Subject: **Genetic Testing for Susceptibility to Colorectal Cancer ***

Effective Date: **October 22, 2013**

Department(s): **Utilization Management**

Policy: Genetic testing for inherited colorectal cancer susceptibility is reimbursable under Plans administered by QualCare, Inc., subject to the criteria and conditions enumerated below.

Objective: To assure proper and consistent reimbursement and to assure that reimbursable genetic tests are limited to those for which scientific evidence demonstrates beneficial effects on health outcomes.

Procedure: Genetic testing for inherited colorectal cancer susceptibility requires prior authorization. Pre and post-testing genetic counseling should occur.

Specific testing criteria are outlined below.

A. Lynch Syndrome (hereditary non-polyposis colon cancer) - accounts for 2-3% of all colorectal cancer and is associated with a lifetime risk of approximately 80%.
   1. Genetic testing for mismatch repair(MMR) genes (MLH1,MSH2, MSH6,PMS2, EPCAM) is considered medically necessary for individuals who meet either the Amsterdam II criteria or the revised Bethesda Guidelines below.

Amsterdam II Criteria (must meet all)

- Three or more family members with histologically verified HNPCC-related cancers (colorectal, endometrium, , ovary, stomach, small intestine, hepatobiliary, upper urinary tract (ureteral or renal cell carcinoma), brain, or skin), one of whom is a first-degree relative (parent, child, sibling) of the other two
- Two successive affected generations
- One or more colon cancers diagnosed before age 50 years
- Exclusion of familial adenomatous polyposis

OR

Revised Bethesda Guidelines (must meet one or more)

- Colorectal cancer diagnosed in a patient who is younger than 50 years of age
- Presence of a synchronous, metachronous colorectal or other HNPCC-related tumor (endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, small intestinal cancers, sebaceous gland adenomas and keratoacanthomas), regardless of age
- Colorectal cancer with the high-level microsatellite instability (MSI-H) histology diagnosed in a patient who is younger than 60 years of age
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related cancer, with one or more neoplasms being diagnosed before age 50 years
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related malignancies, regardless of age

OR

Are a first degree relative of a known MMR mutation carrier. Testing of the tumor of an affected individual or family member should occur first, if possible. When a familial mutation is identified in an affected family member, other family members being tested for risk assessment should be tested for a known familial mutation, and not for other mutations.

OR

Colorectal cancer or endometrial cancer tumor immunohistochemistry(IHC) testing for protein expression of the four mismatch repair genes(MMR) is positive (indicating the absence of protein expression) for at least one- MLH1, MSH2, MSH6, or PMS2, **AND** (for colorectal tumors only) IHC testing is negative for BRAF V600E and MLH1 promotor methylation.

OR

Colorectal or endometrial tumor testing for microsatellite instability with a –high (MSI-H) result , regardless of age at diagnosis.

OR

the individual has a predicted risk for Lynch syndrome >5% on one of the following prediction models: MMRpro, PREMM5, or MMRpredict.

B. Familial Adenomatous Polyposis (FAP), Attenuated Familial Polyposis and MYH-Associated Polyposis- account for approximately 1% of colorectal cancers. Without intervention nearly all such individuals will develop cancer. Testing for APC mutations and deletions/duplications should be performed first, and if negative MYH gene testing may be performed.

1. Genetic testing for the APC and MYH genes is considered medically necessary in individuals with a clinical syndrome of FAP, including Gardner syndrome and Turcot syndrome, as well as multiple(≥*10)*adenomatous polyps.

   OR

2. Are a first degree relative of an individual with a known APC or MYH mutation.

C. Juvenile polyposis syndrome- when one of the following is present-

- At least 3 to5 juvenile polyps in the colorectum
- Multiple juvenile polyps in other parts of the gastrointestinal tract
- Any number of juvenile polyps in a person with a known family history of juvenile polyps

D. Peutz-Jeghers syndrome- individual has two or more of the following present-

- mucocutaneous pigmentation of the mouth, lips , nose ,eyes, genitalia or fingers
- ≥ two hamartomatous Peutz-Jeghers-type polyps in the gastrointestinal tract
- Family history of Peutz-Jeghers Syndrome

E. Cowden syndrome/PTEN Hamartoma tumor syndrome PTEN- the indvidual has a family member with a known PTEN mutation ,
OR the individual has any of the following:

