MARCH–APRIL 2019

BCN Provider News

Medical policy updates

The following applies to Blue Care Network members:

- Noncovered services appear first; covered services follow.
- The effective date is indicated for the service, technology or procedure.

Noncovered services

Genetic and protein biomarkers for the diagnosis and cancer risk assessment of prostate cancer

- **Revised policy**
- **Effective date: March 1, 2019**
- **No referral required – Use appropriate contracted vendor**
- **Procedure codes: *81313, *81479, *81539, *81551, *81559, *88377, 0005U, 0021U**

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening, to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be cured with surgery and radiotherapy.

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for use of these molecular markers to improve selection of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

Genetic and protein biomarkers for the diagnosis and cancer risk assessment of prostate cancer are considered experimental. This includes, but is not limited to, the following:

- Kallikrein markers (for example, 4Kscore™ Test)
- Prostate Health Index (phi)
- *HOXC6* and *DLX1* testing (for example, SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (ExoDx Prostate IntelliScore)
- Autoantibodies ARF 6, NKX3-1, 5′-UTR-BMI1, CEP 164, 3′-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2 (Apifiny)
- *PCA3* testing (Progensa)
- *TMPRSS: ERG* fusion genes
- Gene hypermethylation testing (ConfirmMDx®)
- Mitochondrial DNA mutation testing (Prostate Core Mitomic Test™)
- Candidate gene panels
- MiPS (Mi-ProstateScore)

Single-nucleotide variant testing for cancer risk assessment of prostate cancer is considered experimental.

Genicular nerve blocks

- **New policy**
- **Effective date: March 1, 2019**
- **Procedure codes: *64450, *64640, *64999**

(The above codes are not covered when specified as genicular nerve block.)

Chronic osteoarthritis of the knee is one of the most common diseases of advanced age. With up to 20 million adults in the United States suffering from osteoarthritis of the knee, close to 700,000 cases progress to total knee joint replacement. Many individuals with chronic joint pain, however, are not candidates for invasive procedures due to body mass index, age and other comorbidities. Alternative therapies including arthroscopic debridement or injections are associated with less than optimal clinical outcomes. In addition to osteoarthritis, adults can experience knee pain due to a number of other causes, and an estimated 10 to 34 percent of individuals experience long-term pain after a total knee replacement.

When an individual exhibits knee pain, the pain signals can be generated from the peripheral nerves innervating the knee including several branches of the genicular nerve. Diagnostic nerve blocks are used to determine sources of pain. These blocks typically contain an anesthetic with a known duration of relief. Therapeutic nerve blocks are used to treat painful conditions. Such nerve blocks contain local anesthetic that can be used to control acute pain.

Genicular nerve blocks for the treatment of chronic knee pain are experimental. It has not been scientifically demonstrated to improve patient clinical outcomes.

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Medical policy updates *Cont.*

Patient-specific cutting guides and custom knee implants

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan notification; Plan approval with clinical review**
- **Procedure codes: *27447, *27599, L8699**

Patient-specific instrumentation has been developed as an alternative to conventional cutting guides for joint arthroplasty. Patient-specific cutting guides are constructed with the aid of preoperative three-dimensional computed tomography or magnetic resonance imaging scans and proprietary planning software. The goal of patient-specific instrumentation is to increase surgical efficiency and to improve implant alignment and clinical outcomes.

Use of custom implants or patient-specific instrumentation (for example, cutting guides) for joint arthroplasty including, but not limited to, use in unicompartmental or total knee arthroplasty, is considered experimental. There is insufficient evidence in the peer-reviewed medical literature to determine the effects of the technology on health outcomes.

Covered services

Ambulatory event monitors and mobile cardiac outpatient telemetry

- **Revised policy**
- **Effective date: March 1, 2019**
- **Procedure codes: *33285, *33286, *93268, *93270, *93271, *93272, 0295T, 0296T, 0297T, 0298T**

Ambulatory cardiac monitoring with a variety of devices permits the evaluation of cardiac electrical activity over time, in contrast to static ECG, which only permits the detection of abnormalities in cardiac electrical activity at a single point in time. Various classes of devices are available for situations where longer monitoring than can be obtained with a traditional Holter monitor is needed.

The following ambulatory cardiac monitors are considered established for patients meeting patient selection guidelines:

- Patient-activated or auto-activated external ambulatory event monitors
- Implantable ambulatory event monitors, either patient activated or auto activated
- Continuous ECG rhythm recording and storage devices for longer than 48 hours up to 21 days (codes 0295T-0298T). An example is ZioPatch®.

They are considered useful diagnostic options when indicated.

Inclusions:

- Patient-activated or auto-activated *external* ambulatory event monitors or the use of long-term (greater than 48 hours) external ECG monitoring by continuous rhythm recording and storage (Zio Patch®) are established as diagnostic alternatives to Holter monitoring in patients who meet one or more of these criteria:
  - Patients who experience symptoms suggestive of cardiac arrhythmias (palpitations, dizziness, presyncope or syncope)
  - Patients with atrial fibrillation who have been treated with catheter ablation and in whom discontinuation of systemic anticoagulation is being considered
  - Patients with cryptogenic stroke
- *Implantable* ambulatory event monitors, either patient activated or auto activated, are established for:
  - A small subset of patients who experience recurrent symptoms so infrequently that a prior trial of Holter monitor or other external ambulatory event monitors has been unsuccessful
  - Patients who require long-term monitoring for atrial fibrillation

