MEDICAL POLICY – 12.04.141
Circulating Tumor DNA and Circulating Tumor Cells for Cancer Diagnosis and Management (Liquid Biopsy)

Effective Date: Oct. 1, 2016
Last Revised: Jan. 1, 2017
Replaces: 2.04.37

RELATED MEDICAL POLICIES:
None

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Introduction

Liquid biopsy is a when a blood sample (rather than a piece of tissue) is used to test for cancer cells or small genetic cancer pieces mixing in the blood. The blood sample is taken from the arm and is tested for cells or genetic pieces that cancers shed into the bloodstream. Identifying tumor cell material in the blood might help to diagnose cancer, track changes in a cancer over time or help select the right type of cancer treatment. However, there is not enough information from clinical studies to be certain that this works as well as a tissue biopsy in most people, because we don’t yet know that this works as well as tissue biopsy. This treatment is not yet proven.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Procedure Coverage Criteria

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### Coding

#### CPT

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<td>81479</td>
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<tr>
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<td>Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood);</td>
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<td>86153</td>
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### Related Information

N/A
### Evidence Review

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### Background

Liquid biopsy refers to analysis of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) as a method of noninvasively characterizing tumors and tumor genome from the peripheral blood.

### Circulating Tumor DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). cfDNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs. Unlike apoptosis, necrosis is considered a pathologic process, and generates larger DNA fragments due to an incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. ctDNA can be used for genomic characterization of the tumor.
Circulating Tumor Cells

Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for detecting CTCs is prognostic, through quantification of circulating levels.

Technologies for Detecting ctDNA and CTCs

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed. Highly sensitive and specific methods have been developed to detect ctDNA, for both single-nucleotide mutations (e.g. BEAMing [which combines emulsion polymerase chain reaction [PCR] with magnetic beads and flow cytometry] and digital PCR) and copy-number changes. Digital genomic technologies allow for enumeration of rare mutant variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions (e.g., EGFR and ALK in non-small-cell lung cancer), or untargeted without knowledge of specific mutations present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either on the basis of biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.

Section Summary: Background

Circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) in peripheral blood, referred to as “liquid biopsy,” potentially offer a noninvasive alternative to tissue biopsy for therapeutic decisions and clinical prognosis in patients with cancer.
For individuals who have cancer who receive molecular characterization of tumor using ctDNA, the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study population have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer or are at high risk of developing cancer who receive identification and quantification of CTCs, the evidence includes case series and meta-analyses of these case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and test validity. Published data on analytic validity are lacking. Most of the literature consists of reports of levels of CTCs and cancer prognosis, and have shown a correlation with survival in certain cancer types. However, the cutoff levels that should be used to signal a change in patient management are unknown, and there are no studies showing clinical utility and improved patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Rationale

This medical policy was created in May 2016 with a literature search of the MEDLINE database from January 1, 2011, to March 10, 2016.

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).
**Analytic Validity**

There are a variety of methods used to analyze circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), most marginally validated. More assay validation studies are needed to standardize reproducibility before methodology protocols can be put into clinical use.

Newman et al reported on an ultrasensitive method for quantitating ctDNA, CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) for non-small-cell lung cancer (NSCLC).\(^2\) Circulating tumor DNA was detected in 100% of patients with advanced stage disease and 50% of stage 1 disease, with 96% specificity for mutant allele fractions.

Bettegowda et al reported on the use of digital polymerase chain reaction (PCR) and Safe-Sequencing System (Safe-SeqS) method in a set of cancer patients with different tumor types and disease stages.\(^3\) The diagnostic sensitivity of ctDNA for the detection of clinically relevant KRAS mutations was 87.2%, with a specificity of 99.

**Clinical Validity**

**Circulating Tumor DNA**

Most of the literature on the use of ctDNA consists of studies that compare the results of mutations in ctDNA to tumor tissue biopsy, primarily to guide therapy with targeted agents so that an invasive biopsy or rebiopsy of tumor tissue can be avoided (see Other ctDNA Tests for discussion of screening/diagnostic tests).

Below are representative studies that explore the concordance between mutations found in primary tumors or metastases and those identified using ctDNA. Also included are studies using CTCs for mutation analysis.

**Lung Cancer**

Mao et al conducted a systematic review and meta-analysis to assess whether blood could be used as a substitute for tumor tissue to detect epidermal growth factor receptor (EGFR) mutations for guiding treatment with tyrosine kinase inhibitors (TKIs) in NSCLC.\(^4\) The review included 25 studies (total N=2605 patients). Nineteen studies were carried out mainly with Asian patients and 6 with white patients. Stage of disease varied across studies, with some patients having early-stage disease and others having advanced stage. There was also heterogeneity.
across studies involving the blood tests (whether performed on plasma or serum), which can affect sensitivity and specificity by source used. Pooled overall sensitivity, specificity and concordance rate were 0.61, 0.90, and 0.79, respectively. There were no major differences in a subgroup analysis for mutations in exons 19 and 21 compared with mutations of all exons. EGFR mutations detected in blood were significantly associated with objective response to TKI therapy (risk ratio, 4.08; 95% confidence interval [CI], 2.48 to 6.70), progression-free survival (PFS; hazard ratio [HR], 0.72; 95% CI, 0.64 to 0.80) and overall survival (OS; HR=0.71; 95% CI 0.50 to 0.99). The correlations between mutations for the 3 outcomes for serum were similar to those for tumor tissue and higher than those for plasma.

