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Corporate Medical Policy

Detection of Circulating Tumor Cells and Cell Free DNA in Cancer Management AHS-G2054

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Description of Procedure or Service

National Cancer Institute defines liquid biopsy as a test done on a sample of blood for the detection of cancer cells from a tumor that are circulating in the blood or for the detection of cell free DNA pieces from tumor cells that are in the blood. Liquid biopsies are non-invasive blood tests since circulating tumor cells (CTCs) and cell free tumor DNA (cfDNA) fragments are shed into the bloodstream or lymphatic system (Beije, et al., 2015) from existing tumors and can be detected in blood (Curigliano, 2014). The presence of CTCs can be indicative of metastatic disease (Alix-Panabieres & Pantel, 2013).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for detection of circulating tumor cells and cell free DNA in cancer management when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Detection of Circulating Tumor Cells in Cancer Management is covered

Detection of circulating tumor cells and cell free DNA in cancer management is considered **medically necessary** for EGFR mutations to predict treatment response to an EGFR tyrosine kinase inhibitor in patients with Stage IIIB/IV non-small cell lung cancer (NSCLC) when an invasive biopsy is medically contraindicated or quantity of tissue available for mutation testing is insufficient.

If no genetic alteration is detected by plasma genotyping, or if circulating tumor DNA (ctDNA) is insufficient/not detected, tissue-based genotyping should be considered.

When Detection of Circulating Tumor Cells in Cancer Management is not covered

1. Liquid biopsy for all other mutations in NSCLC (e.g. ALK and ROS rearrangements) is **investigational.**

2. Liquid biopsy for screening, detecting and monitoring any other malignancy or tumor is considered **investigational.**

Policy Guidelines

The science of noninvasive disease monitoring has advanced greatly since circulating cell free DNA (cfDNA) was first reported in body fluids by Mandel and Metais. Since then, the evolution of sensitive cfDNA detection technologies has enabled the development of liquid biopsies with many clinical applications. For example, in oncology, the use of liquid biopsy allows for patient stratification (companion diagnostics), screening, monitoring treatment response and detection of minimal residual disease after surgery/recurrence.

Liquid biopsies have grown in importance because, the genetic profile of tumors can affect how well they respond to a certain treatment. However, this characterization is currently achieved through a biopsy despite the inherent problems in procurement of tissue samples and the limitations of tumor analyses. For example, the invasive nature of a biopsy poses a risk to patients and can have a significant cost.

Tumor sampling from some cancer types also remains difficult resulting in inadequate amount of tissue for genetic testing. In the case of advanced or metastatic non-small cell lung cancers (NSCLC) as many as 31% of cases do not have accessible tissue. Even when tissue can be collected, preservation methods such as formalin fixation can cause C > T transitions through deamination of cytosine, potentially leading to false positive results for genetic tests. Finally, due to tumor heterogeneity, biopsies often suffer from sample bias bias (Bedard, Hansen, Ratain, & Siu, 2013)

Approaches to liquid biopsy analysis

Circulating tumor cells (CTCs)
CTCs are cells shed into the vasculature from a primary tumor and may constitute seeds for subsequent growth of additional tumors (metastasis) in distant organs. They have been detected in various metastatic carcinomas for example breast, prostate, lung, and colorectal cancer (Mavroudis, 2010) but are extremely rare in healthy subjects and patients with nonmalignant diseases. Clinical evidence indicates that patients with metastatic lesions are more likely to have CTCs amenable to isolation but their frequency is low, often ~1-10 CTCs per mL of whole blood (Miller, Doyle, & Terstappen, 2010). As 1 mL of blood contains ~7×10e6 white blood cells and ~5×10e9 red blood cells, technologies capable of reproducibly isolating a single CTC from the background of all other blood components are fundamental. While such levels of sensitivity are challenging, there are several novel developments in this area. These include positive selection, negative selection, physical properties or even enrichment-free assays to efficiently isolate these rare CTCs (Alix P C et al, 2013)).