Exclusions:

- Real-time outpatient cardiac telemetry (also known as mobile cardiac outpatient telemetry, or MCOT, as a diagnostic approach in patients who experience infrequent symptoms (less frequently than every 48 hours) suggestive of cardiac arrhythmias (for example, palpitations, dizziness, presyncope or syncope). This technology is considered not medically necessary as direct evidence for improved health outcomes with the use of continuous, real-time monitoring for suspected arrhythmias is lacking, and evidence for a significant incremental improvement in outcomes with the continuous, real-time monitoring, compared with standard monitoring, is lacking.
- Other uses of ambulatory event monitors, including outpatient cardiac telemetry and mobile applications, are considered experimental, including but not limited to:
  - Monitoring asymptomatic patients with risk factors for arrhythmia
  - Detection of myocardial ischemia by detecting ST segment changes (intracardiac ischemia monitoring systems)
  - Monitoring effectiveness of antiarrhythmic medications who have not met other inclusionary criteria

Cont.

Medical policy updates *Cont.*

Amniotic membrane and amniotic fluid

- **New policy**
- **Effective date: March 1, 2019**
- **Referral required**
- **Procedure codes: Multiple**

Several commercially available forms of human amniotic membrane and amniotic fluid can be administered by patches, topical application or injection. Amniotic membrane and amniotic fluid are being evaluated for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis and ophthalmic conditions.

The safety and effectiveness of select human amniotic membrane products have been established. They may be useful therapeutic options when indicated.

Injection of amniotic fluid is experimental for all indications. The safety, effectiveness and improvement in health outcomes has not been scientifically demonstrated.

Inclusions:

Diabetic Lower Extremity Ulcers

- Treatment of nonhealing** diabetic lower-extremity ulcers using the following human amniotic membrane products (AmnioBand® Membrane, Biovance®, Epifix®, Grafix™)

***Nonhealing is defined as less than a 20 percent decrease in wound area with standard wound care for at least two weeks*

Ophthalmic conditions

Sutured human amniotic membrane grafts may be considered medically necessary for the treatment of any of the following indications:

- Neurotrophic keratitis
- Corneal ulcers and melts
- Pterygium repair
- Stevens-Johnson syndrome
- Persistent epithelial defects when one of the following are met:
  - Failed to close completely after five days of conservative** treatment
  - Failed to demonstrate a decrease in size after two days of conservative** treatment

***Conservative treatment is defined as use of topical lubricants or topical antibiotics or therapeutic contact lens or patching.*

Exclusions:

Ophthalmic conditions

Sutured human amniotic membrane grafts for the treatment of all other ophthalmic conditions including but not limited to:

- Dry eye syndrome
- Burns
- Corneal perforation
- Bullous keratopathy
- Limbus stem cell deficiency
- After photorefractive keratectomy

Other conditions

All other human amniotic membrane products and indications not listed under inclusions, including but not limited to:

- Treatment of lower-extremity ulcers due to venous insufficiency
- Human amniotic membrane without suture (Prokera®, AmbioDisk™) for ophthalmic indications.
- Injection of micronized or particulated human amniotic membrane for all indications, including but not limited to treatment of:
  - Osteoarthritis and plantar fasciitis
- Injection of human amniotic fluid for all indications

Cont.

Medical policy updates *Cont.*

Genetic testing for BRCA1 or BRCA2 for hereditary breast/ovarian cancer syndrome and other high-risk cancers

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan approval with clinical review**
- **Procedure codes: *81162, *81163, *81164, *81165, *81166, *81167, *81212, *81215, *81216, *81217**

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer, or HBOC, and some cases of hereditary site-specific breast cancer have in common causative variants in BRCA (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma and laryngeal cancer occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early onset breast cancer with or without male cases, but without ovarian cancer. For this policy, both will be referred to collectively as hereditary breast or ovarian cancer.

Germline variants in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in the majority of HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA variants are responsible for only a proportion of affected families. BRCA gene variants are inherited in an autosomal dominant fashion through either the maternal or the paternal lineage. It is possible to test for abnormalities in BRCA1 and BRCA2 genes to identify the specific variant in cancer cases, and to identify family members with increased cancer risk. Family members without existing cancer who are found to have BRCA variants can consider preventive interventions for reducing risk and mortality.

The safety and effectiveness of simultaneous testing for inherited BRCA1 and BRCA2 variants have been established. It may be considered a useful diagnostic option when indicated for individuals at high risk of breast and/or ovarian cancer.

Testing for genomic rearrangements of the BRCA1 and BRCA2 genes (for example, BART testing) may be considered established in patients who meet criteria for BRCA1 and BRCA2 testing and whose testing for point variants is negative.

Use of multi-gene panels, including but not limited to BreastNext, OvaNext, BRCAplus, iGene Cancer Panel and BROCA tests is experimental. There is insufficient data on the analytical and clinical validity as well as clinical utility of these tests on patient management and outcomes.

It's highly recommended that genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and post-test counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis.

Note:

- For the purpose of familial assessment, first-, second-, and third-degree relatives are blood relatives on the same side of the family (maternal or paternal), such as:
  - First-degree relatives: parents, siblings and children
  - Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren and half-siblings
  - Third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren and first cousins
- For the purpose of familial assessment, aggressive prostate cancer is defined as Gleason score ≥7.
- Testing for Ashkenazi Jewish or another founder variants, if applicable, should be performed first.