Qiu et al conducted a meta-analysis on the effectiveness of detecting EGFR mutations in NSCLC with ctDNA.\textsuperscript{5} A literature search conducted through September 2014 identified 27 eligible studies, which included 3110 patients with NSCLC who had been diagnosed histopathologically or cytologically, and had EGFR mutation status detected by ctDNA and tumor tissue. Most studies were conducted in Asia and most patients had advanced stage disease. Only 6 studies reported the exact collection time point of the tumor tissues and blood sample. Pooled sensitivity, specificity, and diagnostic odds ratio were 0.62 (95% CI, 0.51 to 0.72), 0.96 (95% CI, 0.93 to 0.98) and 38.3 (95% CI, 21.09 to 69.44), respectively. Overall diagnostic performance, measured by summary receiver operating characteristic curve was 0.91 (95% CI, 0.89 to 0.94).

Sacher et al prospectively validated plasma droplet digital polymerase chain reaction (ddPCR) for the rapid detection of common EGFR and KRAS mutations, and the EGFR T790M acquired resistance mutation.\textsuperscript{6} The study included patients with advanced nonsquamous NSCLC who either had a new diagnosis and a plan for initial therapy, or had developed acquired resistance to an EGFR kinase inhibitor and were planned for rebiopsy of the tumor using molecular analysis. Patients underwent initial blood sampling and immediate plasma ddPCR for EGFR exon 19 deletion, EGFR L858R, T790M, and/or KRAS G12X between July 2014 and June 2015, at a National Cancer Institute–designated comprehensive cancer center. Tissue genotyping from a biopsy specimen was used as the reference standard for comparison of the plasma results. Rebiopsy was required for patients with acquired resistance to EGFR kinase inhibitors. The main outcomes were plasma ddPCR assay sensitivity and specificity. There were 180 patients, 62% female (median age, 62 years; range 37-93 years), with 120 cases being newly diagnosed and 60 had acquired resistance. Tumor genotyping included 80 EGFR exon 19/L858R mutations, 35 EGFR T790M, and 25 KRAS G12X mutations. Plasma ddPCR exhibited a positive predictive value (PPV) of 100% (95% CI, 91% to 100%) for the EGFR 19 deletion, 100% (95% CI, 85% to 100%) for EGFR L858R, and 100% (95% CI, 79% to 100%) for KRAS. The PPV for EGFR T790M was lower, at 79% (95% CI, 62% to 91%). The sensitivity of plasma ddPCR was 82% (95% CI, 69% to 91%) for the EGFR 19 deletion, 74% (95% CI, 55% to 88%) for EGFR L858R, and 77% (95% CI, 60% to 90%) for EGFR T790M; and lower at 64% (95% CI, 43% to 82%) for KRAS.
Pailler et al evaluated whether ALK rearrangements in patients with NSCLC could be diagnosed using CTCs. The study included 32 patients with metastatic NSCLC, 18 of whom were ALK-positive and 14 ALK-negative. The 18 ALK-positive patients were tested for an ALK rearrangement using the Food and Drug Administration (FDA)–approved Vysis ALK Break Apart FISH Probe Kit in the tumor biopsies of primary tumors (8 patients) or metastases (10 patients). Peripheral blood samples were collected from all patients and an optional second sample was collected from patients undergoing crizotinib treatment (at day 30, 45, or 90). ALK rearrangements were determined in CTCs and compared with those present in tumor biopsies. ALK-rearranged CTCs were monitored in 5 patients treated with crizotinib. All ALK-positive patients had 4 or more ALK-rearranged CTCs per 1 mL of blood (median, 9 CTCs per 1 mL; range, 4–34 CTCs per 1 mL), whereas no or only 1 ALK-rearranged CTC (median, 1 per 1 mL; range, 0–1 per 1 mL) was detected in ALK-negative patients.

Pailler et al also evaluated whether ROS1-chromosomal rearrangements could be detected in CTCs in a small group of patients with NSCLC, and addressed tumor heterogeneity of CTCs and tumor biopsies in ROS1-rearranged NSCLC patients. ROS1 rearrangement was examined in CTCs from 4 ROS1-rearranged patients treated with crizotinib, and 4 ROS1-negative patients. ROS1-gene alterations were observed in CTCs at baseline from ROS1-rearranged patients and compared with those present in tumor biopsies and in CTCs during crizotinib treatment. ROS1 rearrangement was detected in the CTCs of all 4 patients with ROS1 rearrangement previously detected by tumor biopsy. Tumor heterogeneity, assessed by ROS1 copy number, was significantly higher in baseline CTCs than in paired tumor biopsies in the 3 patients experiencing partial response or stable disease (p<0.001).

Colon Cancer

Lyberopoulou et al compared mutational status using CTCs to the primary tumor in 52 patients with colorectal cancer (CRC). The mutations studied included KRAS and BRAF from patients predominantly with advanced stage disease (stage III [n= 24] or IV [n=22]). The discordance between mutation and wild-type status for primary tumor and CTCs was 5.8% for KRAS and 3.8% for BRAF.

Tabernero et al retrospectively analyzed the clinical activity of regorafenib in biomarker subgroups of the CORRECT trial population, defined by tumor mutational status or plasma protein levels. Regorafenib is a multikinase inhibitor that has been shown to provide significant benefits in OS and PFS in patients with previously treated metastatic CRC. The CORRECT trial was an international, multicenter, randomized, placebo-controlled phase 3 study in patients with documented metastatic adenocarcinoma of the colon or rectum who had received all approved standard therapies, with disease progression during or within 3 months after the last
administration of the last standard therapy. A total of 760 patients were randomly assigned 2:1 to oral regorafenib or placebo, and treated until disease progression, death, unacceptable toxic effects, or a decision by patient or by physician. Comparison to matched archival tumor samples and fresh plasma showed concordant mutation status in 161 (76%) of 211 patients for KRAS, 183 (88%) of 207 patients for PIK3CA, and 230 (97%) of 236 patients for BRAF.