Typically, CTCs are defined as cells with an intact viable nucleus, cytokeratin positive, epithelial cell adhesion molecule (EpCAM) positive and with the absence of CD45. Unfortunately EpCAM and other markers are not always expressed on CTCs and are down-regulated by processes such as epithelial to mesenchymal transition (Grover, Cummins, Price, Roberts-Thomson, & Hardingham, 2014)In addition, non-tumor epithelial cells are known to circulate in the blood of patients with prostatitis (Murray et al., 2013)or patients undergoing surgery. From a technical standpoint, the heterogeneity of CTCs is a major challenge and this has led to alternative strategies of CTC enrichment, such as the CTC-iChip (Karabacak et al., 2014), which do not rely on tumor antigen expression.

Sequencing the genetic material from CTCs has demonstrated that, even when the isolated cell(s) fit the phenotypic criteria of being a CTC, the majority are not cancer cells. One study by Marchetti A et al (2014) developed a protocol to recover the CTC enriched samples from the cartridge of the Veridex platform and found that from 37 NSCLC patients, the mutation allele abundance ranged between 0.02% and 24.79% with a mean of 6.34%. The number of CTCs found in the blood is therefore highly dependent on how the platform defines a cell as a CTC.

The CellSearch CTC test, a Food and Drug Administration (FDA) approved actionable CTC test, requires that samples are processed within 96 hours of collection after being drawn into the Cellsave preservative tube. This test does not analyze the molecular genetics of the tumor; rather Cellsave is a platform for CTC numeration. A positive test (more than five detected CTCs for metastatic breast and prostate cancer and more than three CTCs for metastatic colorectal cancer per 7.5 mL of blood) is associated with decreased progression-free survival and decreased overall survival in these patients (Aggarwal et al., 2013).

Cell free DNA (cfDNA)

There is currently an intensive research effort to understand the utility of cfDNA in various clinical fields such as cancer research, non-invasive prenatal testing and transplant rejection diagnostics.

In a systematic review and meta-analysis, Luo, Shen And Zheng (2014) concluded that detection of EGFR mutation by cfDNA is of adequate diagnostic accuracy and cfDNA analysis could be a promising screening test for NSCLC.

In a study Jiang P et al (2015) observed that most cfDNA in plasma is reportedly fragmented, around 150-180 bp in length with a higher prevalence of tumor associated mutations in the shorter fragments. Per authors, when analyzing the mutation abundance with massively parallel sequencing a significant correlation was found between mutations and fragments less than 150 bp. Notably, the size of the majority of cfDNA fragments overlaps well with the size of histone DNA.

In another study, Bettegowda C, et al (2014)stated that an advantage of cfDNA is that it can be analyzed from bio-banked biofluids, such as frozen plasma. In addition, a direct comparison of mutation detection on cfDNA vs. CTCs showed a higher abundance of the mutation on the cfDNA from the same patient. Recent large studies comparing the effectiveness of cfDNA analysis to tissue biopsy in NSCLC showed the clinical value of the liquid biopsy approach (Douillard et al., 2014). This positive result led to an approval to use cfDNA analysis for EGFR mutation analysis for IRESSA® in Europe (in patients where a tumor sample was not evaluable), making it the first EGFR tyrosine kinase inhibitor for which cfDNA testing is included in the label.

Although promising, challenges remain when using cfDNA to characterize the mutation status of a tumor. In addition to the low copy number of mutant alleles, the median half-life of cfDNA in circulation ranges from 15 minutes to a few hours.