Inclusions:

Patients with cancer or with a personal history of cancer (affected patients):

Genetic testing for BRCA1 and BRCA2 variants in cancer-affected individuals may be considered appropriate under any of the following circumstances:

- Individuals from a family with a known BRCA1/BRCA2 variant
- Personal history of breast cancer and one or more of the following:
  - Diagnosed age ≤45 years;

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Medical policy updates *Cont.*

- Variant
  - Diagnosed 46 to 50 years with:
    - An additional breast cancer primary at any age
    - One or more close relative with breast cancer at any age
    - One or more close relative with high grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history
  - Diagnosed ≤60 years with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - One or more close blood relative with either:
      - » Breast cancer diagnosed ≤50 years
      - » Ovarian carcinoma or male breast cancer
      - » Metastatic prostate cancer
      - » Pancreatic cancer
    - Two or more additional diagnoses of breast cancer at any age in patient and/or close blood relative
  - Ashkenazi Jewish ancestry
- Personal history of ovarian carcinoma
- Personal history of male breast cancer
- Personal history of pancreatic cancer
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with either:
  - One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer <50 years
  - Two or more close blood relatives with breast or prostate cancer (any grade) at any age
  - Ashkenazi Jewish ancestry
- BRCA1 or BRCA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic or likely pathogenic variant analysis
- Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment
- An individual who does not meet the other criteria but with one or more first- or second-degree blood relatives meeting any of the above criteria.

** Note: If there is a family history of ovarian cancer, it may not be possible to determine if the pathology was epithelial ovarian cancer, germ cell or some other type. Since up to 90 percent of ovarian cancers are epithelial in origin, determining the exact cell type is not necessary,

Testing for genomic rearrangements of the BRCA1 and BRCA2 genes for patients who meet criteria for BRCA testing and whose testing for point variants is negative:

Patients without cancer or without history of cancer (unaffected patients):

Testing of unaffected individuals should ideally only be considered when an appropriate affected family member is unavailable for testing. Testing is appropriate in the following circumstances:

- Individual from a family with a known BRCA1/BRCA2 variant
- A first- or second-degree blood relative meeting any criterion listed above for "patients with cancer"
- Third-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer **and** two or more first -, second -, or third -degree relatives with breast cancer (at least one at age 50 years or below) and/or ovarian/fallopian tube/primary peritoneal cancer

Note:

- For the purpose of familial assessment, first-, second- and third-degree relatives are blood relatives on the same side of the family (maternal or paternal).
  - First-degree relatives are parents, siblings and children.
  - Second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren and half-siblings.
  - Third-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren and first cousins.

Exclusions:

- Patients not meeting any of the above criteria
- Genetic testing for BRCA1 and BRCA2 variants in minors
- BRCA and BART testing as a screening test for cancer in women in the general population.
- BRCA and BART testing for unaffected individuals of high-risk populations (for example, Ashkenazi Jewish descendant) who have no relatives with a history of breast, ovarian, fallopian tube or primary peritoneal cancer at any age
- Genetic testing using multi-gene panels, including but not limited to BreastNext, OvaNext, BRCAplus, iGene Cancer Panel and BROCA tests

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Medical policy updates *Cont.*

Genetic testing for Lynch syndrome and other inherited colon cancer syndromes

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan notification: Plan approval with clinical review**
- **Procedure codes: Multiple**

Lynch syndrome is an inherited disorder that results in a higher predisposition to colorectal cancer and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3 percent to 5 percent of all colorectal cancers. People with Lynch syndrome have a 70 percent to 80 percent lifetime risk of developing any type of cancer. However, the risk varies by genotype.

Preliminary screening of tumor tissue does not identify mismatch repair gene variants but is used to guide subsequent diagnostic testing by DNA analysis for specific variants.

The safety and effectiveness of genetic testing for polyposis and non-polyposis cancer syndromes have been established. They may be considered useful diagnostic options for individuals who meet clinical criteria for increased risk of hereditary colorectal cancer.

Inclusions:

These guidelines refer to the different types of genetic tests available for colorectal cancer.

A. Genetic testing of the adenomatous polyposis coli gene, or adenomatous polyposis coli, is established in any of the following:

- At risk relatives (siblings, parents and offspring) of patients with familial adenomatosis polyposis or attenuated familial adenomatous polyposis and/or a known APC variant
- Patients with a differential diagnosis of attenuated FAP versus MUTYH-associated polyposis (MAP) versus Lynch syndrome. Whether testing begins with APC variants or screening for mismatch repair (MMR) variants depends on clinical presentation

Due to the high lifetime risk of cancer of the majority of the genetic syndromes discussed in this policy, "at-risk relatives" primarily refers to first-degree relatives. However, some judgment must be allowed, for example, in the case of a small family pedigree, when extended family members may need to be included in the testing strategy.

It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis (FAP) or Lynch syndrome be performed in an affected family member so that testing in unaffected family members can focus on the variant found in the affected family member.

