Medical Policy

Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

Policy MP-038

Origination Date: 7/31/19
Reviewed/Revised Date: 7/31/20
Next Review Date: 7/31/19
Current Effective Date: 7/31/19

Description:
Normal and tumor cells commonly release small fragments of DNA into the blood. This is referred to as cell-free DNA (cfDNA). Tumors, metastases may also release entire cells into the circulation or circulating tumor cells (CTCs). The half-life of a CTC is short (1-2 hours), as they are cleared from the blood stream through extravasation into secondary organs. These cells can generate larger DNA fragments due to incomplete and random digestion of genomic DNA. Circulating tumor DNA (ctDNA) can be used for genomic characterization of the tumor. There are two approaches to detecting ctDNA, the first is targeted, which includes the analysis of known genetic mutations from the primary tumor which can impact therapy decisions (e.g., EGFR and ALK in non-small-cell lung cancer), or the second untargeted which is without knowledge of specific mutations present in the primary tumor. Whether it is targeted or untargeted, the approach to testing includes array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing. Technologies for detecting ctDNA is challenging because it is diluted by the nonmalignant circulating DNA and usually represents only a small fraction (<1%) of total cfDNA.

Liquid biopsy refers to the analysis of circulating tumor DNA whether derived from cell free DNA (cfDNA) or circulating tumor cells (CTCs) as a method of noninvasively characterizing tumors and tumor genome from the peripheral blood. This differentiates it from the other common approach to analyzing tumor DNA through assessment of tumor tissue. Liquid biopsy is purported to be helpful in planning or monitoring treatment and determine recurrence though questions related to accuracy of this testing persist.

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the “Policy” section for more information.
Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does NOT cover the use of circulating tumor DNA (ctDNA) and/or circulating tumor cells (CTCs) (liquid biopsy) for cancer management as it is considered investigational for all indications, including but not limited to the following testing examples (not all inclusive):

1. Cancer Intercept® Detect
2. CellMax® Life - (FirstSightCRC™, LBx Liquid Biopsy™, PanCa™ Monitoring Test, Prostate Cancer Test™)
3. CellSearch®,
4. CirculoGene® Theranostics
6. Colvera™
7. FoundationACT®/Foundation Liquid® (FoundationOne® Liquid biopsies)
8. Guardant360®
9. GeneStrat®
10. IVDiagnostics (Velox™, Admonitrix™)
11. LiquidGx™
12. NeoLAB™ MDS/CMML Profile-Liquid BX
13. Tempus|xF Liquid BX
14. OncoBEAM™ for Colorectal Cancer
15. OncoBEAM™ for Lung Cancer
16. OncoBEAM™ for Melanoma
17. Oncotype DX AR-V7 Nucleus Detect
18. PlasmaSELECT®
19. Target Selector™

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Clinical Rationale

Per the 2018 joint review (Merker et. al.) on the clinical use of circulating tumor DNA in patients with cancer, by the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP), several proof-of-principle studies demonstrating correlations between changes in ctDNA levels and tumor response or outcomes as well as studies demonstrating that ctDNA can identify the emergence of resistance variants were identified. The review reported a lack of rigorous, prospective validation studies of ctDNA-based monitoring and no trials were identified demonstrating that treatment before relapse
based on changes in CTCs improves patient outcomes. In conclusion, the evidence is insufficient to demonstrate test performance for currently available ctDNA and CTC tests for predicting relapse. Further high quality, well designed, large prospective studies are needed to explore and establish whether individualized therapeutic decisions based on ctDNA and CTC assays would improve net health outcomes.

In June of 2019, Hayes published a genetic test evaluation (GTE) report for the 70-gene assay FoundationOne Liquid (Foundation Medicine Inc.), it is considered a newer version of FoundationACT which only has a 62-gene assay. No studies reviewed provided any evidence of analytical or clinical validity for FoundationOne Liquid and very low quality of evidence for the 62-gene version. No studies of clinical utility for either test were identified. Hayes found the current body of evidence very limited, further studies are needed to support the test’s claim of aiding physicians and benefiting patient outcomes by incorporating FoundationOne Liquid into the treatment-making decisions.