Brock et al, (2015) in their review article “Liquid biopsy for cancer screening, patient stratification and monitoring” observes that the total concentration of cfDNA in the blood of cancer patients varies considerably with tumor specific mutations ranging from undetectable (less than 1 copy per 5 mL of plasma) to patients with over hundred thousand copies of the mutation per ml of plasma. Thus, the challenge of how to maximize the yield of the cfDNA and pair this with a platform sensitive enough to detect rare variants in the background of wild-type DNA remains. Optimally, the ability to detect mutations in plasma should not be limited to a subpopulation of patients with very high mutant copy numbers in circulation. While many analytical platforms report the mutation load with an allelic frequency compared to the wild-type DNA, platforms relying solely on the allelic frequency without recording the number of mutations have limitations. The allelic frequency is affected by the amount of wild-type DNA not related to the tumor. Therefore, it is important to consider the processes that affect the amount of wild-type DNA in circulation. For example, exercise increases cfDNA levels 10-fold (Breitbach, Sterzing, Magallanes, Tug, & Simon, 2014) and other pre-analytical variables such as blood collection and extraction protocols affect the amount and size range of cfDNA fragments in a sample (Devonshire et al., 2014).

Exosomes

In the last few years, the exosome field has grown exponentially impacting various areas of research. Studies demonstrating that exosomes are actively released vesicles (carrying RNA, DNA and protein) and can function as inter-cellular messengers, have contributed to their elevated recognition in the

scientific community. Yáñez-Mó M, et al, (2015) in a review outlining the biological properties of exosomes and other extracellular vesicles (EV's) highlights these developments. However, Gould SJ, et al (Gould & Raposo, 2013) in a study observed that, with respect to nomenclature, the exosome field still lags behind as the definition and characterization of EV types are not yet firmly established. The majority of exosomes range in size from 30-200 nanometer in diameter and are isolated from all bio-fluids, including serum, plasma, saliva, urine and cerebrospinal fluid.

Due to the size of an exosome, on average just over 100 nanometers, the entire transcriptome cannot be packaged inside every vesicle. By way of comparison, retrovirus particles with a similar size can package only around 10 kb, so it is likely that a single vesicle of that size carries only a limited number of transcripts. However, exosomes are extremely abundant (10e11 per mL of plasma) and when isolating the vesicle fraction, most of the transcriptome can be detected. Per Huang X et al (2013), and Kahlert C et al (2014), Exosomal RNA can be used for mutation detection as well as global profiling of most types of RNA, and the profile alone (without mutation characterization) can be utilized for diagnostics. In a study 'Immune modulation of T-cell and NK (natural killer) cell activities by TEXs (tumour-derived exosomes)' Whiteside TL et al (2013) observed that Exosome investigations have focused on the important physiologic and pathophysiologic functions of these vesicles in micro-metastasis, angiogenesis and immune modulation and as a means for detection of tumor specific mutations in bio-fluids. Consequently, in 2012, interest in this new field increased when the National Institute of Health (NIH) dedicated the large strategic Common Fund to study these new entities of extracellular RNA. The goal of this effort is to better understand how exosomes can be utilized for biomarkers and therapeutics as well as understanding this new mechanism of intercellular communication(NIH, 2017).

Mutation detection and RNA profiling
Analysis of nucleic acids present in bodily fluids can provide a better understanding of the disease, as summarized in Table below.
Comparison of the analysis capability of CTC's, cfDNA and exosomes from: (Brock et al., 2015)

Analysis capability	**Examples**	**CTCs**	**cfDNA**	**Exosom**
Mutations	Point mutations, InDels, amplifications, deletions, translocations	Yes	Yes	Yes
Epigenetic modifications	Methylation patterns	Yes	Yes	Yes
RNA transcription profiles	Levels/activity of mRNA, microRNA, long non codingRNA, RNA splice variants	Yes	No	Yes
Phenotypic studies of cells from the tumor	Cell morphology, protein localization, *in vivo* studies	Yes	No	No
Inflammatory response, stromal and other systemic changes	Inflammatory RNA and protein markers	No	No	Yes
Analysis of RNA as well as DNA and protein profiles from tumor cells	Separate or in combination	Yes	No	Yes
Can utilize bio-banked samples	Frozen plasma, urine and other bio-fluids	No	Yes	Yes

CTCs, circulating tumor cells; cfDNA, cell free DNA; InDels, insertions/deletions.