A. Genetic testing for MUTYH gene variants is established in all of the following:

- Patients with a differential diagnosis of attenuated familial adenomatous polyposis vs. MUTYH-associated polyposis vs. Lynch syndrome
- Negative result for APC gene variants
- Negative family history of no parents or children with FAP is consistent with autosomal recessive MAP

In many cases, genetic testing for MUTYH gene variants should first target the specific variants Y165C and G382D, which account for more than 80 percent of variants in white populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

A. Genetic testing for MMR gene variants (MLH1, MSH2, MSH56, PMS2) to determine the carrier status of Lynch syndrome is established in any of the following:

- Patients with colorectal cancer to test for the diagnosis of Lynch syndrome
- Patients with endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, for the diagnosis of Lynch syndrome
- At-risk relatives of patients with Lynch syndrome with a known MMR variant
- Patients with a differential diagnosis of attenuated FAP versus MAP versus Lynch syndrome. Whether testing begins with APC variants or screening for MMR genes depends on clinical presentation
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria when:
  - No affected family members have been tested for MMR variants.

For patients with colorectal cancer being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test, or the immunohistochemical (IHC) test with or without BRAF gene variant testing, should be used as an initial evaluation of tumor tissue before mismatch repair MMR gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive.

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When indicated, genetic sequencing for MMR gene variants should begin with MLH1 and MSH2 genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications. When MMR gene variants are expected based on IHC or MSI studies, but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

D. Genetic testing for EPCAM gene variants is established when any of the following major criteria (solid bullets) is met:

- Patients with colorectal cancer, for the diagnosis of Lynch syndrome when one of the following are met:
  - Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for a MSH2 germline variant
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in MSH2, MLH1, PMS2, and MSH6
- At-risk relatives of patients with Lynch syndrome with a known EPCAM variant
- Patients without colorectal cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria when both of the following are met:
  - No affected family members have been tested for MMR variants.
  - Sequencing for MMR variants is negative.
- The Amsterdam II Clinical Criteria (all criteria must be fulfilled) are the most stringent criteria for defining families at high risk for Lynch syndrome. Three or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter, or renal pelvis)
- One should be a first-degree relative of the other two
- Two or more successive generations affected
- One or more relatives diagnosed before the age of 50 years
- Familial adenomatous polyposis should be excluded in cases of colorectal carcinoma
- Tumors should be verified by pathologic examination
- Modifications, **either**:
  - Very small families, which cannot be further expanded, can be considered to have hereditary nonpolyposis colorectal cancer (HNPCC) with only two colorectal cancers in first degree relatives if at least two generations have the cancer and at least one case of colorectal cancer was diagnosed by the age of 55 years.
  - 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.

The Revised Bethesda Guidelines (fulfillment of any criterion meets guidelines) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families (Umar et al, 2004). The Bethesda guidelines are also considered more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry:

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old
- Presence of synchronous or metachronous CRC or other HNPCC-associated tumors,** regardless of age
- CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old
- CRC diagnosed in one or more first-degree relatives with a Lynch syndrome-associated tumor, with one of the cancers being diagnosed at younger than 50 years of age
- CRC diagnosed in two or more first or second-degree relatives with HNPCC-related tumors, regardless of age

**HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), sebaceous bland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

E. Genetic testing for BRAF V600E or MLH1 promoter methylation are established to exclude a diagnosis of Lynch syndrome when:

- MLH1 protein is not expressed in a colorectal cancer tumor on immunohistochemical analysis.

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Medical policy updates *Cont.*

F. Genetic testing for SMAD4 and BMPR1A gene variants are established when any of the following major criteria (solid bullets) is met:

- Individual has a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
  - At least three to five juvenile polyps in the colon
  - 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
- Individual is an at-risk relative of a patient suspected of or diagnosed with juvenile polyposis syndrome

G. Genetic testing for STK11 gene variants is established when any of the following major criteria (solid bullets) is met:

- Individual has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following secondary criteria:
  - Presence of two or more histologically confirmed Peutz-Jeghers polyps of the small intestine
  - Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia or fingers
  - Family history of Peutz-Jeghers syndrome
- Individual is an at-risk relative of a patient suspected of or diagnosed with Peutz-Jeghers syndrome

Pre- and post-test genetic counseling is established as an adjunct to genetic testing.

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Exclusions:

Genetic testing for APC gene variants is considered investigational for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

Genetic testing for all other gene variants for Lynch syndrome or colorectal cancer is considered experimental.

Genetic testing-molecular analysis for targeted therapy of non-small cell lung cancer

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan approval with clinical review**
- **Procedure codes: *81235, *81275, *81404, *81405, *81479, *81406**

Treatment options for non-small cell lung cancer, or NSCLC, depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy and best supportive care. Unfortunately, in up to 85 percent of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40 percent of patients with non-small cell lung cancer present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced non-small cell lung cancer have a median survival of eight to 11 months and a one-year survival of 30 percent to 45 percent. More recently, the identification of specific, targetable oncogenic "driver" mutations in a subset of NSCLCs have resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. Testing for EGFR mutations in clinical decision making for the treatment of NSCLC is routine. The use of testing for other mutations to direct targeted therapy is not well-established and continues to evolve.

- EGFR Gene
  - The safety and effectiveness of analysis of somatic variants in exons 18 (such as G719X), 19 (such as L858R, T790M), 20 (such as S678I), or 21 (such as L861Q) within the EGFR gene have been established to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) or osimertinib (Tagrisso) in patients with advanced lung adenocarcinoma or advanced squamous cell NSCLC.

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  - The analysis for other EGFR mutations within exons 22-24, or other applications related to NSCLC, is considered experimental. The peer reviewed medical literature has not yet demonstrated the clinical utility of this testing for this indication.