Other Cancers

Other reports include reviews of the literature on the use of liquid biopsies in liver (hepatocellular carcinoma)\(^ {11}\), melanoma\(^ {12}\), pancreatic cancer\(^ {13}\), and head and neck cancers\(^ {14}\). These studies are small and present preliminary results on the potential use of liquid biopsy in these tumor types.

Clinical Validity of CTCs

Most of the literature on the use of CTCs consists of studies that correlate the quantification of CTCs with survival. Studies on the validation of the use of CTCs for diagnosis or screening are limited. Below are studies that correlate survival and risk of disease progression with quantification of CTCs.

Metastatic Breast Cancer

In 2012, Zhang et al published a comprehensive meta-analysis of studies on the association between CTCs and health outcomes in patients with breast cancer.\(^ {15}\) The analysis included studies of more than 30 patients; used reverse transcriptase-polymerase chain reaction (RT-PCR), CellSearch, or another immunofluorescent technique to detect CTCs; and reported survival data stratified by CTC status. A total of 49 studies met eligibility criteria. In a pooled analysis of 12 studies on metastatic breast cancer, positive CTC results were associated with a significantly increased risk of disease progression (HR=1.78; 95% CI, 1.52 to 2.09). Positive CTC results were associated with a significantly increased risk of death in patients with metastatic breast cancer (HR=2.23; 95% CI, 2.09 to 2.60; 19 studies). The authors presented a subgroup analysis using detection method; this analysis included studies on nonmetastatic and metastatic breast cancers. Pooled analyses using CellSearch found that positive CTC results significantly increased the likelihood of disease progression (HR=1.85; 95% CI, 1.53 to 2.25; 12 studies) and death (HR=2.45; 95% CI, 2.10 to 2.85; 18 studies). Studies using RT-PCR also found that positive CTC results were significantly associated with disease progression and death.
A 2011 meta-analysis by Zhao et al considered only studies on CTC detected by RT-PCR.\textsuperscript{16} A total of 24 studies met inclusion criteria, 5 of which included metastatic breast cancer. The authors did not separately analyze studies on metastatic breast cancer. In a pooled analysis of data from 15 studies (n=2894 patients), the presence of CTCs was significantly associated with a lower OS (HR=3.00; 95% CI, 2.29 to 3.94) and a lower relapse-free survival (RFS; HR=2.67; 95% CI, 2.09 to 3.42). The authors noted substantial heterogeneity among studies, including differences in sampling time, detection methods, and demographic or clinical characteristics of the study population.

Representative prospective studies using CellSearch immunofluorescent technology for identifying CTC in women with metastatic breast cancer are described next.

In 2004, Cristofanilli et al published a multicenter study that included 177 patients with measurable metastatic breast cancer who were followed for 38.7 weeks or longer.\textsuperscript{17} Using the CellSearch System, investigators measured the number of circulating tumor cells before initiating a new line of therapy and at first follow-up (mean [SD], 4.5 [2.4] weeks after baseline sample). Also tested were 145 normal subjects and 200 patients with benign breast diseases. The authors detected 2 or fewer epithelial cells per 7.5 mL of blood in all normal subjects and patients with benign breast diseases. Using a statistically validated threshold of 5 cells per 7.5 mL of blood, they found that patients below threshold at baseline (n=90 [51%]) had longer median (7.0 months vs 2.7 months, respectively; p<0.001) and OS (18 months vs 10.1 months, respectively; p<0.001) than those above threshold (n=87 [49%]). Survival duration of a subgroup (n=33) with values above threshold at baseline but below threshold at first follow-up (i.e., after the first cycle of therapy) was similar to that for patients below threshold at baseline. This subgroup’s median survival also was significantly longer than survival of those who remained above threshold despite therapy. Multivariate analysis showed that being below threshold for level of CTCs was the most statistically significant independent predictor of longer PFS and OS of all parameters studied, including hormone receptor status, HER2/neu status, and site of metastases.

Nole et al (2008) tested 80 patients with metastatic breast cancer for CTC levels before starting a new treatment, after 4 and 8 weeks and every 2 months thereafter.\textsuperscript{18} Forty-nine patients had 5 or more cells at baseline. In multivariate analysis, baseline number of CTCs was associated with PFS (HR=2.5; 95% CI, 1.2 to 5.4). The risk of progression for patients with 5 or more circulating tumor cells at the last available follow-up was 5 times the risk of patients with 0 to 4 CTCs at the same point (HR=5.3; 95% CI, 2.8 to 10.4). Patients with rising or persistent counts of 5 or more CTCs at last available follow-up showed a statistically higher risk of progression than patients who had fewer than 5 CTCs at both times of blood sampling.

In 2012, Pierga et al in France reported on a prospective series of 267 patients with metastatic breast cancer who were starting first-line chemotherapy.\textsuperscript{19} CTCs were analyzed before starting
treatment, before the second cycle of treatment, and at the first radiologic evaluation before the third or fourth cycle of treatment. At baseline, 44% of patients were positive for CTC (>5 CTC per 7.5 mL blood). Patients were followed for a median of 14.9 months. During follow-up, there were 57 (21%) deaths, and 161 (60%) experienced tumor progression. Baseline CTC count was a strong predictor of PFS (p<0.001). Median PFS was 19.9 months in patients with 0 CTCs and 8.2 months in patients with more than 5 CTCs per 7.5 mL blood. Baseline CTC was also significantly associated with OS (p<0.001). In multivariate analysis, baseline CTC positivity was an independent prognostic factor for both PFS and OS.