RNA profiling from biofluids also poses numerous challenges. However, the discovery that exosomes contained RNA made it possible to separate the fragile RNA from the large amounts of RNases and PCR inhibitors that are present in most biofluids. As cell-free RNA in blood is immediately degraded, RNAs in serum and plasma are either protected inside vesicles like an exosome, in protein complexes with the Ago2 protein or associated with HDL particles.

Most of the early studies were limited to the more abundant short (~22 nt) regulatory microRNAs. The levels of these microRNAs are tightly regulated in normal cells and dysregulation has been implicated in a number of human diseases e.g., cardiovascular (Thum & Condorelli, 2015), neurological and is strongly linked to cancer development and progression as reviewed by Croce. However, although robust and readily detectable, microRNAs represent only a minor fraction of the transcriptome. By contrast, if the appropriate methods are used, the nucleic acids in exosomes can be isolated and the entire transcriptome interrogated

A recent research led by Philip Mack, director of molecular pharmacology, University of California, Davis, Comprehensive cancer center studied more than 1500 patients with 50 different tumor types concluded that liquid biopsy can accurately detect mutations in cancer DNA (HealthDay, 2016). In the study, the researchers used a new genetic scan called Guardant360 that analyzes cancer DNA in patients' blood, looking for mutations in 70 different cancer-related genes.

Dr. Mack while presenting at ASCO annual meeting in Chicago (June 2016) said, “If we saw a mutation in the plasma that meant it was in the tumor”. Dr. Joshua Brody, director of the Lymphoma Immunotherapy Program at Mount Sinai's Tisch Cancer Institute in New York City, called the research "a big deal. This will be practice-changing. This is not quite a Star Trek medical magic wand, but it's getting towards there". However, ASCO Chief Medical Officer Dr. Richard Schilsky noted the study results are encouraging, provides important evidence on the road to proving the clinical utility of liquid biopsies, but do not prove that using a liquid biopsy will result in better patient outcomes.”

It is to be noted that the study received funding from Guardant Health Inc., which produces the test Guardant360 used in the study (Thompson, 2016) and (Baldwin, 2016).

On January 10, 2016, Illumina, Inc. (NASDAQ:ILMN) announced GRAIL, a new company formed to enable cancer screening from a simple blood test. Powered by Illumina sequencing technology, GRAIL will develop a pan-cancer screening test by directly measuring circulating nucleic acids in blood. "We hope today is a turning point in the war on cancer," said Jay Flatley, Illumina's chief executive and chairman of Grail. "By enabling the early detection of cancer in asymptomatic individuals through a simple blood screen, we aim to massively decrease cancer mortality by detecting the disease at a curable stage (BuisnessWire, 2016)."

And while tumors are known to drop bits of genetic material into the blood, cancer experts caution that some early cancers may not secrete DNA fragments and require other types of detection.

The most obvious hurdle for all forms of liquid biopsy remains the relative rarity of nucleic acid derived from a tumor against the background of normal material found in most patient samples. In fact, the majority of cell, cell free nucleic acids, microRNAs and exosomes in a liquid biopsy will have originated from normal cells with numbers fluctuating as a consequence of biological variations.

State and Federal Regulations, as applicable

The U.S. Food and Drug Administration (FDA) approved the first liquid biopsy test as a diagnostic for non-small lung cancer (NSCLC). The test — cobas EGFR Mutation Test v2 — from Roche Diagnosticsis purported to detect epidermal growth factor receptor (EGFR) gene mutations in NSCLC patients. The test is intended as a companion diagnostic test for the cancer drug Tarceva (FDA, 2016).

Guidelines and Recommendations:

Foukakis and Bergh (2017) do not recommend evaluating for CTCs routinely for patients with early, nonmetastatic breast cancer. Although CTCs in the peripheral blood has been associated with a poor prognosis, their use to help guide patient care and monitoring in patients with newly diagnosed breast cancer is unclear.