- ALK Gene
  - The safety and effectiveness of analysis of somatic rearrangement mutations of the ALK gene have been established. It is an effective diagnostic option for predicting treatment response to crizotinib (Xalkori®) or ceritinib (Zykadia™) in patients with advanced lung adenocarcinoma and large cell carcinoma or for patients in whom an adenocarcinoma component cannot be excluded,
  - Analysis of somatic rearrangement mutations of the ALK gene is considered experimental in all other situations.
- BRAF V600E Gene
  - Analysis of the BRAF V600E variant is established to predict treatment response to BRAF or MEK inhibitor therapy (for example, dabrafenib [Tafinlar] and trametinib [Mekinist®]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.
- ROS1 gene
  - Analysis of somatic rearrangement variants of the ROS1 gene is established to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded.
- KRAS gene
  - Analysis of somatic mutations of the KRAS gene is established as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC. The peer reviewed medical literature has demonstrated the clinical utility of this testing for this indication.
- Other genes
  - Analysis for genetic alterations in the genes, RET, MET and HER2 for targeted therapy in patients with NSCLC, is considered experimental. The peer reviewed medical literature has not yet demonstrated the clinical utility of this testing for this indication.

Implantable bone-conduction and bone-anchored hearing devices

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan notification, Plan approval with clinical review**
- **Procedure codes: *69710, *69711, *69714, *69715, *69717, *69718, L8625, L8690, L8691, L8692, L8693, L8694**

External bone-conduction hearing devices function by transmitting sound waves through the bone to the ossicles of the middle ear. The external devices must be applied close to the temporal bone, with either a steel spring over the top of the head or a spring-loaded arm on a pair of spectacles.

The safety and effectiveness of unilateral or bilateral fully or partially implanted bone-conduction (bone-anchored) hearing aids have been established. They may be considered a useful therapeutic option when indicated.

Inclusions:

Conductive hearing loss:

Unilateral or bilateral fully- or partially-implantable bone-conduction** (bone-anchored) hearing aids may be necessary as an alternative to an air-conduction hearing aid in patients five years of age and older with conductive or mixed hearing loss who also meet at least one of the following criteria:

- Congenital or surgically-induced malformations (atresia) of the external ear canal or middle ear
- Chronic external otitis or otitis media
- Tumors of the external canal and/or tympanic cavity
- Chronic dermatitis of the external canal prohibiting the usage of an air conduction hearing aid

In addition, meet the following audiologic criteria:

- A pure-tone average bone-conduction threshold measured at 0.5, 1, 2, and 3 kHz or better than or equal to 45 dB Otomag Bone Conduction (OBC) and Baha BP100, Baha 4 and Baha 5 devices, 55 dB (Intenso device), or 65 dB (Cordele II and Baha 5 SuperPower devices).

For bilateral implantation, patients should meet the above audiologic criteria in both ears and have symmetrically conductive or mixed hearing loss as defined by a difference between left and right side bone-conduction threshold of less than 10 dB on average measured at 0.5, 1, 2, and 3 kHz (4 kHz for OBC and Ponto Pro), or less than 15 dB at individual frequencies.

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Medical policy updates *Cont.*

Sensorineural hearing loss:

A unilateral implantable bone-conduction (bone-anchored) hearing aid may be considered medically necessary as an alternative to an air-conduction contralateral routing of signal hearing aid in patients five years of age and older with single-sided sensorineural deafness and normal hearing in the other ear. The pure-tone average air-conduction threshold of the normal ear should be better than 20 dB measured at 0.5, 1, 2, and 3 kHz.

***The Audiant® bone conductor is a bone-conduction hearing device. While this product is no longer actively marketed, patients with existing Audiant devices may require replacement, removal, or repair.*

In patients being considered for implantable bone-conduction (bone-anchored) hearing aids, skull bone quality and thickness should be assessed for adequacy to ensure implant stability. Additionally, patients or caregivers must be able to perform proper hygiene to prevent infection and ensure the stability of the implants and percutaneous abutments.

Exclusions:

Other uses of implantable bone-conduction (bone-anchored) hearing aids, including use in patients with bilateral sensorineural hearing loss, are considered experimental.

Intermittent (72 hours or greater) or continuous invasive glucose monitoring

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan approval with clinical review; Use appropriate contracted vendor**
- **Procedure codes: *85249, *95250, *95251, *A9276, *A9277, *A9278, *A9279, K0553, K0554**

The advent of blood glucose monitors for use by patients in the home more than 20 years ago revolutionized the management of diabetes. Using finger sticks, patients could monitor their blood glucose level both to determine the adequacy of hyperglycemia control and to evaluate hypoglycemic episodes. Tight diabetic control, defined as a strategy involving frequent glucose checks and a target HgA1c in the range of 7 percent, is now considered standard of care for diabetic patients. Randomized controlled trials of tight control have demonstrated benefits for Type 1 diabetes patients in decreasing microvascular complications. The impact of tight control on Type 2 diabetes patients and on macrovascular complications, such as stroke or myocardial infarction, is less certain.

Tight glucose control requires multiple daily measurements of blood glucose (before meals and at bedtime), a commitment that some patients may be unwilling or unable to meet. In addition, the goal of tight glucose control has to be balanced with an associated risk of hypoglycemia. Hypoglycemia is known to be a risk in patients with Type 1 diabetes. While patients with insulin-treated Type 2 diabetes may also experience severe hypoglycemic episodes, there is a lower relative likelihood of severe hypoglycemia compared with patients with Type 1 diabetes. An additional limitation of periodic self-measurements of blood glucose is that glucose levels are seen in isolation, and trends in glucose levels are undetected. For example, while a diabetes patient's fasting blood glucose level might be within normal values, hyperglycemia might be undetected post-prandially, leading to elevated hemoglobin A1c values.

