additional primary[B]**
    - **≥1 close blood relative[C] with breast cancer at any age**
    - **An unknown or limited family history**
  - **Diagnosed ≤60y with a**
    - **Triple negative breast cancer**
  - **Diagnosed at any age with:**
    - **≥1 close blood relative[C] with breast cancer diagnosed ≤50 y**
    - **≥2 close blood relatives [C] with breast cancer at any age**
    - **≥1 close blood relative [C] with epithelial ovarian cancer[D]**
    - **≥2 close blood relatives [C] with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age**
    - **Close male blood relative [C] with breast cancer**
    - **For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required**

- **Personal history of epithelial ovarian cancer [D]**

- **Personal history of male breast cancer**

- **Personal history of pancreatic cancer or prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives [C] with breast and/or ovarian [D] and/or pancreatic or prostate cancer at any age**
    - **For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative [C] is needed.**

- **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 [D] with ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian cancer [D]**

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 – close blood relatives include first-, second-, and third-degree relatives on the same side of the family
D – fallopian and primary peritoneal cancers are included

The current CDC Tier system does not incorporate "Testing for *BRCA1* and *BRCA2*", except to recommend against its use in the general population in Tier 3.[6] Tier 1 includes the use of family history of breast/ovarian cancer or other types of *BRCA*-related cancer for the purpose of "risk prediction," but not the actual *BRCA1* and *BRCA2* genetic test. Therefore the coverage of *BRCA1/2* testing is unclear per the draft coverage benefit in its current form.

Rarely is the family history of cancer alone sufficient enough to warrant the significant changes in surveillance and consideration of preventative surgery that clearly would be recommended if the patient received a positive genetic test result. There is significant medical and economic value in proactively identifying mutation carriers prior to the onset of disease. A publication by Holland et al.[72] and a more recent update by Kaldate et al.[73] determined that genetic testing of the *BRCA1* and *BRCA2* genes for unaffected women is cost-effective using current guidelines.

The result of unclear coverage of *BRCA1* and *BRCA2* testing is that mutation-positive individuals will remain undetected and therefore unable to take the necessary steps for risk-reduction and cancer prevention. *BRCA1* and *BRCA2* mutation carriers have up to an 87% and 44% chance of developing breast or ovarian cancer, respectively, in addition to a significantly increased risk of developing multiple primary cancers.[74-76] The published medical management recommendations for these individuals include increased surveillance (including breast MRI), risk-reducing oophorectomy between ages 35 and 40, and consideration of risk-reducing mastectomy.[67] All of the published studies demonstrating the efficacy of these approaches in reducing risk or preventing breast and/or ovarian cancer have included mutation carriers not yet affected by cancer.[77-82]

BRCA1 and *BRCA2* genetic testing has been considered a standard of care for the evaluation of patients with personal and/or family histories of breast and ovarian cancer for over a decade

given its documented clinical utility in both affected and unaffected at-risk individuals[table 3]. A pivotal prospective multi-center cohort study was conducted to assess the relationship of risk reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) on cancer outcomes in *BRCA* mutation carriers.[71] This study found that RRM was associated with a lower risk of breast cancer and that RRSO was associated with lower risk of ovarian cancer, primary breast cancer, all-cause mortality (HR 0.40), breast cancer-specific mortality (HR 0.44) and ovarian cancer specific mortality (HR 0.21).

Table 3: 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

CMS and Societal Guideline Support

CMS[3], as well as Colorado Medicaid and all commercial insurers, have long been covering *BRCA1* and *BRCA2* testing for patients. In addition, multiple evidenced-based societal guidelines (ASCO[7], NCCN[67], SGO[83], American Society of Breast Surgeons[84], U.S. Preventive Services Task Force[146]) as well as the Affordable Care Act (via Public Health Services Act section 2713) also support *BRCA1* and *BRCA2* testing for patients for at-risk patients. Of note, the ACA recommendation regarding *BRCA* evaluation was clarified to include "referral for genetic counseling and ***BRCA* testing**, if appropriate."

Conclusion:

Based upon the CDC definition of tiers, given CMS coverage and societal guidelines support, *BRCA1* and *BRCA2* genetic testing should be considered a covered service for patients meeting the current NCCN Genetic/Familial High-Risk: Breast and Ovarian testing guidelines as non-coverage would significantly deviate from the standard of care for patients as outlined by CMS coverage and societal guidelines.