Bidard et al (2016) reviewed the use of CTC in breast cancer patients. The authors concluded that CTC detection proved to be a significant prognostic factor in both early and metastatic breast cancer, but further research is required to establish clinical utility of testing. Adamczyk et al (Adamczyk et al., 2015) conducted a review of methods for CTC detection, progress in non-CNS tumors and the potential value of CTC in CNS tumors. The authors concluded that liquid biopsies have significant clinical potential in CNS malignancies and requires urgent further research.

Ignatiadis and Dawson (2014) reviewed the use of circulating tumor DNA (ctDNA) and CTCs as complementary tools to improve the outcome of patients with cancer. The authors stated that liquid biopsies hold great promise as biomarkers in cancer management. However, future research should focus on establishing the clinical utility of ctDNA and CTC testing through appropriately designed prospective clinical trials

Seeberg et al (2015) conducted a prospective study to assess the prognostic and predictive value of CTCs in 194 patients with colorectal liver metastasis referred to surgery. Patients with two or more CTCs experienced reduced time to relapse/progression. Two or more CTCs was a strong predictor of progression and mortality in all subgroups of patients. The authors concluded that "CTCs predict nonresectability and impaired survival. CTC analysis should be considered as a tool for decision-making before liver resection in these patients."

Ma et al (2014) conducted a systematic review and meta-analysis of published literature evaluating the correlation between CTCs or DTCs counts in patients with prostate cancer and patient survival. Thirty-three studies (27 on CTCs 6 on DTCs) met the inclusion criteria. The authors concluded that CTCs had strong prognostic value and were promising biomarkers that should be used for managing patients with prostate cancer.

Groot et al (2013) performed systematic review and meta-analysis to investigate the prognostic value of CTCs in patients with resectable colorectal liver metastases or widespread metastatic colorectal cancer (CRC). The results of 12 studies representing 1,329 patients were suitable for pooled analysis. The overall survival and progression-free survival were worse in patients with CTCs. The authors concluded that "the detection of CTCs in peripheral blood of patients with resectable colorectal liver metastases or widespread metastatic CRC is associated with disease progression and poor survival."

Zhang et al (2012) conducted a meta-analysis of published literature on the prognostic value of CTC in breast cancer. Forty-nine eligible studies enrolling 6,825 patients were identified. The presence of CTC was significantly associated with shorter survival in the total population. The prognostic value of CTC was significant in both early and metastatic breast cancer. The authors concluded that "the detection of CTC is a stable prognosticator in patients with early-stage and metastatic breast cancer. Further studies are required to explore the clinical utility of CTC in breast cancer."

Per Sequist and Neal (2017), liquid biopsies are becoming more popular as they provide an opportunity to genotype in a less invasive and expensive manner. However, the low sensitivity (sensitivity ranges between 60-80%) and higher number of false negative cases compared to traditional tissue biopsy are limitations associated with liquid biopsies (Sequist & Neal, 2017).

In 2016 Oxnard et all found that: "Sensitivity of plasma genotyping for detection of T790M was 70%. Of 58 patients with T790M-negative tumors, T790M was detected in plasma of 18 (31%). ORR and median PFS were similar in patients with T790M-positive plasma (ORR, 63%; PFS, 9.7 months) or T790M-positive tumor (ORR, 62%; PFS, 9.7 months) results. Although patients with T790M-negative plasma had overall favorable outcomes (ORR, 46%; median PFS, 8.2 months), tumor genotyping distinguished a subset of patients positive for T790M who had better outcomes (ORR, 69%; PFS, 16.5 months) as well as a subset of patients negative

for T790M with poor outcomes (ORR, 25%; PFS, 2.8 months)"(Oxnard et al., 2016). The authors concluded that "upon availability of validated plasma T790M assays, some patients could avoid a tumor biopsy for T790M genotyping."

In 2017, Sacher et al found that: Plasma genotyping of cell-free DNA detected EGFR and KRAS mutations rapidly with the high specificity needed to select therapy and avoid repeat biopsies. This assay may also detect EGFR T790M missed by tissue genotyping due to tumor heterogeneity in resistant disease (Sacher et al., 2016).