Recently, measurements of glucose in interstitial fluid have been developed as a technique of automatically measuring glucose values throughout the day, producing data that show the trends in glucose measurements, in contrast to the isolated glucose measurements of the traditional blood glucose measurements. Although devices measure glucose in interstitial fluid on a periodic rather than a continuous basis, this type of monitoring is referred to as continuous glucose monitoring (CGM).

The safety and effectiveness of FDA-approved continuous glucose monitoring systems, on an intermittent (72 hours or greater) or continuous basis, have been established. Both may be considered useful therapeutic devices for patients meeting the relevant patient selection criteria.

Inclusions:

Seventy-two-hour monitoring of glucose levels in interstitial fluid, to optimize patient management, may be considered established in the following situations when any of the following criteria are met:

- Patients with Type 1 diabetes who, despite current use of best practices, have poorly controlled diabetes, including hemoglobin A1C not in acceptable target range for the patient's clinical situation, unexplained hypoglycemic episodes, evidence suggesting postprandial hyperglycemia, or recurrent diabetic ketoacidosis
- Patients with Type 1 diabetes prior to insulin pump initiation to determine basal insulin levels
- Women with Type 1 diabetes who are pregnant or about to become pregnant and have poorly controlled diabetes

Cont.

Medical policy updates *Cont.*

Continuous (long-term) monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique in diabetic monitoring may be considered established in any of the following situations:

- Patients with Type 1 diabetes who have demonstrated an understanding of the technology, are motivated to use the device correctly and consistently, are expected to adhere to a comprehensive diabetes treatment plan supervised by a qualified provider, and are capable of using the device to recognize alerts and alarms
- Patients with Type 1 diabetes who have recurrent, unexplained, severe (generally blood glucose levels <50 mg/dL) hypoglycemia or impaired awareness of hypoglycemia that puts the patient or others at risk
- Patients with poorly controlled Type 1 diabetes who are pregnant; poorly controlled Type 1 diabetes includes unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia and recurrent diabetic ketoacidosis.

Intermittent monitoring of glucose levels in interstitial fluid may also be considered established in patients with Type 1 diabetes prior to insulin pump initiation to determine basal insulin levels.

Exclusions:

Other uses of continuous monitoring of glucose levels in interstitial fluid (including real-time monitoring) as a technique of diabetic monitoring are considered experimental, including:

- Patients not meeting the inclusionary criteria above
- For convenience purposes, such as (but not limited to) lifestyle or employment circumstances.

Replacement:

Replacement of a continuous glucose monitoring system may be considered when:

- The transmitter is out of warranty.
- The transmitter is malfunctioning.
- There is documented evidence the member is compliant with his or her current CGMS device. Compliance is defined as at least 70 percent use rate of the device (for example, five out of seven days) based on the log data.

Continuation of sensor use after one year may be considered when:

- The CGMS has been previously approved by the Health Plan or the CGMS is in use prior to the user enrolling in the Health Plan
- There is documented evidence the member is compliant with his or her current CGMS device. Compliance is defined as at least 70 percent use rate of the device (for example, five out of seven days) based on the log data.

All covered supplies must be compatible with the CGMS.

Laboratory testing for heart and kidney transplant rejection

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan notification, Plan approval with clinical review**
- **Procedure codes: *81595, *0085T, *0055U, *81479**

Post-transplant, acute cellular rejection is most likely to occur in the first six months, with a significant decline in the incidence of rejection after this time. Although immunosuppressants are required on a life-long basis, dosing is adjusted based on graft function and the grade of acute cellular rejection determined by histopathology.

Allograft dysfunction is typically asymptomatic and has a broad differential, including graft rejection. Diagnosis and rapid treatment is recommended to preserve graft function and prevent loss of the transplanted organ.

Noninvasive methods of detecting cellular rejection have been explored. It is hoped that noninvasive tests will assist in determining appropriate patient management and avoid overuse or underuse of treatment with steroids and other immunosuppressants that can occur with false-negative and false-positive biopsy reports.

The safety and effectiveness of gene expression profiling (AlloMap) has been established for the detection of heart transplant rejection. It may be considered a useful therapeutic option when specified criteria have been met.

The breath test (Heartsbreath™) for the evaluation of heart transplant rejection is considered experimental. The effectiveness and clinical utility of this test has not been clearly established.

Cont.

Medical policy updates *Cont.*

The use of peripheral blood measurement of donor-derived cell-free DNA in the management of patients after renal transplantation including, but not limited to, the detection of acute renal transplant rejection or renal transplant graft dysfunction, is experimental. The effectiveness and clinical utility of this test has not been clearly established.