**Metastatic Prostate Cancer**

A 2014 systematic review and meta-analysis by Ma et al examined studies on the relation between CTCs and disseminated tumor cells (DTCs) on the prognosis of prostate cancer (localized and metastatic). To be included in the review, studies had to report the correlation of CTCs or DTCs with 1 or more survival outcomes. The authors assessed 54 studies for eligibility. Thirty-three studies (27 on CTCs 6 on DTCs) met the inclusion criteria. A pooled analysis of all studies found significantly lower OS in patients with circulating tumor cells (HR=2.43; 95% CI, 2.07 to 2.86). Eight studies (total N=946 patients) used CellSearch technology to detect CTCs. A pooled analysis limited to these studies also found a significant association between CTCs and OS (HR=2.36; 95% CI, 1.95 to 2.85).

Previously, in 2011, Wang et al published a meta-analysis of studies on the association between CTCs and prognosis in patients with metastatic castration-resistant or hormone-refractory prostate cancer. The authors searched the literature for studies with at least 30 patients and sufficient data to calculate relative risk (RR) of OS. The authors identified 19 relevant articles, 4 of which met study inclusion criteria (total N=486 patients). All studies used the CellSearch System to detect CTCs. In with those with higher levels (>5 CTC in 7.5 mL blood; RR=2.51; 95% CI, 1.96 to 3.21). In a sensitivity analysis removing the study with the largest sample size (de Bono et al), the RR was marginally higher (RR=3.25; 95% CI, 2.01 to 5.24). The test for study heterogeneity was not statistically significant.

The study by de Bono et al (2008) was prospective and included patients with castration-resistant progressive prostate cancer who were initiating a new cytotoxic therapy. CTC levels were measured using the CellSearch System at baseline and before each course of therapy until disease progression or up to 18 months. A total of 276 patients were enrolled; of these, 33 were subsequently found to not meet eligibility criteria (e.g., did not have an evaluable baseline blood sample or scan or lacked progressive disease) and 2 patients withdrew consent, leaving 231 patients in the analysis. At baseline, 219 patients were evaluable for CTCs; of these, 125 had elevated levels (≥5 cells per 7.5 mL of blood) and 94 did not (<5 cells per mL). The primary study
outcome was the association between elevated CTCs 2 to 5 weeks after initiating treatment and OS. An evaluable CTC level was available for 203 patients at the 2- to 5-week follow-up, and CTCs were elevated in 39 (19%). The group of patients with elevated CTCs after initiating treatment had a significantly shorter median survival time (9.5 months) than those without elevated CTC (20.7 months; p<0.001). Moreover, patients with elevated CTCs at all time points (n=71) had the shortest median OS (6.8 months). OS in this group was significantly shorter compared with other groups, specifically the group of patients with elevated baseline CTCs who converted to a nonelevated level after treatment (n=45; median OS=21.3 months) and the group of patients with nonelevated CTCs throughout the study (n=88; median OS, >26 months). Only 26 patients had nonelevated CTCs at baseline and elevated CTCs after treatment; this group had a mean OS of 9.3 months. A limitation of the study was that only 203 (74%) of the 276 enrolled patients were included in the primary analysis.

**Metastatic CRC**

In 2015, Huang et al published a meta-analysis of studies on the association between CTCs detected with the CellSearch System and CRC prognosis. Eleven studies with a total of 1847 patients met eligibility criteria. Pooled data analyses found that detection of CTCs in patients with CRC was associated with a significantly worse OS (HR for death, 2.00; 95% CI, 1.49 to 2.69; 9 studies) and PFS (HR for progression or death, 1.80; 95% CI, 1.52 to 2.13; 8 studies). In addition, a pooled analysis of 3 studies found that the response to adjuvant chemotherapy was significantly lower in patients with detectable CTCs than those without CTCs (risk ratio, 0.79; 95% CI, 0.63 to 0.99).

Previously, a 2013 meta-analysis by Groot Koerkamp et al reviewed studies on the prognostic value of CTCs and on the detection of DTCs in bone marrow. To be selected, studies had to include at least 20 patients with metastatic CRC and report long-term outcomes. Sixteen eligible studies were included, and 12 had data suitable for meta-analysis. Most studies included detection of CTCs; only 4 included detection of DTCs. Pooled analyses found that detection of CTCs or DTCs in patients with metastatic CRC was associated with a worse OS (HR for death, 2.47; 95% CI, 1.74 to 3.51; 11 studies) and a worse PFS (HR for progression or death, 2.07; 95% CI, 1.44 to 2.98; 9 studies).

**CTC Cutoffs for CRC**

Studies have used different cutoffs of CTCs. CellSearch materials recommend using a cutoff of at least 3 CTCs in CRC. That cutoff used in the 2008 multicenter industry-sponsored study by Cohen et al. Eligible participants needed to be initiating any first- or second-line systemic...
therapy, or third-line therapy with an EGFR inhibitor. CTC were assessed at baseline and at regular intervals after starting treatment. In a preplanned interim analysis, the authors determined that at least 3 CTCs per 7.5 mL blood was the optimal cutoff to indicate elevated CTC level. The primary outcome was the agreement between CTC level at the 3- to 5-week follow-up and response to therapy. Agreement was defined as either a nonelevated level of CTC corresponding to lack of disease progression or an elevated level corresponding to progressive disease. A total of 481 patients were enrolled; 430 were evaluable patients, 320 of whom were assessable for the primary outcome. Thirty-eight (12%) of 320 patients had elevated levels of CTCs 3 to 5 weeks after starting treatment. By the end of the study, 20 (53%) of these 38 patients had progressive disease or died before receiving a follow-up imaging study. By comparison, 54 (19%) of the 282 patients without elevated CTCs at the 3- to 5-week follow-up had progressive disease or had died (p value not reported). OS and PFS were reported as secondary outcomes. Patients with elevated baseline CTC levels (≥3 per 7.5 mL blood) had shorter mean PFS and OS than patients with nonelevated baseline CTCs (<3 per 7.5 mL blood). Median PFS was 4.5 months and 7.9 months, respectively (p<0.001), and median OS was 9.4 months and 18.5 months, respectively (p<0.001). A study limitation is that only 320 (67%) of 481 enrolled patients were included in the primary analysis.