- Bannayan-Riley-Ruvalcaba syndrome(BRRS)
- Adult Lhermitte-Duclos disease(cerebellar tumors)
- Autism spectrum disorder and macrocephaly
- Two or more biopsy proven trichilemmomas
- Two or more major criteria(one must be macrocephaly)(see below)
- Three major criteria, without macrocephaly(see below)
- One major and ≥3 minor criteria (if the individual has two major criteria w/o macrocephaly, one of these can be used as a minor criteria to meet testing criteria) (see below)
- ≥4 minor criteria (see below)
- An at risk individual (has any one major criteria or two minor criteria) with a relative with a clinical diagnosis of Cowden syndrome or BRRS for whom testing has not been performed.

Major criteria for Cowden syndrome:

- Breast Cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)

- Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)

- Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):

Multiple trichilemmomas (≥3, at least one biopsy proven)

Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)

Mucocutaneous neuromas (≥3)

Oral papillomas (particularly on tongue and gingiva), multiple (≥3)

OR biopsy proven OR dermatologist diagnosed

Minor criteria for Cowden syndrome:

Autism spectrum disorder

Colon cancer

Esophageal glycogenic acanthosis (≥3)

Lipomas (≥3)

Mental retardation (ie, IQ ≤75)

Renal cell carcinoma

Testicular lipomatosis

Thyroid cancer (papillary or follicular variant of papillary)

Thyroid structural lesions (eg, adenoma, multinodular goiter)

Vascular anomalies (including multiple intracranial developmental venous anomalies)
Single GI hamartoma or ganglioneuroma

F. Li Fraumeni syndrome(LFS)-the individual has a family member with a known TP53 mutation, OR

Meets the classic or Chompret criteria for LFS:

Classic:
Individual diagnosed age <45 y with a sarcoma AND a first- degree relative diagnosed age <45y with cancer AND an additional first or second degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age.

Chompret criteria for LFS:
Individual with a tumor from the LFS spectrum(e.g. soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) before 46 years of age, AND at least one first or second degree relative with any of the aforementioned cancers(other than breast if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age.
OR
Individual with multiple tumors (except multiple breast tumors), two of which belong to the LFS spectrum with the initial cancer occurring before the age of 46 years
OR
Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype at any age of onset, regardless of family history
OR

breast cancer before age 31 yr

G. Multi-gene panel testing using next generation sequencing technology that simultaneously analyzes a set of genes associated with a specific family colorectal cancer phenotype or multiple phenotypes can be considered for reimbursement when the following is present-

1. A cancer genetics consultation report recommends the testing
   AND
2. More than one gene can explain an inherited cancer syndrome, including BRCA1/2(see separate medical policy on BRCA testing).
   AND
3. The individual meets testing criteria for one or more syndromes above.
   AND
4. All genes in the panel are relevant to the personal and family history for the individual being tested.
   AND
5. Gene testing results will impact medical management through application of evidence-based management guidelines for all genes on the panel (e.g. NCCN guidelines).
   OR
6. Separate from 2 through 5 above, the individual has tested negative for a single syndrome, but the personal or family history remains

strongly suggestive of an inherited susceptibility.

Multi-gene panel tests that include combinations of the following genes that may confer high or moderate risk for colorectal cancer are reimbursable when the above criteria are met:

APC	PTEN	GREM1	*AXIN2*
BMPR1A	STK11	POLD1	CHEK2
Lynch Syndrome (MLH1,MSH2, MSH6, PMS2, EPCAM)	SMAD4	POLE	*MSH3* *NTHL1*
MUTYH biallelic mutations	TP53	APCI1307K mutation	MUTYH heterozygotes

CPT codes covered if medical necessity criteria are met:
81201, 81202, 81203, 81292 through 81301
81317, 81318, 81319, 81321, 81323, 81401, 81403, 81404, 81405, 81406 [81479, when used to report BMPR1A(juvenile polyposis) testing]

H. Genetic testing of the general population not meeting the criteria specified above for inherited colorectal cancer susceptibility are not reimbursable under Plans administered by QualCare, Inc., because available evidence does not support their efficacy and/or beneficial effects on health outcomes.

References

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*Consistent with Summary Plan Description (SPD). When there is discordance between this policy and the SPD, the provisions of the SPD prevail.