Inclusions:

All major bullets must be met:

- Gene expression profiling (AlloMap) may be appropriate as a screening technique for heart transplant rejection in recipients who meet both of the following:
  - At least 15 years old
  - Six months post-heart transplant
- Recipient must have stable heart allograft function demonstrated by all of the following:
  - Left ventricular ejection fraction ≥ 45 percent which has been confirmed by echocardiogram
  - No evidence of congestive heart failure
  - No evidence of severe cardiac allograft vasculopathy
- Recipient must have a low probability of moderate or severe acute cellular rejection as demonstrated by all of the following:
  - Clinical assessment (for example, International Society for Heart and Lung Transplantation rejection status Grade of 0R or 1R)
  - No history or evidence of antibody mediated rejection

Exclusions:

- Gene expression profiling (AlloMap) for any other indication
- Breath testing (Heartsbreath™)
- Peripheral blood measurement of donor-derived cell-free DNA to detect acute renal transplant rejection or renal transplant graft dysfunction
- myTAIHEART™ testing

Magnetic resonance imaging for detection and diagnosis of breast cancer

- **Revised policy**
- **Effective date: March 1, 2019**
- **No referral required – Use appropriate contracted vendor**
- **Procedure codes: *77046, *77047, *77058, *77059**

Magnetic resonance imaging of the breast can be used to screen, detect, and diagnose breast cancer. MRI can be used as a replacement for mammography screening, as an additional imaging test alone, or in combination with other imaging modalities.

The safety and effectiveness of magnetic resonance imaging of the breast have been established. It may be considered a useful diagnostic option for patients meeting criteria.

Inclusions:

Note: All of the following policy statements refer to performing MRI of the breast with a breast coil and the use of contrast. MRI of the breast without the use of a breast coil, regardless of the clinical indication, is considered experimental.

A. MRI of the breast may be considered medically appropriate for screening for breast cancer in patients at high risk of breast cancer.

High-risk considerations

There is no standardized method for determining a woman's risk of breast cancer that incorporates all possible risk factors. There are validated risk prediction models, but they are based primarily on family history.

Some known individual risk factors confer a high risk by themselves. The following list includes factors known to indicate a high risk of breast cancer:

- Lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH)/atypical ductal hyperplasia (ADH)
- A known *BRCA1* or *BRCA2* variant
- Another gene variant associated with high risk, for example, *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome), *CDH1*, *STK11*, *ATM*, *CHEK2*, *PALB2*, *NBN*, *NF1*
- High-risk (lifetime risk about 20 percent or greater) of developing breast cancer as identified by models that are largely defined by family history
- Received radiotherapy to the chest between 10 and 30 years of age

Cont.

Medical policy updates *Cont.*

A number of factors may increase the risk of breast cancer but do not by themselves indicate high risk. It is possible that combinations of these factors may be indicative of high risk, but it is not possible to give quantitative estimates of risk. As a result, it may be necessary to individualize the estimate of risk, whereby one would need to take into account the numerous risk factors. A number of risk factors, not individually indicating high risk, are included in the National Cancer Institute Breast Cancer Risk Assessment Tool (also called the Gail model). Risk factors in the model can be accessed online (**cancer.gov/bcrisktool/Default.aspx**).

National Cancer Care Network guidelines state there is insufficient evidence for any recommendations for breast MRI for patients with the following variants: *BARD1*, *BRIP1*, *FANCC*, *MRE11A*, *MUTYH*, *RAD50*, *RINT1*, SLX4, *SMARCA*, or *XRCC2*. Moreover, there are conflicting data regarding risks associated with *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* gene deletion (**nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf**)

MRI of the breast is medically appropriate for the following indications:

- Detection of a suspected occult breast primary tumor in patients with axillary nodal adenocarcinoma (negative mammography and physical exam)
- Presurgical planning in patients with locally advanced breast cancer (before and after completion of neoadjuvant chemotherapy) to permit tumor localization and characterization
- Determining the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumor
- Evaluation of the contralateral breast in those patients with a new diagnosis of breast cancer when clinical and mammographic findings are normal
- Preoperative tumor mapping of the involved (ipsilateral) breast to evaluate the presence of multicentric disease in patients with clinically localized breast cancer who are candidates for breast-conservation therapy
- Evaluation of a documented abnormality of the breast prior to obtaining an MRI-guided biopsy when there is documentation that other methods, such as palpation or ultrasound, are not able to localize the lesion for biopsy

Exclusions:

- Screening technique in average-risk patients
- Screening technique for the detection of breast cancer when the sensitivity of mammography is limited (for example, dense breasts)
- Diagnosis of low-suspicion findings on conventional testing not indicated for immediate biopsy and referred for short-interval follow-up
- Diagnosis of a suspicious breast lesion to avoid biopsy

Stereotactic radiosurgery and stereotactic body radiotherapy

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan notification; Plan approval with clinical review**
- **Procedure codes: Multiple**

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are techniques that use highly focused, conformal radiation beams to treat both neoplastic and non-neoplastic conditions. Platforms available for SRS and SBRT are distinguished by their source of radiation; they include gamma radiation from cobalt 60 sources; high-energy photons from LINAC systems; and particle beams (for example, protons). Particle beam therapy is not covered in this evidence review.

The safety and effectiveness of stereotactic radiosurgery and stereotactic body radiotherapy using gamma-ray or linear-accelerator units are established and are considered useful therapeutic options when indicated.

Reference AIM criteria for clinical preference.

Inclusions:

- Stereotactic radiosurgery (intracranial) using a gamma-ray or linear-accelerator unit (LINAC) is considered established for the following indications:
- Arteriovenous malformation
- Acoustic neuromas
- Pituitary adenomas
- Non-resectable, residual or recurrent meningiomas
- Craniopharyngiomas
- Glomus jugulare tumors
- Solitary or multiple brain metastases in patients having good performance status
- Primary malignancies of the central nervous system (CNS), including but not limited to high-grade gliomas (initial treatment or treatment of recurrence)
- Trigeminal neuralgia refractory to medical management

Cont.

Medical policy updates *Cont.*

Stereotactic body radiotherapy (extracranial) is considered established for the following indications:

- Spinal or vertebral body tumors that include:
  - Metastatic or primary
  - Irradiated or unirradiated
- Spinal or vertebral metastases that are radioresistant (for example, renal cell carcinoma, melanoma and sarcoma)
- Members with stage T1 or T2a non-small cell lung cancer (not larger than 5 cm) showing no nodal or distant disease and who are not candidates for surgical resection
- In the treatment of primary and metastatic liver malignancies
- Low- or intermediate-risk localized prostate cancer

Stereotactic radiosurgery or stereotactic body radiotherapy using fractionation is considered established when used for indications listed above.

Note:

- *Fractionated SRS refers to stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) performed more than once on a specific site*
- *SBRT is commonly delivered over three to five fractions*
- *SRS is most often single-fraction treatment; however multiple fractions may be necessary when lesions are near critical structures.*

Exclusions:

Stereotactic body radiotherapy is considered experimental for all other diagnoses not specified in this policy, including malignant neoplasms of the following:

- Pancreas
- Kidney
- Adrenal glands

Stereotactic radiosurgery is considered experimental for the treatment of seizures and functional disorders (other than trigeminal neuralgia) including chronic pain, tremor and uveal melanoma.

Medical formula for inborn errors of metabolism

- **New policy**
- **Effective date: Jan. 1, 2019**
- **Use appropriate contracted vendor**
- **Procedure codes: B4157, B4162**

Inborn errors of metabolism are a large group of inherited biochemical disorders. The broadest definition of IEM describes endogenous processes, such as biosynthesis, as well as the exogenous process of ineffective metabolism of food substances. The focus of this policy is medical treatment of individuals who are unable to metabolize typical food sources.

Treatment involves the exclusion of the offending substance and supplementation of nutrients. However, for some conditions this requires purchase of specially-manufactured formula that excludes the offending substance. The medical formula is required for life. New IEM conditions continue to be identified as research of rare conditions leads to IEM as a causative process.

The safety and effectiveness of oral medical formula for individuals with inborn errors of metabolism have been established. Oral medical formula is considered an established treatment option when policy criteria are met.

Inclusions:

Oral medical formula (medical formula for consumption by mouth), for individuals of any age, is considered established when all of the following are met:

- The individual has a diagnosis of an inborn error of metabolism**
- The oral medical formula is labeled and used for nutritional management of an IEM that interferes with the metabolism of specific nutrients (for example, phenylketonuria, homocystinuria, maple syrup urine disease)
- The oral medical formula nutrition is ordered by a clinical or medical biochemical geneticist or by other qualified medical professionals in consultation with a clinical or medical biochemical geneticist

*See Appendix A at the end of the policy in Provider Secured Services (at BCN Provider Publications and Resources) for a list of inborn errors of metabolism

Cont.

Medical policy updates *Cont.*

Exclusions:

- Formula for any condition other than an inborn error of metabolism (for example, diabetes, hypercholesterolemia)
- Formula that does not require a physician order for purchase
- Formula not specifically used for the nutrition of an individual with IEM
- Medical food product that is not *formula* (for example, food modified to be low in protein, such as meat or cheese substitutes, or pasta)
- Nutrition by tube feeding (refer to the Enteral Nutrition policy for guidelines)

Focal treatments for prostate cancer

- **Revised policy**
- **Effective date: March 1, 2019**
- **Plan approval with clinical review**
- **Procedure codes: *55873, *55899, C9747**

Localized prostate cancer is most often treated by one of two approaches: watchful waiting and monitoring, or treatment by radiation therapy or surgery. Focal therapy offers a middle-ground option. The goal of focal treatment is to reduce the amount of damage to the prostate gland and surrounding tissue while effectively treating the cancer.

Modalities used in focal treatment include cryoablation, high-intensity focused ultrasound, also called HIFU, focal laser ablation, radiofrequency ablation and photodynamic therapy.

Cryoablation of the prostate is considered established as treatment of clinically localized (organ-confined) prostate cancer when performed, either:

- As initial treatment
- As salvage treatment of disease that recurs following radiotherapy, when criteria are met

High-intensity focused ultrasound of the prostate is considered established:

- As salvage treatment of disease that recurs following radiotherapy, when criteria are met

Focal laser ablation, radiofrequency ablation and photodynamic therapy for the treatment of localized prostate cancer are considered experimental, as they have not been shown to improve patient clinical outcomes.

Inclusions:

Cryosurgery may be considered established for the initial treatment of clinically localized (organ-confined) prostate cancer.

Cyrosurgery or high-intensity focused ultrasound may be considered established for local treatment of recurrent prostate cancer when all these conditions are met:

1. Primary treatment of prostate cancer was radiation therapy
2. All of the following:
   - Original clinical stage T1-T2, NX or N0
   - Life expectancy >10 y
   - PSA now <10 ng/mL
3. Transrectal ultrasound guided biopsy is positive
4. Studies are negative for distant metastases

Exclusions:

- Local treatment of recurrent prostate cancer that does not meet criteria

Focal laser ablation, radiofrequency ablation and photodynamic therapy for the treatment of localized prostate cancer are considered experimental.