I. POLICY

Evaluation of AFP-L3 biomarkers may be considered medically necessary in the screening, diagnosis, or monitoring of patients with suspected or known hepatocellular cancer.

II. PRODUCT VARIATIONS

[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids  
[N] PPO  
[N] HMO  
[N] SeniorBlue HMO  
[N] SeniorBlue PPO  
[N] Indemnity  
[N] SpecialCare  
[N] POS  
[N] FEP PPO

III. DESCRIPTION/BACKGROUND

In improving outcomes of patients with cancer, early detection may result in discovery of cancer at an earlier and more curable stage. This approach has been successful in improving outcomes of patients with breast, cervical, and colorectal cancer.

In contrast to countries such as China and Japan, hepatocellular carcinoma (liver cancer) is not a common malignancy in the United States. However, it does occur at an increased rate in
patients with chronic liver disease such as chronic hepatitis C. As with other cancers, research is being conducted on techniques that permit earlier diagnosis of this malignancy.

Alpha-fetoprotein (AFP) is one marker that has been used in following up patients with chronic liver disease. However, as noted in a recent study, the clinical usefulness of AFP in hepatocellular cancer (HCC) is debatable. (1) This study looked at serum AFP levels at diagnosis in 1,158 patients with HCC and found a sensitivity of 54%.

Researchers are studying AFP-L3 (lens culinaris agglutinin-reactive AFP) as an improved biomarker in patients with HCC. AFP-L3 is a glycoform of AFP. It is generally reported as a percent of the total AFP level. This policy deals only with use of this biomarker in patients with suspected or known HCC.

The Wako LBA AFP-L3 test received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA) in May 2005 to assist the physician in determining the risk of developing liver cancer in patients with chronic liver disease. (2) Center for Devices and Radiological Health (CDRH) consumer information indicates that the Wako LBA AFP-L3 test helps to determine the risk of developing liver cancer for a patient with chronic liver disease within the next 21 months. If the AFP-L3% is greater or equal to 10%, the risk is (increased) seven-fold

IV. RATIONALE

Taketa reported results on AFP-L3 (as a % of AFP) in a group of 424 patients with acute and chronic liver disease including cirrhosis and hepatocellular carcinoma. (3) Using a cutoff level of 15% (15% or more was abnormal) they found sensitivity of 55% and specificity of 95% for hepatocellular carcinoma. Thirty-eight percent of tumors less than 20 mm in diameter were positive for AFP-L3. AFP-L3 exceeded the cutoff level of 15% an average of 4.0 months before detection by imaging techniques.

Oka and colleagues reported on a prospective study of AFP-L3 (lens culinaris agglutinin-reactive fraction of alpha-fetoprotein) in 388 patients with newly diagnosed hepatocellular cancer (HCC) at 9 Japanese hospitals. (4) The cutoff level for an abnormal value was reduced from ≥15% to ≥10% during the study. Patients with abnormal levels were found to have more aggressive cancers. Tada reported that AFP-L3 percentage of ≥10% was associated with pathologic features of HCC that indicated aggressive tumor such as capsule infiltration and portal vein invasion. (5)

In summary, while a number of studies show a relationship between this biomarker and hepatocellular cancer (both presence and severity), no studies have shown how prospective use of this marker in clinical care will improve patient outcomes. Thus, use of this assay is considered investigational.
Of note, neither the US Preventive Services Task Force (USPSTF) nor the National Comprehensive Cancer Network clinical guidelines discuss the use of this test in screening or clinical care for patients with known or suspected hepatocellular cancer. (6, 7)

2008 update

A literature search was conducted for the period December 2006 through March 2008. None of the studies identified lead to a change in the policy statement. In a prospective cohort of 332 HCV patients observed for 2 years at 7 North American institutions, Sterling et al compared AFP-L3% with or without AFP to AFP. (8) The authors used cutoff points of 10% for AFP-L3 and 20 ng/ml for AFP. Overall sensitivity of AFP-L3 was 44.1%, increasing with AFP from 31% for AFP values less than 20 ng/ml to 60% for AFP values greater than 200 ng/ml; sensitivity for AFP was 52.9%. Overall specificity of AFP-L3 was 91.6%, varying with AFP from 86.6% to 100%; specificity for AFP was 71.1%. Using area under the ROC curves, there was no statistical difference (p=0.586) between AFP-L3 (r=0.75) and AFP (r=0.72).