Many of the published studies on CTC testing have centered on their utility in breast cancer. In one systematic review and meta-analysis (Zhang et. al., 2012) reported on published literature of the prognostic relevance of CTCs in patients with both early and advanced breast cancer. Out of the 49 eligible studies 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 notable in both early (DFS: HR, 2.86; 95% CI, 2.19-3.75; OS: HR, 2.78; 95% CI, 2.22-3.48) and metastatic breast cancer (PFS: HR, 1.78; 95% CI, 1.52-2.09; OS: HR, 2.33; 95% CI, 2.09-2.60). Further subgroup analyses showed that results were stable irrespective of the CTC detection method and time point of blood withdrawal. In conclusion, the analysis indicated that the detection of CTC is a stable prognosticator in patients with early stage and metastatic breast cancer. However, further studies are needed to determine the clinical utility of CTC in breast cancer.

In another systematic review Wang et. al. (2017) aimed to determine the prognostic value of HER2-positive circulating tumor cells (CTCs) in patients with breast cancer. A total of 550 patients within 4 studies with stage I to IV breast cancer were included. Two of the studies used the CellSearch® System to detect CTCs and the other 2 used reverse transcription polymerase chain reaction. HER2-positive CTCs were not associated with worse overall survival (OS [overall survival]; HR [hazard ratio], 1.489, 95% confidence interval [CI], 0.873-2.540, \( P = .144 \)) or progression-free survival (PFS; HR, 1.543; 95% CI, 0.636-3.744; \( P = .338 \)). In patients without metastasis, HER2-positive CTCs were associated with worse OS (HR, 2.73; 95% CI, 1.340-3.853; \( P = .002 \)) and worse PFS (HR, 2.870; 95% CI, 1.298-6.343; \( P = .009 \)). Subgroups of patients with metastasis had no significant relationship between HER2-positive CTCs and survival. The authors concluded, patients with breast cancer who have HER2-positive CTCs have worse OS and may benefit from more aggressive/targeted therapies. However, further studies are needed with consistent detection methods to evaluate the value of determining HER2-positive CTCs at different tumor stages and sampling times.

A 2014, randomized controlled trial (Smerage et. al.), reviewed the results of patients with metastatic breast cancer (MBC) that had persistent increase in circulating tumor cells (CTC) levels to test whether changing chemotherapy after one cycle of first-line therapy would improve the primary outcome of overall survival (OS). 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 randomized 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 randomized to arms C1 or C2. There was no
difference in median OS between arms C1 (10.7 months) and C2 12.5 months; 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). The authors concluded that this trial demonstrated the prognostic significance of CTCs in patients with MBC receiving first-line chemotherapy. Patients whose CTC levels persistently increased after 21 days of first-line chemotherapy and were switched early to an alternate cytotoxic therapy did not produce a different effect on OS then those who were not switched. Therefore, a more effective treatment other than standard chemotherapy is needed for this population.

Additional breast cancer studies included a prospective study by Liu et. al. in 2017 intended to establish the predictive value of the peptide-based nanomagnetic CTC isolation system (Pep@MNPs) as a promising tool in the management of metastatic breast cancer and Xu et. al. in 2018 which used a cross sectional study to examine CTC detection in subjects with newly diagnosed non-metastatic breast cancer. In the Lui study a direct association was not found between CTC status and tumor response at baseline (p=0.822) or at first clinical evaluation (p=0.367). The authors concluded that larger studies are needed to validate the clinical utility of the results found in this study. In the Xu 2018 cross-sectional study, The detection of CTCs was significantly less in benign tumors when compared to subjects with breast cancer (p=0.007). Also, higher triploid CTC counts were significant in subjects with increased tumor size (T1/T3: p=0.048; T2/T3: p=0.006). These authors also concluded, only a few studies have been published in CTC detection for non-metastatic breast cancer, therefore, in order to validate its clinical utility, more stringent and larger studies are needed.