Section 3: Genetic Companion Diagnostic Covered Services and Limitations:

3a: BRACAnalysis CDx™

It is respectfully requested that Colorado Medicaid consider coverage for Myriad's BRACAnalysis CDx™ as a companion diagnostic to Lynparza (olaparib).

BRACAnalysis CDx Background:

The Food and Drug Administration (FDA) announced approval of BRACAnalysis CDx™ on December 19, 2014, Premarket Approval Number (PMA) P140020.[85] This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, per the FDA label. The BRACAnalysis CDx device is a companion diagnostic for AstraZeneca's drug Lynparza™ (olaparib), a poly ADP-ribose polymerase (PARP) inhibitor. The BRACAnalysis CDx test is a service that is intended to detect germline *BRCA1* and *BRCA2* variants and provide a clinical interpretation of the identified variants. Results of the test may be used as an aid in

identifying ovarian cancer patients with deleterious or suspected deleterious germline *BRCA* variants eligible for treatment with Lynparza™ (olaparib).[86]

The National Cancer Institute estimated that for 2014 there will be 21,980 new cases of ovarian cancer reported, and an estimated 14,270 deaths from this disease. The incidence of ovarian cancer increases with advancing age, and the median age of diagnosis is 63 years.[87] The majority of cases (75%) present with advanced disease that is treated with surgery and chemotherapy, and the risk of relapse for these cases is as high as 70% after response to initial therapy. Due to the majority of ovarian cancer patients requiring multiple lines of therapy, the development of targeted therapies to improve outcomes is an ongoing area of focus for this patient population, as well as identification of biomarkers that are predictive of a response to optimize care of patients with recurrent ovarian cancer.[88]

BRCA1 and *BRCA2* mutations are important contributors to ovarian cancer, as the risk for a woman with a germline *BRCA* mutation to develop ovarian cancer by age 70 is up to 44% compared to the general population risk of 1.3%.[87,89] *BRCA* mutation prevalence studies in unselected ovarian cancer cohorts have demonstrated that up to 15% of epithelial ovarian cancer patients have a germline *BRCA1* or *BRCA2* mutation.[90,91] While early age of diagnosis and family history of cancer can be indicators of a *BRCA1* or *BRCA2* mutation, over two-thirds of *BRCA* positive ovarian cancer patients are diagnosed over the age of 50, 25% are diagnosed over the age of 60, and over half of *BRCA* positive ovarian cancer patients have no significant family history of cancer. [90,91] A new paradigm for testing has emerged for ovarian cancer patients with the FDA approval of BRACAnalysis CDx.[85]

Early studies with PARP inhibitors demonstrated that cells possessing at least one normal *BRCA1* and *BRCA2* allele are relatively resistant to PARP inhibition, while cells with *BRCA1* or *BRCA2* dysfunction lacking wild-type *BRCA1* or *BRCA2* (homologous recombination deficient mutant cells) are profoundly sensitized to PARP inhibition leading to chromosomal instability, cell cycle arrest and apoptosis.[92,93] Based on these findings, many clinical trials with PARP inhibitors, including Lynparza (olaparib) trials, have looked at *BRCA* mutation status as part of outcome subgroup analysis and/or inclusion criteria.[94,95] Lynparza (olaparib) is the first FDA approved PARP inhibitor, and is indicated as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (**as detected by an FDA-approved test**) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

As part of the FDA PMA process for BRACAnalysis CDx, the following validation and verification studies were performed and submitted to the FDA by Myriad Genetic Laboratories: 17 non-clinical studies for analytical verifications, 6 comparators studies, variant classification validation, clinical bridging study, two extraction studies, process validation study, equipment qualifications, software validation, facilities validation, and clinical validation studies. The performance characteristics as well as clinical study endpoints support the clinical utility of BRACAnalysis CDx as a companion diagnostic to Lynparza (olaparib).

Conclusion:

The CDC tier system indicates that when the "FDA label requires use of a test to inform choice or dose of a drug" that service would be considered a Tier 1 test and therefore have coverage under the current draft benefits.[6] The Lynparza label specifically states, "Lynparza is a poly (ADP-ribose) polymerase (PARP) indicated as monotherapy in patients with deleterious or

suspected deleterious *BRCA* mutated (**as detected by an FDA-approved test**) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy." BRACAnalysis CDx is the only FDA approved BRCA test. FDA labelling for BRACAnalysis CDx states that, "Results of the test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza (olaparib). This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108."

Based upon the CDC definition of tiers, given that Lynparza's FDA label requires use of an FDA-approved test to identify BRCA mutations and BRACAnalysis CDx is the only FDA approved *BRCA* test, it appears that BRACAnalysis CDx should be considered a Tier 1 test. Therefore, it is respectfully requested that Colorado Medicaid consider BRACAnalysis CDx as a covered service for the evaluation of *BRCA* mutation status as a companion diagnostic to Lynparza.

Section 4: Prognostic Markers Covered Services and Limitations

4a: Prolaris®

It is respectfully requested that Colorado Medicaid consider coverage of Prolaris for patients with localized prostate cancer.

Clinical Background: Prostate Cancer

Screening programs for prostate cancer allow for its early detection, which has been faulted for leading to overtreatment of localized disease.[96-98] However, it is clear that newly diagnosed men can have either aggressive or indolent tumors, and current clinical and pathologic features are limited in their ability to distinguish between the two.[99-101] Faced with this uncertainty, nearly 90% of men will receive definitive treatment (which may include radical prostatectomy, radiation therapy, androgen deprivation therapy, or some combination thereof), despite the risk of treatment-related complications and the fact that many prostate cancers do not cause death even when initial management is conservative.[102-104] Under-treatment of men with more aggressive cancer also remains a significant clinical risk. There is no question that prostate cancer is a leading cause of death in men, and most of the 30,000 annual deaths from prostate cancer now occur in men who underwent primary treatment for localized disease.[105] This is evidence that there is still room to adjust treatment intensity for those men with aggressive prostate cancer.

Prolaris was developed and has been validated to give greater insight into the indolence or aggressiveness of tumors by more precisely stratifying risk of cancer progression in men with localized prostate cancer. The prostate cancer literature is replete with evidence that decreasing therapeutic burden is associated with less morbidity. As documented in a study by Nam *et al*, patients undergoing definitive treatment for prostate cancer were 17.9 times more likely to be admitted to the hospital, 6.8 times more likely to undergo a urologic procedure, twice as likely to have a rectal or anal procedure, and 6.0 times as likely to have an open surgical procedure as compared to the general population.[106] Additionally, the recently published results of the PIVOT study showed that men with localized prostate cancer do not benefit from prostatectomy when measured against patients who were simply observed.[107] Patients who receive the Prolaris test

benefit from the additional prognostic information that informs whether they can safely defer treatment and reduce the therapeutic burden that can result from unnecessary treatment and side effects.

Prolaris Background:

Prolaris is a novel prognostic test that directly measures tumor biology in order to accurately stratify patients with localized prostate cancer according to disease aggressiveness. The test combines the RNA expression levels of 31 genes involved in cell cycle progression and 15 housekeeping genes to generate a Prolaris Score, which has been proven in five published studies on more than 2,200 patients to be the most powerful variable for predicting 10-year prostate cancer progression and 10-year disease-specific mortality.[108-112] In order to ensure that Prolaris would be a clinically useful test, all studies assessed not just its prognostic performance, but also its superiority to existing clinical and pathologic variables.

The improved prognostic accuracy of the Prolaris test has been assessed in terms of reclassification power. Results from the clinical validation cohorts demonstrate that, within each American Urological Association (AUA) clinical risk group (Low, Intermediate, and High), Prolaris provides further stratification of the risk of prostate cancer death for individual patients. Men in the AUA Low Risk category had an average risk for death within 10-years of 4.8%; after adding the Prolaris Score, the actual 10-year mortality risks for individual patients ranged from 1.8-6.7%. The magnitude of the 10-year mortality risk stratification afforded by the addition of Prolaris is even more striking for the AUA Intermediate Risk group (11.3% average risk for the group, to a range of 3.9% to 36.8% for individual patients after Prolaris) and the High Risk group (29.0% average risk for the group, to a range of 8.0-83.1% for individual patients after Prolaris).[109,113]

Test and Clinical Validation

The Prolaris assay has been extensively validated, with 5 publications on nearly 2200 prostate tumors from eight separate patient cohorts published in peer-reviewed studies (Cohorts 1 – 8 summarized in Table 4). In multivariate analysis, the Prolaris Score is the most predictive variable for predicting the risk of prostate cancer progression, as determined by the clinically meaningful oncologic endpoints of biochemical recurrence, prostate cancer-specific mortality, and metastasis.

Table 4: Prolaris Clinical Validation Studies

	COHORT, SPECIMEN TYPE	PRIMARY ENDPOINT	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS		ABILITY OF PROLARIS TO PREDICT ENDPOINT*
Published:							
Cuzick 2011[1]	**Cohort 1, Post-prostatectomy:** U.S. men, radical prostatectomy from 1985-95; tumor registry. N=353	Biochemical recurrence	HR=1.89	$p=5.6x10^{-9}$	HR=1.77	$p=4.3x10^{-5}$	Prolaris and PSA were most predictive
	Cohort 2, Transurethral resection of the prostate: Conservatively managed U.K. patients diagnosed after TURP from 1990-1996. N=337	10-year mortality	HR=2.92	$p=6.1x10^{-22}$	HR=2.57	$p=8.2x10^{-11}$	Prolaris most predictive
Cuzick 2012[2]	**Cohort 3, Biopsy:** Conservatively managed U.K. patients diagnosed by needle biopsy from 1990-1996. N=349	10-year mortality	HR=2.02	$p=8.6x10^{-10}$	HR=1.65	$p=2.6x10^{-5}$	Prolaris most predictive
Cooperberg 2013[3]	**Cohort 4, Post-prostatectomy:** Contemporary cohort of U.S. men, radical prostatectomy from 1994-2006. N=413	Biochemical recurrence	HR=2.1	$p=2.2x10^{-6}$	HR=2.01	$p=5.7x10^{-5}$	Prolaris most predictive
Freedland 2013[4]	**Cohort 5, Biopsy:** U.S. men, external beam radiation therapy (EBRT) from 1991-2006. N=141	Biochemical recurrence	HR=2.55	p=0.0017	HR=2.11	p=0.34	Prolaris most predictive
Bishoff 2014[5]	**Combined Cohorts 6-8** **Cohort 6, Biopsy:** German men, radical prostatectomy from 2005-2006. N=283 **Cohort 7, Biopsy:** U.S. men, radical prostatectomy from 1994-2005. N=176 **Cohort 8, Biopsy:** U.S. men, radical prostatectomy from 1997-2004. N=123	Biochemical recurrence	HR=1.60	$p=2.4x10^{-7}$	HR=1.47	$p=4.7x10^{-5}$	Prolaris and PSA were most predictive
		Metastatic disease	HR=5.35	$p=2.1x10^{-8}$	HR=4.19	$p=8.2x10^{-6}$	Prolaris most predictive
Accepted for presentation at American Urological Association, May 2014:							
Cuzick 2014[6]	**Cohort 9, Biopsy:** Contemporary cohort of conservatively managed U.K. patients diagnosed by needle biopsy from 1990-2004. N=757	Disease specific mortality	HR=2.32	$p=<10^{-17}$	HR=1.86	$p=<10^{-6}$	Prolaris most predictive

Improvement in Net Health Outcomes and Clinical Utility

There is now substantial literature supporting the use of decision impact studies in diagnostics as a form of analysis for clinical utility in those cases where medical management outcomes are clearly differentiated and important.[114] The Center for Medical Technology Policy (CMTP) recognizes that prospective randomized controlled trials of molecular diagnostic tests in oncology may not be necessary when evidence exists to link treatment choices to patient outcomes.[115] Data from multiple reputable sources demonstrate that reducing unnecessary definitive interventions for prostate cancer treatment improves morbidity outcomes for men.[116,117] CMTP supports the use of prospective observational studies (Crawford *et al* described below[118]) to demonstrate clinical utility in specified circumstances, including when "there is genuine uncertainty on the part of the expert medical community regarding the preferred clinical pathway;" as is the case for the treatment of localized prostate cancer.

The clinical utility of Prolaris has been documented in two decision impact studies.[118,119] The first study (Shore *et al*) was retrospective and designed to assess clinical intent among physicians who were participating in a clinical validation trial of Prolaris.[119] The data from this study indicated that the test would have the net effect of shifting patients from more aggressive treatment to more conservative treatment, and the change in treatment was associated with lower Prolaris scores, with the majority of changes (62%) in patients with a lower than expected mortality risk. The second clinical utility study (Crawford *et al*) was a prospective observational study designed to measure change in clinical decision-making based on the Prolaris test result among physicians ordering Prolaris on needle biopsy specimens and participating in an open clinical registry.[118] The study assessed pre-Prolaris treatment recommendations with post-Prolaris recommendations, and actual treatment selections were verified via a third-party audit of patient charts. Overall, 65% of cases showed a change between intended therapy options pre- and post-Prolaris test reporting, including a 49.5% reduction in surgical interventions and a 29.6% reduction in radiation treatment, that were directionally aligned with test results (tests results indicating lower risk led to reductions in treatment and higher risk led to increases in interventional treatment). This study included participation of US physicians from 31 US states ordering Prolaris on low, intermediate and high risk localized prostate cancer needle biopsy specimens in the real-world clinical setting and provides evidence that the impact of Prolaris is attainable outside the investigational setting.

Cost Effectiveness:

Stratification of localized prostate cancer based on disease aggressiveness remains challenging, resulting in overtreatment of low-risk patients and under-treatment of high-risk patients. As discussed above, the Prolaris test is a well-validated molecular diagnostic test that can aid physicians in accurately predicting prostate cancer aggressiveness, leading to more appropriate management. An economic impact study on Prolaris was recently presented at the Society of Urologic Oncology meeting. This study evaluated the total cost of care for patients following current clinical practice and a test scenario where patient management was altered via Prolaris results. The study found that the Prolaris score reduced costs by $2,850 per patient tested over 10 years after accounting for the cost of the test. This would translate into a $16 million savings for a health plan with 10 million members.[120] **Economic modeling would estimate nearly $3 million in savings for the Colorado Medicaid program over the next 3 years with the use of Prolaris due to increased active surveillance in low-risk patients, compared with the current approach.**

CMS and Societal Guideline Support:

In January 2015, Medicare via Palmetto's MolDX program issued a Local Coverage Determination for Prolaris (LCD: L35629).[121] MolDX was developed in 2011 by Palmetto to evaluate molecular diagnostic tests to complete technical assessments to determine the clinical utility and coverage. MolDX conducts its technical assessments by evaluating the evidence around a test's analytical validity, clinical validity, and clinical utility. The test's scientific information is reviewed by unbiased subject matter experts. If a test demonstrates analytical validity, clinical validity, and clinical utility, a coverage determination will be established. Prolaris went through the rigorous MolDX review process and was granted a coverage determination.

Within CMS, molecular diagnostic services are issued LCDs. Noridian, the Medicare Administrative Contractor (MAC) that covers Myriad, administers the MolDX program's decisions, and in this case will process all claims related to Prolaris. The Medicare Managed

Care Manual (Chapter 4) provides information on how services are covered when an LCD exists and just one MAC will process those claims:

> ***90.2.1 – MACS with Exclusive Jurisdiction over a Medicare Item or Service (Rev. 115, Issued: 08-23-13, Effective: 08-23-13, Implementation: 08-23-13)***
> *A MAC outside of the plan's service area sometimes has exclusive jurisdiction over a Medicare covered item or service. In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one supplier of a particular item, medical device or diagnostic test (for example; certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage requirements or LCD of the MAC that enrolled the supplier and processes all of the Medicare claims for that item, test or service.*

Given that Noridian will administer the Prolaris service based upon the Palmetto/MolDX's coverage determination and that Noridian will process all of the claims for Prolaris as performed by Myriad Genetic Laboratories, this wording indicates that Prolaris will have national Medicare coverage as Medicare would follow the coverage determination of Noridian for Prolaris as Myriad is the only laboratory offering this testing service.

In October 2014, the NCCN incorporated the use of tumor-based molecular biomarkers to better stratify localized prostate cancer risk of biochemical recurrence or disease-specific mortality into their Prostate Cancer treatment guideline.[122] They acknowledged that the currently available tools to predict disease progression in prostate cancer continue to leave uncertainty and therefore men continue to over-select treatment for prostate cancer that will likely not progress. To help address this issue, they stated that this is, "…uncertainty that could be reduced by a molecular biomarker that can be measured accurately and reproducibly and provide prognostic or predictive information beyond NCCN risk group assignment and currently available tables and nomograms." Given this, they incorporated Prolaris into their Prostate Cancer treatment guidelines as a tool to stratify risk of biochemical recurrence or disease-specific mortality in prostate cancer patients to help inform treatment decision making, noting that "Prolaris has changed treatment recommendations in 32% to 65% of cases and may enhance adherence to the treatment recommended."

Conclusion:

The above data demonstrate that Prolaris provides new important information that more accurately stratifies patients with localized prostate cancer according to risk of disease progression. This information has been shown to directly impact patient care by allowing clinicians to more confidently provide disease progression risk to patients. This more precise understanding helps to ensure that patients receive the appropriate level of care based upon their particular prostate tumor biology to help promote the health and well-being of patients by minimizing unnecessary treatments that are associated with high levels of morbidity while ensuring those that require more intensive treatment are identified. In addition, by tailoring treatment recommendations to match the true risk of disease progression, economic modeling would estimate nearly $3 million in savings for the Colorado Medicaid program over the next 3 years due increased use of active surveillance for truly low risk patients, compared to the current approach. This approach represents a significant advance in prostate cancer risk stratification which will promote the health and well-being of Colorado Medicaid members by

ensuring that they receive the most appropriate care based upon a more precise understanding of their risk for disease progression. **Therefore, based upon the CDC definition of tiers, given Prolaris' CMS coverage and guideline support, as well as the strong evidence of analytic/clinical validity and clinical utility, it appears that Prolaris should be considered a Tier 1 test. Therefore, it is respectfully requested that Colorado Medicaid consider Prolaris as a covered service for men with localized prostate cancer.**

Section 5: Evidence for Disease Activity Coverage Recommendations

Section 5a: Vectra DA®

It is respectfully requested that Colorado Medicaid consider coverage of Vectra DA for patients with rheumatoid arthritis.

Rheumatoid Arthritis Background:

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes disability from painful swelling in joints and from progressive, irreversible damage to cartilage and bone in the affected joints. The treatment paradigm for RA has evolved over the last two decades. It is now recommended that clinicians assess severity of disease activity and adjust therapy as needed to achieve remission, or the lowest possible level of disease activity, as rapidly possible.[123,124] The goal is to reduce signs and symptoms and prevent long-term accumulation of joint damage, improving patient outcomes with improved physical function and quality of life, reduced need for surgery and other treatments, reduced need for ancillary care, and improved longevity.[125]

Several factors contribute to this new treatment paradigm:

- It is well understood that a "window of opportunity" exists whereby early remission improves patient outcomes by reducing the initial amount of joint damage and the longer-term rate of progression, even compared with patients achieving the same level of disease control later after disease onset.[126]
- Biologic agents, i.e., TNF inhibitors and others, have improved patient outcomes by making remission or low disease activity available to more patients than ever before. The improvements in quality of life, physical function and employment status that occur in many patients justify the use of biologic therapies.[127] Consequently, expectations for treatment efficacy have increased and TNF inhibitors have become a standard of care.
- Several studies have demonstrated that, compared with standard practice, patient outcomes are better with a tight control strategy, sometimes called treat-to-target, whereby disease activity is assessed regularly and therapy adjusted as needed to achieve remission or low disease activity.[128]
- Patients who appear to be in remission often have joint inflammation, termed "subclinical synovitis," that can be seen by magnetic resonance imaging (MRI) or ultrasound of joints. Joint damage can result from subclinical synovitis.[129] Identifying these patients early to adjust their treatment should improve their outcomes.
- As health care reform in the US accelerates, the requirement for assessing severity of RA disease activity is increasingly supported by organizations responsible for promoting and documenting delivery of cost-effective care.[130] The goal of providing the right care for the right reasons requires that disease activity be assessed accurately.

This new paradigm makes assessing severity of disease activity a key component of current treatment guidelines. Given the importance of measuring disease activity to the goal of getting patients to minimal or no disease activity, objective quantification of RA disease activity is essential to guide therapy.

In recommendations by the American College of Rheumatology (ACR) on the use of disease modifying anti-rheumatic drugs (DMARDs) and biologic agents for the treatment of rheumatoid arthritis, low disease activity or remission is the target for all patients with early (≤6 months duration) or established RA.[123,131] The panel recommended initial non-biologic DMARD therapy for early RA and identified a sequence of three decision-making junctures where a change in therapy will be needed if disease activity is still elevated:

1. Initiating or switching between non-biologic DMARDs,
2. Switching from a non-biologic DMARD to a biologic agent, and
3. Switching between biologic agents due to lack of benefit or loss of benefit.

In each case, the change in treatment was recommended to occur after three months of prior treatment, indicating that the recommended interval for assessing patients who have not achieved low disease activity or remission is every three months.

The number of tools for assessing RA disease activity reflects that they and their components all have shortcomings limiting their utility as measures of joint inflammation and as predictors of progressive joint damage. Tender and swollen joint counts are partially or entirely subjective.[132] Patient-reported outcomes are entirely subjective and can be affected by factors unrelated to arthritis or inflammation. The CRP and ESR blood tests are objective but are insensitive measures of inflammation. In a U.S. study of 9135 patients with active RA in the CORONNA registry, CRP and ESR were both normal in 58% of patients.[133] ESR and CRP are thus unreliable for estimating disease activity.[134,135] Damage caused by joint inflammation can be quantified with X-rays of hands and feet, using the total Sharp score (TSS). However, the TSS is used only in clinical trials and never in clinical practice because it is time-consuming and requires special expertise. Magnetic resonance imaging of joints is accurate for assessing inflammation but it sees only a few joints per exam, is expensive and time-consuming, and is not recommended by the ACR for routine patient assessment.[136]

The inadequacies of conventional assessment tools can have important consequences for patients and repercussions for the health care system: 1) Joint damage and disability may progress if subclinical disease is not detected and treated[129] and 2) common comorbidities such as osteoarthritis, obesity or non-inflammatory pain may lead to inaccurate assessment.[132] For example, generalized, non-inflammatory pain of fibromyalgia, which occurs in 12% to 21% of patients with RA, can make RA appear worse than it really is when assessed with conventional physician and patient-reported measures, and potentially lead to inappropriate use of biologic agents.[137] A more convenient, objective and effective means for measuring RA disease activity is needed to optimize clinical outcomes with cost-effective care.

Vectra DA Background:

Vectra DA is a multi-biomarker disease activity blood test that objectively quantifies disease activity in patients with RA.[138] Vectra DA uses a multiplex immunoassay to measure serum concentrations of 12 proteins involved in the pathophysiology of RA. A validated algorithm combines the biomarker concentrations to score disease activity on a scale of 1 to 100, with ranges of low (<30), moderate (30−44) and high (>44).[139] While multi-biomarker tests are well

established in other fields, including oncology, endocrinology and cardiology, Vectra DA has no precedent in rheumatology.

Vectra DA was validated by its correlation with DAS28-CRP and other clinical measures of RA disease activity.[139-141] As a biomarker-based instrument; however, Vectra DA is fundamentally different. Vectra DA is often discordant with conventional measures.[139-141] Studies have used hand and foot X-rays taken at the time of Vectra DA testing and one year later to assess the amount of new joint damage (radiographic progression in one year) as an independent indicator of clinically important disease activity. These studies show that the Vectra DA score predicts risk for subsequent joint damage more effectively than conventional measures, including when they are discordant.[142,143] Thus, disagreements between Vectra DA and conventional measures of RA disease activity support the superior clinical utility of Vectra DA.

In patients with established RA receiving ongoing DMARD treatment, a high Vectra DA score was a significantly better predictor of risk for progression than a high DAS28-CRP. In addition, a low Vectra DA score was a significant predictor of non-progression, whereas remission by DAS28-CRP or the stringent ACR-EULAR Boolean criteria was not.[142] Moreover, for patients in DAS28-CRP-defined remission (a standard for clinical trials), progression was markedly more frequent when Vectra DA was high. These findings strongly suggest that the use of Vectra DA to detect destructive subclinical disease activity should lead to more effective treatment and improved outcomes.