More recent studies have used other cutoffs. For example, a 2014 prospective study by Seeberg et al used a cutoff of 2 or more CTCs per 7.5 mL blood. The study included 194 patients with colorectal liver metastases. The presence of more than 2 CTCs was associated with significantly shorter survival time in the whole group of patients (p<0.001) and in patients with resectable disease (p=0.037) compared with patients with fewer than 2 CTCs. Moreover, the presence of 2 or more CTCs was associated with significantly shorter RFS in the total patient population (p=0.002) and in resectable patients (p<0.001). A 2015 prospective study by Bork et al used a cutoff of at least 1 cell per 7.5 mL blood. The study included 287 patients with potentially curable CRC. CTC detection was significantly associated with worse OS in the entire cohort (48.4 months for CTC-positive patients vs 33.6 months for CTC-negative patients, p<0.001). Additional prospective studies are needed to confirm the prognostic value of the 1 or 2 cells per 7.5 mL blood cutoff.

Other Cancer Conditions

Studies have evaluated CTC levels as a diagnostic and/or prognostic marker for patients with other types of cancer. There are no FDA-cleared tests for these indications, and none of the studies evaluated patient management decisions using CTC levels. Conditions studied include lung, bladder, pancreatic, gastric, hepatocellular, and head and neck cancers, as well as melanoma. A meta-analysis of lung cancer predominantly included studies using the CellSearch System. This analysis was published in 2014 by Zhang et al. The authors identified 7
studies with 440 small-cell lung cancer patients. All studies were prospective, and 5 used the CellSearch system. Meta-analyses found that higher baseline CTC level was associated with a lower OS (HR for death, 1.90; 95% CI, 1.19 to 3.04) and lower PFS (HR for progression or death, 2.60; 95% CI, 1.90 to 3.54). Data from all 7 studies were included in the OS analysis; only 3 studies contributed data to the PFS analysis.

An additional proposed use of CTCs is for real-time monitoring during systemic therapy. A study that addresses is that by Smerage et al, which reported the results of a randomized controlled trial of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve OS (the study primary outcome).^4^ Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomly assigned to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomly assigned to arm C1 or C2. There was no difference in median OS between arms C1 and C2 (10.7 months and 12.5 months, respectively; p=0.98). CTC levels were strongly prognostic, with a median OS for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively (p<0.001). This study showed the prognostic significance of CTCs in patients with metastatic breast cancer receiving first-line chemotherapy, but also that there was no effect on OS if patients with persistently increased CTC levels after 21 days of first-line chemotherapy were switched to an alternative cytotoxic therapy.

Other ctDNA Screening/Diagnostic Tests

Colorectal Cancer

- SEPT9 Methylated DNA
  - (ColoVantage, Various Manufacturers)
  - Epi proColon, Epigenomics, Berlin)

There is a fairly large literature on the association of SEPT9 methylation with colon cancer in general. In case–control studies involving more than 3000 patients, overall sensitivity of SEPT9 DNA methylation screening was 60% to 70% and specificity was 89%.^45^-46, 54^-56 Modifications to ColoVantage methodology increased sensitivity to 90% with little decrement to specificity. ^45^-46 A systematic review published in 2016 reviewed 39 studies of the diagnostic performance of SEPT9
methylation for detecting colon cancer. The combined sensitivity was 62% (95% CI 56-67%) and the combined specificity was 91% (89-93%). There was no significant impact on the accuracy of testing according to target gene number, tumor stage, geographical region, or method of analysis.

Only one test has received FDA approval, the Epi proColon test, which was approved in 2016 for use in average risk patients who decline other screening methods. There is a smaller number of studies that specifically evaluate the performance of the commercially available epi proColon test. A case-control study that compared Epi proColon® with fecal immunochemical testing (FIT) for CRC screening enrolled 102 patients with CRC and 199 patients who presented for screening. Colonoscopy was the reference standard. Sensitivity and specificity were 73% and 82% for Epi proColon®, respectively, and 68% and 97%, respectively, for FIT. In 290 paired samples, sensitivity of the 2 tests was similar (=70%), but specificity of Epi proColon® was lower (81% vs 97%). Similar results were observed in a subsequent retrospective case-control study that used a second-generation version of the test.

In 2014, Church et al reported an international prospective screening study of Epi proColon®, called PRESEPT. Patients 50 years of age or older with average risk of CRC who were scheduled for colonoscopy were enrolled (N=7941). Of these, 1516 (19%) were selected for laboratory analysis in stratified random sampling; colonoscopy identified 53 (3%) patients with invasive adenocarcinoma, 315 (21%) with advanced adenoma, 210 (14%) with nonadvanced adenoma, and 938 (62%) with no evidence of disease. Overall sensitivity, specificity, PPV, and NPV for Epi proColon® detection of invasive adenocarcinoma were 48%, 92%, 5%, and 100%, respectively. Sensitivity for advanced adenoma was low (11%). As observed by the study investigators, detection of only half of preclinical cancers and a small proportion of advanced adenomas limits clinical utility of the test.