Investigators were blinded to AFP-L3% results, which were therefore not guiding treatment decisions. A retrospective analysis of 272 patients referred to a single center for HCC, chronic liver disease or liver masses evaluated the performance characteristics of AFP-L3%. (9) The objective was to determine the added benefit of the AFP-L3% test over AFP alone. Because all patients in the cohort with AFP of 200ng/ml or greater had HCC and the AFP-L3% is often not reported if AFP is less than 10 ng/ml, the relevant group was the subset of patients with AFP 10ng/ml or greater but less than 200ng/ml. In this group, the areas under the ROC curve for distinguishing between HCC and chronic liver disease were nearly significant (p=0.074), with areas of 0.76 and 0.59 for AFP-L3% and AFP, respectively. The sensitivity and specificity (using the 10% cutoff point for AFP-L3%) were 71% and 63%, respectively. In this cohort, both AFP of 200 or greater and AFP-L3% of 10% or more were predictive of poor survival, but once the AFP level was taken into account, there was no prognostic value of the AFP-L3%. These equivocal findings are insufficient to change the policy statement at this time. This is investigational because the impact of this testing on health outcomes is uncertain.

2009 Update

A MEDLINE search was conducted for the period March 2008 through March 2009. All of the studies identified for this update compared AFP, AFP-L3% and des-Γ-carboxyprothrombin (DCP), an abnormal prothrombin produced by malignant hepatocytes. The prognostic use of AFP-L3% as a predictor of post-treatment survival or recurrence of HCC was addressed in 3 studies from Japan that addressed different aspects of prognosis; AFP-L3% values did not affect treatment decisions in any of them. Kitai and colleagues incorporated biomarker information into the Japan Integrated Staging (JIS) tool, where, within strata of the existing JIS staging system, patients with elevated values of 2 or 3 biomarkers had poorer survival compared to those with no biomarker elevations. (10) The 2 other studies used either pretreatment biomarker levels, (11) or pre- and post-treatment biomarker levels (12) as prognostic indicators for survival and recurrence of HCC treated with ablation or hepatectomy. The Owaga study (12) noted a statistically significant prognostic effect in a
subset (n=19) of the study population of 124 patients; in a multivariate model, only AFP-L3% elevated (>15%) before and reduced after treatment (radiofrequency ablation) compared to AFP-L3% elevated both before and after treatment showed statistically significant improvement in both survival and recurrence. Neither post-treatment improvements in AFP (from >200ng/ml to <200ng/ml) nor DCP (from >100mAU/ml to <100mAU/ml) levels showed statistical improvements despite comprising slightly larger subsets of the main population. In the Toyoda cohorts (11), multivariate analyses showed that pretreatment levels of none of the 3 studied tumor markers significantly affected survival when hepatectomy was the treatment (n=345), but that elevated pretreatment AFP-L3% (15% or greater) and DCP (100mAU/ml or greater) levels were prognostic indicators of survival among patients treated with locoregional thermal ablation (n=456). Elevated pretreatment DCP was the only biomarker to statistically predict tumor recurrence.

A fourth study was the only one to address test characteristics and their utility for surveillance in high risk patients. (13) In this study from the US, 240 patients with either HBV or HCV with (n=144) or without (n=96) HCC attending a liver center were identified. Stored samples were tested for AFP, AFP-L3%, and DCP. Receiver-operator curves identified optimal cutpoints for the 3 biomarkers (25ng/ml, 10%, and 84mAU/l respectively). HCC was diagnosed using the American Association for the Study of Liver Diseases Practice Guidelines. The sensitivity, specificity and positive predictive value for each marker was as follows: 69%, 87% and 70% for AFP; 56%, 90%, and 56% for AFP-L3%; and 87%, 85%, and 87% for DCP. Combining tests yielded no additional improvements in predictive power. The biomarkers were not used for surveillance, nor were they used to guide treatment decisions; rather this was a retrospective assessment of their potential to guide surveillance activities.

The roll of AFP-L3% in improving health outcomes of patients with known or suspected HCC has yet to be determined, particularly in comparison or conjunction with DCP. Adding biomarker data may be helpful when staging HCC, as shown by Katai (10), although the contribution made by each biomarker was not demonstrated in this study.

2014 Update
Review of the literature revealed no new information that would alter the conclusions reached above. Therefore, the policy statement is unchanged.

V. DEFINITIONS
N/A

VI. BENEFIT VARIATIONS
The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s
individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>82107</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>HCPICS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>155.0</td>
<td>Malignant neoplasm of liver, primary</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.
The following ICD-10 diagnosis codes will be effective October 1, 2015.

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C22.0</td>
<td>Liver cell carcinoma</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES


Other:
Novitas Solutions. Local Coverage Determination (LCD) L33142 Biomarkers for Oncology. Effective 1/1/14.

X. Policy History

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Effective Date</th>
<th>Description</th>
</tr>
</thead>
</table>

Health care benefit programs issued or administered by Capital BlueCross and/or its subsidiaries, Capital Advantage Insurance Company®, Capital Advantage Assurance Company® and Keystone Health Plan® Central. Independent licensees of the BlueCross BlueShield Association. Communications issued by Capital BlueCross in its capacity as administrator of programs and provider relations for all companies.