Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Oncoprotein Des-gamma-carboxy Prothrombin (DCP) Immunoassay

Description/Background

Hepatocellular (liver) carcinoma (HCC) accounts for 80-90% of all liver cancers. It is the 5th most common cancer in the world according to the World Health Organizration. It ranks 4th in annual cancer mortality rates. The disease is most prevalent in parts of Africa and Asia where thre is high incidence of reported viral hepatitis B and hepatitis C infections. However, the incidence in western countries is rising.

Des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonists II (PIVKA II), is an abnormal form of prothrombin, a clotting factor produced by the liver. This test measures the amount of DCP in the blood to help evaluate whether treatment for 1 type of liver cancer (HCC), is effective. Des-gamma-carboxy prothrombin (DCP) (also known aa PIVKA II) levels are raised in a majority of patients with HCC. It has been proposed that DCP could be used to screening for HCC.

HCC is a primary liver cancer that originates from liver cells. HCC most commonly develops in those with underlying cirrhosis, a slowly progressing disease in which healthy liver tissue is replaced with scar tissue. The etiology of cirrhosis includes alcohol abuse, autoimmune diseases of the liver, chronic inflammation of the liver, hepatitis B and C viruses or hemochromatosis. Before HCC is far-advanced, clinical recognition is often difficult due to non-specific symptoms such as right-sided abdominal pain, weakness and weight loss.

Treatment options for HCC are limited. Tumor resection or liver transplantation can be used to treat selected non-metastatic tumors if they are diagnosed early; however, resection is feasible in only approximately 15% of subjects, and relatively few individuals are suitable for transplantation. Recurrence rates for HCC remain high. Chemotherapy and radiation treatments

are not usually effective. Surveillance and screening for HCC remains controversial. The American Association for the Study of Liver Disease recommends HCC screening, but the National Cancer Institute does not. Early detection of HCC could improve individual survival. Currently, the recommended surveillance tests for HCC are based on imaging techniques such as ultrasound evaluation and contrast-imaging techniques (CT and MRI) of the liver. The use of biomarkers is promising but the diverse aetiology and complex pathophysiological mechanisms of HCC make it difficult to find an ideal combination.

Tumor markers are substances that are produced in low quantities by cells in the body. Levels higher than normal usually indicate the presence of a cancerous condition. These markers can be detected and quantitated in blood. The tumor marker alpha-fetoprotein (AFP) has been used for over 40 years in screening HCC subjects. Not all HCCs produce AFP, resulting in both false-positive and false-negative results. The search for an ideal marker for HCC continues.

Regulatory Status:

N/A

Medical Policy Statement

The clinical utility of des-gamma-carboxy prothrombin (DCP) as a tumor marker for hepatocellular carcinoma (HCC) has not been demonstrated. The peer reviewed medical literature has not shown that a measurement of DCP concentrations has sufficient sensitivity and accuracy to be useful in surveillance. Des-gamma-carboxy prothrombin (DCP) immunoassay is experimental/investigational.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

83951

Rationale

Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th edition, states that alpha-fetoprotein (AFP) is normally present in high concentrations in fetal serum but in only minute amounts thereafter. Reappearance of high serum levels of alpha-fetoprotein strongly suggests the diagnosis of hepatocellular carcinoma. This holds especially true in populations in which hepatocellular carcinoma is most prevalent. Alternative markers have not proved to be more useful than alpha-fetoprotein.

Des-gamma-carboxy prothrombin (DCP) levels are raised in a majority of individuals with hepatocellular carcinoma. In populations in which the incidence of hepatocellular carcinoma is low, the abnormal prothrombin might arguably be a better marker than alpha-fetoprotein, however, DCP is less sensitive and less specific than alpha-fetoprotein. If the diagnostic cutoff level of DCP is increased in an attempt to eliminate false-positive results, the sensitivity for detecting hepatocellular carcinoma declines from 91-67%.

Toyoda et al conducted a prospective study to evaluate the significance of simultaneous measurement of 3 tumor markers: alpha-fetoprotein (AFP), Lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP). The study consisted of 685 individuals diagnosed with initial HCC between 1995 and 2004. Findings concluded that 55.8 percent of the individuals were positive for AFP, 34.1 percent were positive for AFP-L3 and 54.2 percent were positive for DCP. In addition, individuals who were positive for AFP-L3 alone had a greater number of tumors, whereas patients positive for DCP alone had larger tumors and higher prevalence of portal vein invasion.

Nakamura et al discussed a retrospective study of 1,361 consecutive individuals who were diagnosed with HCC for the first time between June 1997 and September 2003 at Okayama University hospital in Japan. The researchers cited that previous studies comparing the usefulness of AFP to DCP found that sensitivities and specificities were quite different. Possible reasons for the differences include the use of different marker cut-off values in each study, differing causes of the underlying liver disease and differences in tumor stages. The study results indicate that AFP identified a higher percentage of individuals with small tumors, while DCP identified a higher percentage of individuals with large tumors. The mechanism of this unique characteristic of DCP is not well understood. Additional studies by Lok et al supported the conclusion that neither DCP nor AFP is optimal.