Tham et al (2014) reported on a smaller prospective cohort study in Singapore (N=150). Investigators measured methylation levels of 7 genes, including SEPT9, in patients with stage I-III CRC who underwent curative resection. Blood samples were collected 1 week before and 6 months and 1 year after surgery. At median follow-up of 59 months (range, 5-79 months), 43 patients (29%) developed recurrence. Although a statistically significant association between methylated SEPT9 level at 1 year and recurrence was found, interpretation of this result is limited by lack of correction for multiple comparisons. Additionally, cutoff values for a positive test were determined by median levels rather than prespecified. ROC analysis using optimized cutoffs for SEPT9 at 1 year yielded an AUC of 0.70 (95% confidence interval [CI], 0.58 to 0.82). AUC for carcinoembryonic antigen at 1 year was similar (AUC=0.69 [95% CI, 0.57 to 0.80]).

Orntoft et al published a case-control study examining whether the prognostic information is impacted by other clinical and demographic variables. 150 cases of CRC were matched with 150 controls from a database of 4698 individuals undergoing colonoscopy for evaluations of...
CRC. The variables that were examined together with the results of the Epi proColon test were age, gender, comorbidities, tumor site, and tumor stage. The overall sensitivity of Epi proColon was 73% (95% CI 64-80%). Sensitivity varied by tumor stage. The sensitivity was 37% for stage I tumors; 91% for stage II; 77% for stage 3; and 89% for stage IV. In addition to tumor stage, age and comorbidities impacted the accuracy of testing. Elderly patients greater than 65 years old had both lower sensitivity and specificity of testing. Patients with arthritis had decreased sensitivity, while patients with CAD and diabetes had decreased specificity. Diabetes was particularly associated with a positive test, with an odds ratio of 5.2 (95% CI 1.4 to 19.1) for a positive test compared to patients without diabetes.

Evidence for clinical validity of CRC screening includes case-control studies and 2 prospective screening studies. These studies report that sensitivity of testing is in the range of 60-80% and specificity is in the range of 85-95%. Test performance characteristics were better in case-control studies, suggesting that tests intended for screening be prospectively tested in the screening setting. One study indicated that age and comorbidities were potential confounders of testing. Based on results from these studies, the clinical validity of SEPT9 methylated DNA screening is limited by low sensitivity and low PPV of the test. The sensitivity of the test is lower than imaging screening strategies. Compared to stool-based strategies, the sensitivity is in the same range and the specificity is lower.

Studies comparing survival outcomes in patients who undergo CRC screening with SEPT9 methylated DNA testing versus standard screening were not identified. Such comparative studies with clinically meaningful outcomes (survival) are necessary to demonstrate incremental improvement in net health outcome compared with current standard screening approaches (FIT, colonoscopy) and to address lead-time bias for cancers identified through screening. Because evidence for clinical validity is currently lacking, an indirect chain of evidence establishing clinical utility of SEPT9 methylated DNA cannot be established.

**Summary: SEPT9 Methylated DNA**

Studies comparing survival outcomes in patients who undergo CRC screening with SEPT9 methylated DNA testing (ColoVantage, Epi proColon) versus standard screening were not identified. Such comparative studies with clinically meaningful outcomes (survival) are necessary to demonstrate incremental improvement in net health outcomes compared with current standard screening approaches (FIT, colonoscopy) and to address lead-time bias for cancers identified through screening. Evidence on clinical validity has reported that the test has a lower sensitivity compared to other screening methods. If the test is restricted only to patients who would otherwise not be screened, outcomes will be improved. However, if the test is used as a substitute for other screening tests that have higher sensitivity, outcomes may be harmed.
ColonSentry

Marshall et al (2010) conducted a genome-wide association study in 189 whole blood samples (98 controls, 91 patients with CRC) and identified 45 differentially expressed gene biomarker candidates using microarray hybridization. Through logistic regression and bootstrapping (subsampling with replacement) in a training set of 232 samples (120 controls, 112 patients with CRC), 7 genes were selected for further development. Sensitivity, specificity, PPV, and NPV for detecting CRC were 82%, 64%, 68%, and 79%, respectively. AUC was 0.80 (95% CI, 0.74 to 0.85). In a test set of 410 samples (208 controls, 202 patients with CRC), sensitivity, specificity, PPV, and NPV were 72%, 70%, 70%, and 72%, respectively. AUC was 0.80 (95% CI, 0.76 to 0.84). The authors applied subsequent Bayesian modeling to incorporate the prevalence of CRC in the average-risk population (0.7%) and proposed relative risk categories to further stratify average-risk patients for CRC screening. Because of its cross-sectional design, follow-up of controls to determine which strata developed CRC was not reported, limiting conclusions that can be drawn about the accuracy of the test for risk prediction. In a subsequent publication, the investigators reported test performance stratified by left- versus right-sided cancers and tumor stage.

Yip et al (2010) conducted a similar cross-sectional study in 210 blood samples (111 controls, 99 CRC) from patients in Malaysia. The Malaysian population has different ethnic groups with different CRC incidences (e.g., 0.02% in Chinese Malaysians, 0.01% in ethnic Malays), and CRC in Asian populations is more likely to be nonpolypoid (i.e., flat or depressed) compared with western populations in whom the test was developed. Sensitivity and specificity for detecting CRC were 61% and 77%, respectively. AUC was 0.76 (95% CI, 0.70 to 0.82). With optimized cut points, sensitivity and specificity were 72% and 71%, respectively. As previously, the cross-sectional design of the study limits conclusions that can be drawn.

Two cross-sectional studies do not permit full characterization of the ability of ColonSentry® to predict CRC risk.

No studies examining the clinical utility of ColonSentry® were identified. Factors that support an indirect chain of evidence for predicting CRC risk are lacking, primarily because evidence for clinical validity of the test is lacking.

