ARBenefits	Medical Policy
ARBenefits Approval: 10/19/2011	Title: Alpha-Fetoprotein-L3 for Prediction of risk of Hepatocellular Cancer and Cholangiocarcinoma
Effective Date: 01/01/2012	Document: ARB0014
Revision Date:	
Code(s): 82107 Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)	
Administered by: QualChoice®	

Public Statement:

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 patient with chronic liver disease such as patients with 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 than has been used in following patients with chronic liver disease. However, as noted in a recent study, the clinical usefulness of AFP in hepatocellular cancer (HCC) is debatable.

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. The role of AFP-L3% in improving health outcomes of patients with known or suspected HCC has yet to be determined. AFP-L3% is therefore considered investigational.

Medical Policy Statement:

Evaluation of AFP-L3 biomarkers in the screening, diagnosis, or monitoring of patients with suspected or known hepatocellular cancer, cholangiocarcinoma or any other indication not supported by medical literature is considered investigational or experimental as there is a lack of scientific evidence of effectiveness.

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 patient with chronic liver disease such as patients with 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 than has been used in following patients with chronic liver disease. However, as noted in a recent study, the clinical usefulness of AFP in hepatocellular cancer (HCC) is debatable. This study looked at serum AFP levels at diagnosis is 1158 patients with HCC and found a sensitivity of 54%.

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The Wako LBA AFP-L3 test received 510(k) marketing clearance from the FDA in May 2005 to assist the physician to determine the risk of developing liver cancer in patients with chronic liver disease. CDRH (Center for Devices and Radiological Health) 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.

The FDA classifies the testing equipment into Class II (special controls). "FDA has identified the risks to health associated with this type of device as inappropriate risk assessment and improper patient management. Failure of the system to perform as indicated, or error in interpretation of results, could lead to inappropriate risk assessment and improper management of patients with chronic liver diseases. Specifically, a falsely low AFP-L3% could result in a determination that the patient is at a lower risk of developing hepatocellular carcinoma, which could delay appropriate monitoring and treatment. A falsely high AFP-L3% could result in a determination that the patient is at a higher risk for hepatocellular carcinoma, which could lead to unnecessary evaluation and testing, or inappropriate treatment decisions. Use of assay results without consideration of other laboratory findings, imaging studies, and clinical

assessment could also pose a risk." (Federal Register, Vol. 70, No. 191, Tuesday, Oct 4 2005, pages 57748-577590).

- There are no studies on the sensitivity, specificity, primary predictive value, or negative predictive value from United States medical institutions found on MedLine as of 3 Jan 07.
- AFP-3% measurement has also been described in pediatric patients with tyrosinemia type I & hepatocellular carcinoma.
- AFP-3% measurement has also been described as a potential marker for Down's syndrome.
- AFP-3% measurement has also been described as a potential marker for testicular cancer.

A MEDLINE search was conducted through March 2009. All of the studies identified for this update compared AFP, AFP-L3% and des-?-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 (Kitai et al, 2008). The 2 other studies used either pretreatment biomarker levels, (Toyoda et al, 2008), or pre- and post-treatment biomarker levels, (Ogawa et al, 2008), as prognostic indicators for survival and recurrence of HCC treated with ablation or hepatectomy. The Owaga study noted a statistically significant prognostic effect in a subset 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 levels showed statistical improvements despite comprising slightly larger subsets of the main population. In the Toyoda cohorts, multivariate analyses showed that pretreatment levels of none of the 3 studied tumor markers significantly affected survival when hepatectomy was the treatment, but that elevated pretreatment AFP-L3% and DCP levels were prognostic indicators of survival among patients treated with locoregional thermal ablation. 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 (Durazo et al, 2008). In this study from the US, 240 patients with either HBV or HCV with or without 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. 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 role 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 et al, 2008, although the contribution made by each biomarker was not demonstrated in this study.

Application to Products

This policy applies to ARBenefits. Consult ARBenefits Summary Plan Description (SPD) for additional information.

Last modified by: Date: