GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Description:

Familial Adenomatous Polyposis (FAP) and Associated Variants:
FAP typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will go on to develop colorectal cancer. The mean age of colon cancer diagnosis in untreated individuals is 39 years.

Mutations in the adenomatous polyposis coli (APC) gene are responsible for FAP. A subset of individuals with FAP may have attenuated FAP (AFAP), characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, colorectal cancer occurring at an average age of 50-55 years, but a high lifetime risk of colorectal cancer of about 70% by age 80 years. Some individuals with AFAP have mutations in the MUTYH (formerly MYH) gene and are then diagnosed with MUTYH-associated polyposis (MAP).

It is important to distinguish among classical FAP, attenuated FAP, and MAP by genetic analysis because recommendations for surveillance and cancer prevention vary according to the syndrome.

Lynch Syndrome:
Formerly known as hereditary nonpolyposis colorectal cancer (HNPCC). Individuals with Lynch syndrome have a predisposition to colorectal cancer and other malignancies such as endometrial, ovarian, urinary tract and biliary tract cancer. Lynch syndrome includes those with an existing cancer and those who have not yet developed cancer. Females with Lynch syndrome have a predisposition to endometrial cancer. Lynch syndrome is estimated to account for 2% of all endometrial cancers in women and 10% of endometrial cancers in women younger than 50 years of age.

Lynch syndrome is associated with any of a large number of possible mutations in one of several DNA mismatch repair (MMR) genes, known as MLH1, MSH2, MSH6, PMS2 and rarely MLH3. Estimated cumulative risks of any associated cancer for a carrier of a mutation in any MMR gene do not begin to increase until after age 30 years. Prior to cancer diagnosis, individuals may have multiple adenomatous polyps and thus may have an initial differential diagnosis of attenuated FAP versus MUTYH-associated polyposis versus Lynch syndrome.

About 70% of individuals with Lynch syndrome have mutations in either MLH1 or MSH2. Testing for MMR gene mutations is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2 testing. Thus, additional indirect testing is needed to determine which individuals should proceed to direct sequencing for MMR gene mutations. Available testing includes microsatellite instability (MSI) testing or immunohistochemical (IHC) testing.
GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Description: (cont.)

Lynch Syndrome: (cont.)
BRAF testing is an optional screening method that may be used in conjunction with IHC testing for MLH1 to improve efficiency. A methylation analysis of the MLH1 gene can largely substitute for BRAF testing, or be used in combination to slightly improve efficiency. The BRAF gene is often mutated in colorectal cancer; when a particular BRAF V600E mutation is present; to date, no MLH1 gene mutations have been reported. Therefore, individuals negative for MLH1 protein expression by IHC, and, therefore, potentially positive for an MLH1 mutation, could first be screened for a BRAF mutation. BRAF-positive samples need not be further tested by MLH1 sequencing. MLH1 gene methylation largely correlates with the presence of BRAF-V600E and in combination with BRAF testing can accurately separate Lynch from sporadic colorectal cancer in IHC MLH1-negative cases.

Recently, novel deletions have been reported to affect the expression of the MSH2 MMR gene in the absence of a MSH2 gene mutation, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and/or IHC shows a lack of MSH2 expression, but no MSH2 mutation is found by sequencing.

Definitions:

Genetic Testing:
Analysis of DNA, RNA, chromosomes, proteins and certain metabolites in order to detect alterations related to an inherited disorder.

Gene:
A hereditary unit consisting of segments of DNA that occupies a specific location on chromosomes. Genes undergo mutation when their DNA sequence changes.

Genetic Counseling:
Instruction that provides interpretation of genetic tests and information about courses of action that are available for the care of an individual with a genetic disorder or for future family planning.

Affected Individual:
An individual displaying signs or symptoms characteristic of a suspected or specific inherited disorder.

Unaffected Individual:
An individual who displays no signs or symptoms characteristic of a suspected or specific inherited disorder.
Definition:
Screening: Genetic screening is the testing of an individual with no symptoms for a specific inherited disorder to determine if the individual carries an abnormal gene. Screening can be used to predict risk or potential risk for the individual or their offspring.

1st Degree Relative:
Blood-related sibling, parent or child.

2nd Degree Relative:
A relative removed by one generation, e.g., grandparent, grandchild, aunt/uncle, niece/nephew or first cousin.

3rd Degree Relative:
A relative removed by two generations, e.g., great-grandparent, great-grandchild, great-aunt/uncle, grandniece/nephew or second cousin.

Criteria:

- Genetic testing and/or counseling of an unaffected individual, regardless of risk factors is considered screening and not eligible for coverage.

- Genetic testing and/or counseling of an affected individual to confirm a disease when confirmation of the diagnosis would not impact the care and/or management is considered not medically necessary and not eligible for coverage.
GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Criteria: (cont.)

APC Gene Mutations:

- Genetic testing and/or counseling for APC gene mutations is considered medically necessary for an affected individual with documentation of ONE of the following:

  1. One or more colonic polyps and a 1st degree relative with diagnosed familial adenosis polyposis (FAP). In the case of a small family pedigree, some judgment must be used for "at-risk relatives", when extended family members may need to be included to obtain sufficient information.
  2. Differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation.

BRAF V600E/MLH1:

- Genetic testing and/or counseling for BRAF V600E or MLH1 promoter methylation is considered medically necessary to exclude a diagnosis of Lynch syndrome when MLH1 is not expressed in a colorectal cancer on immunohistochemical (IHC) analysis.