Lastly, a large multicenter study (Rack et. al., 2014) evaluated CTCs using the CellSearch® System in 2026 patients with early breast cancer before adjuvant chemotherapy and in 1492 patients after chemotherapy for a median of 35 months (range=0-54). Before chemotherapy, CTCs were detected in 21.5% of patients (n = 435 of 2026), with 19.6% (n = 136 of 692) of node-negative and 22.4% (n = 299 of 1334) of node-positive patients showing CTCs (P < .001). No association was found with tumor size, grading, or hormone receptor status. After chemotherapy, 22.1% of patients (n = 330 of 1493) were CTC positive. The presence of CTCs was associated with poor disease-free survival (DFS; P < .0001), distant DFS (P < .001), breast cancer-specific survival (P = .008), and overall survival (OS; P = .0002). CTCs were confirmed as independent prognostic markers in multivariable analysis for DFS (hazard ratio [HR] = 2.11; 95% confidence interval [CI] = 1.49 to 2.99; P < .0001) and OS (HR = 2.18; 95% CI = 1.32 to 3.59; P = .002). The prognosis was worst in patients with at least five CTCs per 30 mL blood (DFS: HR = 4.51, 95% CI = 2.59 to 7.86; OS: HR = 3.60, 95% CI = 1.56 to 8.45). The presence of persisting CTCs after chemotherapy showed a negative influence on DFS (HR = 1.12; 95% CI = 1.02 to 1.25; P = .02) and on OS (HR = 1.16; 95% CI = 0.99 to 1.37; P = .06). Some limitations of this study include the short median follow-up (35 months) cells detected by the CellSearch system is limited to cells with expression of Epcam and cytokeratin and those numbers are relatively low. In conclusion, the data suggests that there may be clinical potential of using CTCs to assess the individual risk of patients at the time of primary diagnosis and in the absence of other strong quantitative markers, may be used for tailoring treatment.

A 2015 study investigated the possibility of circulating tumor cells (CTCs) being prognostic for biochemical recurrence-free survival (bRFS) in patients with locally advanced high-risk prostate cancer (LAPC) undergoing neoadjuvant chemotherapy (NCHT) and radical prostatectomy (RP) (Thalgott et. al.). CTCs were detected before and after NCHT, after RP and at follow-up using the CellSearch System for 59 blood samples (20 ml) from patients with LAPC (n=15) and, additionally, for 15 control samples. The median 5-year progression risk was 90%. CTCs (≥1/20 ml) were detected in 53.3% of patients, with a detection rate of 18.6% in sample-adjusted analysis. CTCs were detected at baseline in 20% of patients with LAPC and 6.7% of controls (p=0.6). CTC findings displayed no association with clinicopathological characteristics. The median bRFS of CTC-negative versus CTC-positive patients was 43.7 (95% confidence
interval not reached) vs. 29.2 months (95% confidence interval=26.8–60.6 months), without statistical significance (p=0.76). According to the authors, to their knowledge, this is the first study intended to detect CTCs during the course of neoadjuvant therapy followed by a RP in LAPC. During various steps of treatment detection rates varied and had uncertain value for each individual. They went on to state, more long-term studies, with improved technologies are needed to use CTCs as a treatment guidance tool for treatment in localized prostate cancer.

In 2016, Villaflor et. al. reviewed a descriptive single institution study of subjects with non-small cell lung cancer (NSCLC) undergoing analysis of circulating tumor DNA (ctDNA) using Guardant360 next-generation sequencing assay. Only 68 of the total 90 patients submitted for ctDNA analysis as part of clinical care, provided informed consent for inclusion in this study. Thirty-eight subjects were tested using the 54-gene ctDNA panel, which did not include ALK, RET, or ROS1 fusions, while the remaining 31 samples were analyzed on the 68-gene ctDNA panel. Tissue-based testing was performed on 44 subjects using 9 different testing platforms. The majority of patients had a diagnosis of lung adenocarcinoma (n = 55, 81%), with the remainder lung squamous cell carcinoma (n = 12, 17.7%) and other lung cancers (n = 1, 1.3%). Over 80% of patients had detectable ctDNA. Thirty-one patients had matched tissue and blood samples; there was no documented reason for lack of tissue results for the remaining 37 patients. In cases with detectable ctDNA and completed tissue analysis, an EGFR activating was found in both tissue and blood in 5 paired samples, and in only 2 tissue samples (71% concordance). The time between biopsy and blood draw ranged from 0 days to 7 years, with an average of 8.8 months and median of 1.4 years between biopsy and blood draw. The investigators found no correlation between concordance and timing of blood draw versus tissue biopsy. A total of 9 subjects with paired tissue and blood samples had an EGFR driver mutation identified in plasma and tissue (n = 5), plasma only (n = 1) or tissue only (n = 3). Eight of these individuals were treated with erlotinib or afatinib at first or second line. Two patients were still responding to therapy at the time of data analysis. Of the 6 remaining patients, the median progression-free survival was 11.5 months (range 7.5 months–29 months; 95% CI=5.7–28.7). The investigators concluded, the data suggest that biopsy-free ctDNA analysis is a viable first choice when the diagnostic tissue biopsy is insufficient for genotyping or if a repeated invasive tissue biopsy is not possible and/or preferred at the time of progression. However, they also concluded that the numbers in this series are small and further research in larger prospective cohorts is needed.