Summary: ColonSentry
ColonSentry® is intended to stratify patients with average CRC risk who are averse to screening to identify those who may be at increased risk and therefore choose screening. However, 2 cross-sectional studies are insufficient to demonstrate the risk predictive ability of the test; that
is, clinical validity has not been established. Direct and indirect evidence of clinical utility is currently lacking.

**Clinical Utility**

Published literature on the clinical utility of ctDNA and CTC levels and patient outcomes are lacking. A number of the situations where clinical utility might be demonstrated are listed below. However, because of the uncertainties in analytic and clinical validity, it is not currently possible to establish whether clinical utility is present. These situations are provided as examples of how clinical utility could be demonstrated if analytic and clinical validity were considered adequate.

- For diagnosis or molecular characterization of tumors as an alternative to tissue biopsy, clinical utility can be demonstrated if the test is as accurate as tissue biopsy and avoids the need for an invasive procedure.

- For diagnosis or molecular characterization of tumors in circumstances when tumor tissue is in a location where it cannot be easily accessed or tumor tissue is not available, clinical utility can be demonstrated if the test is able to make a diagnosis or characterization when other methods cannot, and the information from the test leads to management changes that improve outcomes.

- For assessment of the evolution of targeted therapy resistance in real time to allow adaptive treatment strategies, clinical utility can be demonstrated if a management strategy using results from liquid biopsy is superior to a standard management strategy.

- For prognosis including correlation with survival, disease progression, and risk of metastatic relapse, based primarily on quantification of circulating tumor in the blood, clinical utility can be demonstrated if the test provides incremental prognostic information and if this information leads to management changes that improve outcomes.

- For early detection of cancer or as an alternative to current screening methods, possibly before the development of clinically or radiologically detectable cancer in order to treat at an early stage, clinical utility can be demonstrated if a screening strategy using results from liquid biopsy is superior to a screening strategy using standard methods.

**Future Challenges and Questions That Remain for the Use of ctDNA and CTC Levels**

- For targeted therapy, how will the various methods of ultrasensitive detection of mutations from ctDNA be validated and standardized?
• Will liquid biopsy replace or complement analysis of primary tumor or metastases for tailoring treatment selection?

• Will liquid biopsy address intratumor genomic heterogeneity? It is not clear whether ctDNA is representative of only some or all relevant tumor clones located in different areas of the tumor, either primary tumor or metastases.

• When is the optimal time during targeted therapy to use ctDNA to test for therapy resistance?

• How and when would real-time monitoring of therapy during systemic chemotherapy be performed, and at what level of detection or persistence of tumor in the blood would a change in chemotherapy be considered?

• For early detection of cancer and prognosis, how will collection and processing methods for CTCs be standardized and what is the optimal cutoff number of CTCs that should be used to change management decisions? Will earlier detection using these methods change management decisions and will it lead to improved patient outcomes?

• Other questions that need to be addressed include how the following affect the use of ctDNA and CTCs: the presence of cancer-associated mutations that occur with increasing age in individuals who never develop cancer, whether ctDNA concentrations represent the true burden of viable tumor cells, and the release of epithelial cells into the bloodstream in nonmalignant conditions.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in the Table 1.

Table 1. Summary of Key Trials

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<thead>
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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
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<td>NCT02418234</td>
<td>T790M Mutation on ctDNA in patients with NSCLC after EGFR-TKI failure</td>
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<td>Analysis of plasma tumor DNA in lung cancer patients</td>
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<td>NCT02284633</td>
<td>Blood sample monitoring of patients with EGFR mutated lung cancer</td>
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<td>NCT02140463</td>
<td>Next generation personalized therapy with plasma DNA Trial 2 in refractory solid tumors (The NEXT-2 Trial)</td>
<td>165</td>
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NCT: national clinical trial

**Summary of Evidence**

For individuals who have cancer who receive molecular characterization of tumor using circulating tumor DNA (ctDNA), the evidence includes case series and systematic reviews of these case series. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, morbid events, and medication use. Ultrasensitive methods to detect mutations from ctDNA have been developed, but there is limited evidence on the analytic validity of these methods. There is a need for further optimization and standardization of testing methods. Clinical validity consists of case series that report correlations between mutations detected in ctDNA with mutations detected in tumor tissue. Results have shown variable results for clinical sensitivity. Although some reports have suggested that clinical sensitivity may be high, this finding has not been consistent. Published studies have consistently reported high clinical specificity; however, most study population have consisted of small and heterogeneous, and it is not known to what degree mutations detected by ctDNA are representative of the primary tumor. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether mutation analysis by ctDNA can replace mutation analysis in tissue. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cancer or are at high risk of developing cancer who receive identification and quantification of circulating tumor cells (CTCs), the evidence includes case
series and meta-analyses of these case series. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and test validity. Published data on analytic validity are lacking. Most of the literature consists of reports of levels of CTCs and cancer prognosis, and have shown a correlation with survival in certain cancer types. However, the cutoff levels that should be used to signal a change in patient management are unknown, and there are no studies showing clinical utility and improved patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network (NCCN) guidelines for colon cancer (v.2.2016), non-small-cell lung cancer (v.4.2016), and prostate cancer (v.2.2016) do not address CTCs or ctDNA. NCCN guidelines for breast cancer (v.2.2016) state that the use of CTCs in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.44

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Information**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Biocept Inc. offers assays that target mutations found in lung and breast cancers. Target Selector assay is one such test for metastatic lung cancer.