In patients with recent onset RA treated in a tight-control strategy with methotrexate (MTX) monotherapy, then with additional DMARDs or an anti-TNF if MTX response was inadequate, Vectra DA was shown to be significantly associated with radiographic progression and to discriminate radiographic progressors from non-progressors more effectively than DAS28-ESR, CRP or ESR.[143] Radiographic progression was relatively frequent among patients with moderate DAS28 or low CRP, whereas virtually all progressors had a high Vectra DA score.[143] Thus, in patients with recent onset RA, for whom it is critical to achieve remission within the "window of opportunity," Vectra DA is superior to other measures for establishing when this goal has been achieved.

These findings indicate that disease activity detected by Vectra DA is more closely associated with the destructive pathophysiology of RA than disease activity detected by conventional measures – including clinical measures, such as DAS28, and blood tests, such as CRP. This property of Vectra DA supports its superiority as a measure of RA disease activity and for predicting risk for joint damage. Thus, we expect that: 1) achieving reductions in the Vectra DA score will lead to reductions in signs and symptoms of RA, based on its correlation with DAS28-CRP, and 2) treatment based on Vectra DA will reduce subsequent radiographic progression more effectively than when management is guided only by signs and symptoms, as is conventionally done.

The ability of Vectra DA to influence decision-making has been established by a prospective study of 101 patients for whom Vectra DA was ordered as part of routine clinical practice in the U.S. Treatment plans were documented upon evaluating the patient, and then reviewed after receiving the Vectra DA result for that visit. It was found that knowledge of Vectra DA scores changed treatment plan in 38% of patients, but with little overall change in amount of drug use.[144] This result indicates that Vectra DA has potential to improve patient outcomes without increasing drug expenditure.

CMS Coverage:

In July 2013, Medicare via Palmetto's MolDX program issued a Local Coverage Determination for molecular diagnostic services including Vectra DA (LCD: L33541).[145] MolDX was developed in 2011 by Palmetto to evaluate molecular diagnostic tests to complete technical assessments to determine the clinical utility and coverage. MolDX conducts its technical assessment by evaluating the evidence around a test's analytical validity, clinical validity, and clinical utility. The test's scientific information is reviewed by unbiased subject matter experts. If a test demonstrates analytical validity, clinical validity, and clinical utility, a coverage determination will be established. Vectra DA went through the rigorous MolDX review process and was granted a coverage determination.

Within CMS, molecular diagnostic services are issued LCDs. Noridian, the Medicare Administrative Contractor (MAC) that administers the MolDX program's decisions, will process all claims related to Vectra DA. The Medicare Managed Care Manual (Chapter 4) provides information on how services are covered when an LCD exists and just one MAC will process those claims:

> ***90.2.1 – MACS with Exclusive Jurisdiction over a Medicare Item or Service***
> ***(Rev. 115, Issued: 08-23-13, Effective: 08-23-13, Implementation: 08-23-13)***
> *A MAC outside of the plan's service area sometimes has exclusive jurisdiction over a Medicare covered item or service. In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one supplier of a particular item, medical device or diagnostic test (for example; certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage requirements or LCD of the MAC that enrolled the supplier and processes all of the Medicare claims for that item, test or service.*

Given that Noridian will administer the Vectra DA service based upon the Palmetto/MolDX's coverage determination and that Noridian will process all of the claims for Vectra DA, this wording indicates that Vectra DA has national Medicare coverage as Medicare would follow the coverage determination of Noridian for Vectra DA.

Conclusion:

The above data demonstrate that Vectra DA provides new important information that more accurately measures disease activity in patients with rheumatoid arthritis. This information has been shown to directly impact patient care by allowing for an objective measure of disease activity. This more precise understanding helps to ensure that patients receive the appropriate level of care based upon their disease activity. This approach represents a significant advance in rheumatoid arthritis management which will promote the health and well-being of Colorado Medicaid members by ensuring that they receive the most appropriate care which. **Therefore, based upon the CDC definition of tiers, given Vectra DA's CMS coverage, it appears that Vectra DA should be considered a Tier 1 test. Therefore, it is respectfully requested that Colorado Medicaid consider Vectra DA a covered service for patients with rheumatoid arthritis as non-coverage would significantly deviate from the standard of care for patients as outlined by CMS coverage and societal guidelines.**

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