A 2017 retrospective-prospective study (Vidal et. al.) analyzed the use of ctDNA during therapy as an alternative to determine baseline status and subsequent monitoring of RAS mutations as a factor of routine clinical practice. The OncoBEAM CRC® colorectal cancer assay was used to detect RAS mutations in plasma (collected before administration of anti-EGFR treatment) and in tissue samples from two Spanish institutions, from June 2009 to August 2016, which included 115 patients with histologically confirmed metastatic colorectal cancer (mCRC) that were anti-EGFR treatment naive. The median time from tumor tissue specimen collection to ctDNA collection was 47.5 days (range 0-1783 days). Of the 115 patients included in the study, 55 (47.8%) and 59 (51.3%) were shown to have RAS mutations in their tumor samples as detected by standard of care RAS tissue testing and as detected in ctDNA by OncoBEAM assay and standard techniques for tissue analysis was 93% (107/115 patients), kappa index 0.844 (95% CI 0.746-0.914). There were several limitations to this study, the fact that it was a retrospective analysis, a limited number of patients received long-term blood extractions, and the conclusions from associations with P-values marginally <0.05% were only from a few patients with specific clinic-pathological characteristics. While this study was encouraging, further trials are needed to determine clinical validity.
A 2017 cross-sectional cohort study of prostate cancer patients (Scher et al.) if expanding the positivity criteria to include both nuclear and cytoplasmic AR-V7 localization ("nuclear-agnostic") identifies more patients who would benefit from a taxane over an androgen receptor signaling inhibitor (ARSi). A total of 191 pre-therapy blood samples from 161 metastatic castration-resistant prostate cancer patients were collected and processed, before starting a new line of systemic therapy for disease progression. One criterion required nuclear-specific AR-V7 localization, and the other required an AR-V7 signal that was agnostic to protein localization in CTCs. A total of 34 (18%) samples were AR-V7-positive using nuclear-specific criteria, and 56 (29%) were AR-V7-positive using nuclear-agnostic criteria. Following ARSi treatment, none of the 16 nuclear-specific AR-V7-positive samples and 6 of the 32 (19%) nuclear-agnostic AR-V7-positive samples had greater than or equal to 50% post-therapy prostate-specific antigen change at 12 weeks. The strongest baseline factor influencing OS was the interaction between the presence of nuclear-specific AR-V7-positive CTCs and treatment with a taxane (HR 0.24, 95% CI: 0.078 to 0.79; p = 0.019). In conclusion, the inability to determine whether the AR-V7 message has been translated into protein and, if so, whether the protein is present in the nucleus, highlights an important limitation of mRNA-based approaches in CTCs. Nuclear-specific localization is needed to reliably inform treatment selection using an AR-V7 protein biomarker in CTCs.

Rozenblum et al. conducted a retrospective study in 2017, on the impact of treatment decisions and clinical outcomes with the influence of hybrid capture (HC)-based next generation sequencing (NGS) testing. A total of 101 patients with advanced lung cancer had HC-based NGS with broad gene panels testing performed between November 2011 and October 2015 in a single cancer center. HC-based NGS was performed off-site on tumor samples with FoundationOne® (n = 82) or on blood samples using a liquid biopsy approach with Guardant360® if the tissue sample had been exhausted (n=18). The study focused on gene analyses (GAs) with potential clinical relevance. A total of 101 patients were included (median age 63 years [53% females, 45% never-smokers, and 85% with adenocarcinoma]). HC-based NGS was performed upfront and after EGFR/ALK testing yielded negative or inconclusive results in 15% and 85% of patients, respectively. In 51.5% of patients, HC-based NGS was performed before first-line therapy, and in 48.5%, it was performed after treatment failure. HC-based NGS identified clinically actionable genomic alterations in 50% of patients, most frequently in EGFR (18%), Ret proto-oncogene (RET) (9%), ALK (8%), Mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase gene (6%), and erb-b2 receptor tyrosine kinase 2 gene (ERBB2) (5%). In 15 patients, it identified EGFR/ALK aberrations after negative results of prior standard testing. Treatment strategy was changed for 43 patients (42.6%). The overall response rate in these patients was 65% (complete response 14.7%, partial response 50%). Median survival was not reached. Immunotherapy was administered in 33 patients, mostly without an actionable driver, with a presenting disease control rate of 32%, and an association with tumor mutation burden. In conclusion, HC-based NGS has several limitations, despite its strengths, and the efficacy of using it as a tool to aid in therapeutic decision making has not been carefully evaluated. Therefore, further large prospective trials are needed.