CancerIntercept (Pathway Genomics) is a 96-gene mutation panel designed to detect mutations in 9 driver genes involved primarily in breast, ovarian, lung, and colorectal cancers, as well as melanoma.
CellSearch® System (Janssen Diagnostics, formerly Veridex) is the only FDA-approved device for monitoring patients with metastatic disease and circulating tumor cells. In January 2004, the CellSearch® System was cleared by FDA for marketing through the 510(k) process for monitoring metastatic breast cancer, in November 2007 for monitoring metastatic colorectal cancer, and in February 2008 for monitoring metastatic prostate cancer. The system uses automated instruments manufactured by Immunicon Corp. for sample preparation (CellTracks® AutoPrep) and analysis (CellSpotter Analyzer®), together with supplies, reagents, and epithelial cell control kits manufactured by Veridex. FDA product code: NQI.

Circulogene’s (Theranostics) liquid biopsy uses a finger stick volume of blood and NGS to monitor known tumor mutations (~3000) in 50 cancer-associated genes for targeted therapy. The test uses a proprietary method to recover necrotic and apoptotic cell-death-associated cell-free DNA.

**ColonSentry® (GeneNews, Ontario, Canada; Innovative Diagnostic Laboratory, Richmond, VA)**

ColonSentry® is a PCR assay that uses a blood sample to detect expression of 7 genes found to be differentially expressed in CRC patients compared with controls.\(^5^0\): ANXA3, CLEC4D, TNFAIP6, LMNB1, PRRG4, VNN1, and IL2RB. Per the company website, these genes are early warning signs of colon cancer, and test results can indicate the odds of having CRC compared with an average-risk person. An average-risk person is defined as one who is “at least 50 years old, is asymptomatic for CRC, has no personal history of benign colorectal polyps, colorectal adenomas, CRC, or inflammatory bowel disease, and does not have a first degree relative with CRC.”\(^5^1\) The test is intended for use in adults who are averse to colonoscopy and/or fecal occult blood testing. “Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules.”\(^5^2\)

Foundation ACT (Foundation Medicine) detects mutations in over 60 genes for targeted therapy in metastatic cancer.

Guardant360 (Guardant Health) is a circulating cell-free tumor-specific DNA genotyping test that includes four major types of genomic alterations, specifically EGFR single nucleotide variants (SNVs) and indels; ERBB2 SNVs, indels and copy number amplification (CNA); BRAF SNV; MET CNA and exon 14 skipping indel; KRAS and HRAS SNV; KIT SNV and indel; PDGFRA SNV and indel; ALK translocation; RET translocation; and ROS1 translocation.
Oncotype SEQ™ is the first liquid biopsy test from Genomic Heath and it is planned to launch in mid-2016. The test uses next-generation sequencing (NGS) to identify actionable genomic alterations for late-stage lung, breast, colon, melanoma, ovarian, and gastrointestinal cancers.

**SEPT9 Methylated DNA (ColoVantage, Various Manufacturers; Epi proColon, Epigenomics, Berlin)**

Serum biomarkers that are shed from colorectal tumors have been identified and include Septin 9 hypermethylated DNA (SEPT9). Septin 9 protein is involved in cell division, migration, and apoptosis, and acts as a tumor suppressor; when hypermethylated, expression of SEPT9 is reduced. ColoVantage blood tests for serum SEPT9 methylated DNA are offered by several laboratories.

(ARUP® Laboratories, Quest Diagnostics®, Clinical Genomics). Epi proColon® (Epigenomics, Berlin) received FDA approval in the US in May 2016. Epigenomics has licensed its Septin 9 biomarker technology to ARUP and Quest. ColoVantage and Epi proColon® are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., DNA preparation, PCR primers, probes). Serum SEPT9 methylated DNA testing is intended for individuals 50 years of age or older who have an average risk of colorectal cancer.46

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### References


50. Shirts B, von Roon AC, Tebo AE. The entire predictive value of the prometheus IBD sgi diagnostic product may be due to the three least expensive and most available components. Am J Gastroenterol. Nov 2012;107(11):1760-1761. PMID 23160303


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## History

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<td>07/12/16</td>
<td>New policy, add to Pathology/Laboratory section. Policy created with a literature review through March 10, 2016. Policy statement that the use of circulating tumor DNA and circulating tumor cells is considered investigational for all indications. Policy incorporates policy statement and other information from 2.04.37 Circulating Tumor Cells, which is now deleted.</td>
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<td>Interim Update. Information regarding screening/diagnostic tests ColoVantage, ColoSentry and Epi proColon extracted from medical policy 12.04.121 and added as examples of ctDNA tests. Title revised to include &quot;Diagnosis&quot;, reflecting the expanded scope of the policy. CPT code 88399 added with supporting information for Target Selector Test. Policy moved into new format and renumbered/moved to Genetic Testing section; previously 2.04.141 and now 12.04.141 – previous version is now deleted.</td>
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<tr>
<td>01/01/17</td>
<td>Coding update; added new CPT code 81327 effective 1/1/17.</td>
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Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Espanol (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Тагало (Tagalog):

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ประกาศนี้มีสาระสำคัญ ประกาศนี้มีสาระสำคัญที่เกี่ยวกับการขอรับสิทธิหรือการปรับสิทธิของคุณ Premera Blue Cross และจะมีผลบังคับใช้ในกรณีที่คุณต้องการดูเอกสารที่เกี่ยวข้องที่ล่วงหน้าเพื่อให้ทราบถึงสิทธิของคุณในการซื้อสิทธิหรือการปรับสิทธิที่มีไว้ข้างต้น คุณสมัครในภาพที่มีสิทธิประโยชน์และสิทธิในผลประโยชน์ในสิทธิของเขาหรือเธอ โปรดโทร 800-722-1471 (TTY: 800-842-5357).

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