FDA approval of use of the cobas EGFR Mutation Test in plasma was based evaluation of plasma samples from the ENSURE study (Wu et al., 2015), a multicenter, open-label, randomised, Phase III study of stage IIIB/IV NSCLC patients. Of the patients enrolled, 98.6% (214/217) had a plasma sample available for testing. The agreement between the cobas EGFR Mutation Test in plasma and tissue was evaluated for detection of EGFR mutations. In 76.7% of tissue-positive specimens, plasma was also positive for an EGFR mutation. Plasma was negative for EGFR mutation in 98.2% (95.4%, 99.3%) of tissue-negative cases. The patients whose plasma results were positive for exon 19 deletion and/or an L858R mutations treated with erlotinib had improved progression-free survival (PFS) compared to those treated with chemotherapy(FDA, 2016).

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

2017 NCCN guidelines for non-small cell lung cancer (NCCN, 2017d) strongly advises "broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC". Furthermore that "Recent data suggest that plasma genotyping (also known as liquid biopsy or plasma biopsy) may be considered instead of tissue biopsy; however, if the plasma biopsy is negative, then tissue biopsy is recommended if feasible (Oxnard et al., 2016; Sacher et al., 2016)".

In 2017, the NCCN stated that "the clinical use of Circulating Tumor Cells (CTC) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer (NCCN, 2017b)for disease assessment and monitoring." The NCCN guidelines further stated that "in spite of prognostic ability, CTC has failed to show a predictive value."

In 2017, the NCCN found that although the presence of androgen receptor splice variant 7 (AR-V7) in CTCs is associated with abiraterone and enzalutamide resistance, it has not been validated and has a low prevalence (3%) in patients before treatment with abiraterone, enzalutamide, and taxanes. The NCCN panel believes that at this time testing for AR-V7 CTCs would not be useful to inform treatment decisions in prostate cancer(NCCN, 2017c).

NCCN guidelines for colon cancer and small cell lung cancer do not address use of circulating tumor cells or circulating tumor DNA for patient management(NCCN, 2017a).

American Society of Clinical Oncology (ASCO)

In 2007, ASCO published recommendations for the use of tumor markers in the prevention, screening, treatment, and surveillance of breast cancer (Harris et al., 2007). ASCO stated that circulating tumor markers has demonstrated insufficient evidence to support routine use in clinical practice.

In 2016, ASCO published updated recommendations for the use of tumor markers in treatment ofmetastatic breast cancer (Poznak et al., 2016). ASCO found that although CTCs may be prognostic, they are not predictive for clinical benefit when used to guide or influence decisions on systemic therapy for metastatic breast cancer. ASCO recommends clinicians to not use these markers as adjunctive assessments.

National Academy of Clinical Biochemistry (NACB)

In 2008, the NACB issued practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast and ovarian cancers (Sturgeon et al., 2008). The NACB panel's recommendation on measurement of circulating prostate cancer cells in peripheral blood stated that "although initial results are encouraging, these techniques are not yet sufficiently validated to warrant recommending their application in routine clinical practice."

In 2010, the NACB issued practice guidelines for the use of tumor markers in liver, bladder, cervical, and gastric cancers. It found that CTC's were of only questionable clinical utility in the assessment of liver cancer and did not recommend their use (Sturgeon et al., 2010).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81235, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 5/2019

Medical Director review 7/2019

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for detection of circulating tumor cells and cell free DNA in cancer management when it is determined to be medically necessary and

criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

6/11/19 Reviewed by Avalon 1st Quarter 2019 CAB. Added CPT 81479 to Billing/Coding section. Deleted CPT codes 86152 and 86153 from Billing/Coding section. No change to policy statement. Medical Director review 5/2019. (lpr)

7/30/19 Under "When Covered" section: removed item B. "Testing is performed using the Cobas EGFR Mutation Test, Guardant360 test, or OncoBEAM test." Medical Director review 7/2019. (lpr)

11/12/19 Deleted coding table from Billing/Coding section. Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. Minor reformatting of policy statements; no change to policy statement intent. (hb)