EPCAM Gene Mutations:

- Genetic testing and/or counseling for EPCAM gene mutations for the diagnosis of Lynch syndrome in an affected individual with colorectal cancer is considered medically necessary with documentation of ANY of the following:

  1. Tumor tissue shows a high level of microsatellite instability and individual is negative for a germline mutation in MSH2, MLH1, PMS2, and MSH6, OR
  2. Tumor tissue shows lack of MSH2 expression by immunohistochemistry and individual is negative for a germline mutation in MSH2
GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Criteria: (cont.)

MMR Gene Mutations:

- Genetic testing and/or counseling for MMR gene mutations (e.g. MLH1, MLH3, MSH2, MSH6, PMS2) is considered medically necessary for an affected individual with documentation of ONE of the following:

  1. Individual meets either the Amsterdam II criteria or the Revised Bethesda Criteria:

     - Amsterdam II Criteria requires ALL of the following:
       a. Three or more relatives with a histologically-verified Lynch syndrome related cancer (i.e., colorectal cancer or cancer of the endometrium, small intestine, ureter or renal pelvis), one of whom is a 1st degree relative of the other two
       b. Lynch syndrome related cancer affects two or more successive generations
       c. Cancer in at least one relative was diagnosed before age 50

     Modifications are allowed for the following:

       - Very small Lynch syndrome families: These families must have two colorectal cancers in 1st degree relatives involving at least two generations, with at least one individual diagnosed before age 55
       - In families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient

     - Revised Bethesda Criteria requires ONE of the following:

       a. Presence of synchronous (at the same time) or metachronous (at another time) colorectal cancers or Lynch syndrome associated tumors1, regardless of age
       b. Colorectal cancer with ANY of the following:

         - Diagnosis before age 50
         - MSI-H (high frequency microsatellite instability) histology diagnosed before age 60
         - One or more 1st degree relatives with colorectal and/or Lynch syndrome associated tumors1 diagnosed before age 50
         - Two or more 1st or 2nd degree relatives with Lynch syndrome associated tumors1, regardless of age
GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Criteria: (cont.)

MMR Gene Mutations: (cont.)

- Genetic testing and/or counseling for MMR (mismatch repair) gene mutations (e.g. MLH1, MLH3, MSH2, MSH6, PMS2) is considered medically necessary for an affected individual with documentation of ONE of the following: (cont.)

  2. Individual with colorectal cancer, for the diagnosis of Lynch syndrome, depending on results of either the microsatellite instability (MSI) test or the immunohistochemistry (IHC) test as an initial evaluation of tumor tissue prior to MMR gene analysis

  3. Individual with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer1, for the diagnosis of Lynch syndrome

  4. Differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis vs. Lynch syndrome. Whether testing begins with APC mutations or screening for MMR mutations depends upon clinical presentation

MUTYH Gene Mutations:

- Genetic testing and/or counseling for MUTYH (formerly MYH) gene mutations is considered medically necessary for an affected individual with documentation of ALL of the following:

  1. Differential diagnosis of attenuated FAP vs. MUTYH-associated polyposis (MAP) vs. Lynch syndrome

  2. Negative result for APC gene mutations

Microsatellite Instability (MSI) Test:

- Genetic testing and/or counseling utilizing the microsatellite instability (MSI) test and the immunohistochemistry (IHC) test is considered medically necessary to determine if an affected individual with colorectal cancer who also meets the Amsterdam or Revised Bethesda criteria should undergo HNPCC genetic testing.
GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Criteria: (cont.)

- Genetic testing and/or counseling for all other gene mutations for Lynch syndrome or colorectal cancer not previously listed or if above criteria not met is considered experimental or investigational based upon:

  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  4. Insufficient evidence to support improvement outside the investigational setting.

1 Lynch syndrome associated tumors/cancers include colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

Resources:

Literature reviewed 03/15/16. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 12/11/12 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’ é atah nílííníí Blue Cross Blue Shield of Arizona haadá yit’éego bíí nía’dilkídgo éí doodago Háída bijá aníyeeedígíí t’áadoo le’é yína’dilkídgo beeház’ááníí hóló díí t’áá házaadk’éhéí háká a’doo wólgo beeház’á doo bááh nílíígóó. Atá’ halné’ilígíí koj’é bich’i’hódilínih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để đổi chuyển với một thống dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو أدى شخص تساعدك أسأله بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أي تكلفة للتحدث مع مترجم اتصل ب 877-475-4799.
GENETIC TESTING FOR LYNCH SYNDROME AND OTHER INHERITED COLON CANCER SYNDROMES (cont.)

**Multi-Language Interpreter Services:** (cont.)

Tagalog: Kung ikaw, o ang iyong tinsuotianan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799までお電話ください。

Farsi: اگر شما یا کسی که شما و یا کمک می‌کنید، سوالات مربوط به Blue Cross Blue Shield of Arizona دارد، می‌توانید به کمک رایگان دریافت کنید. دریافت کنید 877-475-4799.

Assyrian: Blue Cross Blue Shield of Arizona یاری که نیاز دارید، می‌توانید به کمک رایگان دریافت کنید. دریافت کنید 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: คุณสามารถได้รับความช่วยเหลือและข้อมูลภาษาอื่น ๆ ของคนได้โดยไม่เสียเงิน ที่ 877-475-4799.