A 2017 study on liquid biopsy for urologic malignancies (Di Meo et al.) recognized that there is a growing trend towards exploring the use of a minimally invasive "liquid biopsy" to identify biomarkers in a number of cancers. Multiple aspects can be assessed in circulating cell-free DNA, including cell-free DNA levels, integrity, methylation and mutations. Other prospective liquid biopsy markers include circulating tumor cells, circulating RNAs (microRNA [miRNA], long non-coding RNAs [lncRNAs] and messenger RNA [mRNA]), cell-free proteins, peptides and exosomes have also emerged as non-invasive cancer biomarkers. These circulating molecules can be detected in various biological fluids, including blood, urine, saliva and seminal plasma. Conclusions from this study found that although CTCs, circulating RNAs, cell-free proteins, and exomes can be obtained through liquid biopsy, and may provide additional insight into tumor biology, it is still unclear as to whether the molecules are coming from the
tumor or the metastatic lesion. Further studies are warranted to help determine which area the molecules are coming from.

Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network have published guidelines on use of CTC or cfDNA testing in certain malignancies. ASCO’s clinical practice guideline on appropriate use of breast tumor biomarker assay to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer, last updated in 2016, recommended clinicians not use CTC’s to guide decisions on adjuvant systemic therapy. The NCCN guidelines for breast cancer (v.1.2019) state that “the use of circulating tumor cells in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring.” The NCCN guidelines for Prostate Cancer (v.1.2019) also state that “the panel does not recommend use of these tests to determine treatment selection at this time.”

The NCCN guidelines for cutaneous melanoma (v.1.2019) reference papers on ctDNA in the discussion of molecular characteristics of metastatic disease with the statement, "A number of tests have been developed for detecting BRAF and KIT mutations common in metastatic melanoma. The sensitivity and accuracy of these tests vary, and improved assays are in development."

NCCN guidelines for non-small cell lung cancer (v.3.2019) states that cfDNA/ctDNA should not be used in lieu of a tissue biopsy. Studies have demonstrated cell-free tumor DNA testing generally has very high specificity, but significantly compromised sensitivity, with up to a 30% false-negative rate. Standards for analytical performance characteristics of cell-free tumor DNA have not been established and no guidelines exist regarding the recommendation of the performance characteristics of this type of testing. Also cell-free tumor DNA can identify alterations that are unrelated to the lesion of interest.

**Applicable Coding**

**CPT Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0011M</td>
<td>Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and urine, algorithms to predict high-grade prostate cancer risk (CancerIntercept®, GeneStrat)</td>
</tr>
<tr>
<td>0023U</td>
<td>Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin</td>
</tr>
<tr>
<td>0037U</td>
<td>Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden FoundationACT® (FoundationOne Liquid biopsies)</td>
</tr>
<tr>
<td>0091U</td>
<td>Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result (CellMax® Life-FirstSightCRC)</td>
</tr>
<tr>
<td>86152</td>
<td>Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood) (CellSearch);</td>
</tr>
</tbody>
</table>
86153  Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required (CellSearch)

81479  Unlisted molecular pathology procedure

81599  Unlisted multianalyte assay with algorithmic analysis (when specified as molecular profiling for malignant tumors, e.g., Molecular Intelligence Service [Target Now], GeneKey or OncInsights)

HCPCS Codes
No applicable codes

References:
Disclaimer:
This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member’s individual benefit plan that is in effect at the time services are rendered.

The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

U of U Health Plans makes no representations and accepts no liability with respect to the content of any external information cited or relied upon in this policy. U of U Health Plans updates its Coverage Policies regularly, and reserves the right to amend these policies without notice to health care providers or U of U Health Plans members.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from U of U Health Plans.

"University of Utah Health Plans" and its accompanying logo, and its accompanying marks are protected and registered trademarks of the provider of this Service and or University of Utah Health. Also, the content of this Service is proprietary and is protected by copyright. You may access the copyrighted content of this Service only for purposes set forth in these Conditions of Use.

© CPT Only – American Medical Association