Zhu et al (2014) performed a meta-analysis which evaluated the performance of DCP in the diagnosis of HCC. The study found DCP had moderate diagnostic accuracy in HCC. However, due to the poor quality of the included studies, the analysis is limited by publication bias, and most studies were retrospective. Further, the number of subjects with early-stage HCC was not mentioned, or it was too small to assess the value of DCP in the diagnosis of early HCC. Larger, well-designed studies with multiregional cooperation are needed to further examine the role of DCP as a diagnostic tool for HCC.

Ji et al evaluated the performance of des-gamma-carboxy prothrombin (DCP) for identifying hepatitis B virus-related HCC in a multicenter study from 4 large academic medical centers in China. The study population included 1034 subjects, of whom 521 were in the cohort for

differential diagnosis (cohort A), 447 were in the cohort for high-risk population surveillance (cohort B) and 66 were in the treatment-monitoring cohort (cohort C). Blind parallel detections were conducted for DCP and AFP. The area under the receiver operating characteristic curve (AUC) was used to evaluate the diagnostic efficacies. In cohort A, which included individuals with HCC, liver metastasis, liver cirrhosis (LC), and liver hemangiomas as well as healthy controls (HCs), the accuracy of DCP for distinguishing HCC from various controls was 6.2–9.7% higher than that of AFP. The accuracy of DCP was even higher (12.3–20.67% higher than that of AFP) in cohort B which included individuals with HCC, LC, and chronic hepatitis B as well as HC. The superiority of DCP to AFP was more profound in the surveillance of early HCC and AFP-negative HCC and in discriminating HCC from LC. Higher DCP levels were associated with worse clinical behaviors and shorter disease-free survival. The study authors concluded that DCP is complementary to AFP in identifying AFP-negative HCC and in excluding AFP-positive non-HCC (liver cirrhosis). Additionally, DCP demonstrates improved performance in HCC surveillance, early diagnosis, treatment response and recurrence monitoring in the HBV-related population.

De et al reported on a systematic review to evaluate DCP as a diagnostic standard for primary hepatocellular carcinoma (PHC). A total of 38 studies involving 11,124 cases were included (5,298 cases in the PHC group and 5,826 cases in the control group) and a meta-analysis was performed. The overall sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) of DCP for the detection of PHC were 0.66 (95% confidence interval [CI]: 0.65-0.68), 0.88 (95% CI: 0.87-0.90), 7.13 (95% CI: 5.73-8.87), and 0.33 (95% CI: 0.29-0.38), respectively. The area under the curve (AUC) of the summary receiver-operating characteristic curve (SROC) was 0.9002. The review and analysis found DCP has moderate diagnostic utility for PHC. However, due to the heterogeneity and limitations of the included studies, additional high-quality studies are needed.

Balaceanu (2019) reported on the use of biomarkers versus imaging in the early detection of hepatocellular carcinoma and prognosis. The review systematically summarized the existing data on the role of biomarkers in early diagnosis and prognosis of HCC. Several international clinical guidelines were reviewed and shared a foundation of diagnosis by ultrasound surveillance and contrast imaging techniques. No biomarkers were shown to have a high accuracy in the early detection of HCC, although some may have clinical utility in the near future. Authors concluded that although there have been important advances in our understanding of the roles of various biomarkers in certain stages of the disease, especially in combinations, large studies involving certain population groups are needed before biomarkers can be introduced into clinical practice on a large scale. The different predominant etiologies of certain geographical areas (*i.e.*, high incidence of HBV, HCV, alcoholic and non-alcoholic fatty liver disease, cryptogenic disease) make it difficult to find a unique combination of biomarkers for the diagnosis of HCC. Nonetheless, imaging techniques still play a leading role in both HCC surveillance and diagnosis.

Piñero et al (2020) described HCC serum and tissue biomarkers while focusing on their clinical utility in HCC surveillance, early diagnosis, prognosis and post-treatment assessment. DCP has been described as a useful tool for HCC surveillance since it is independent of AFP secretion. However, its efficacy as a screening tool is still controversial. DCP has also been explored as a prognostic marker in HCC. Although, DCP has been widely associated with larger tumors, poor differentiation, and vascular invasion, the identification of useful biomarkers for surveillance and early HCC diagnosis is still deficient. Available serum biomarkers show

low sensitivity and heterogeneous specificity despite different cut-off points, even when assessed longitudinally, or with a combination of serum biomarkers. The clinical utility of serum or tissue biomarkers for HCC has not been widely accepted. A huge amount of publications with different and heterogeneous cut-offs with corresponding sensitivities and specificities were noted. Most of the biomarkers have been associated with poor prognosis, either in early or advanced HCC. Authors concluded that available tumor biomarkers have shown to be associated with poor prognosis in different HCC stages and post-treatment assessment. Appropriate candidate selection for each therapeutic modality based solely on these biomarkers is still far away from its clinical applicability in the clinical decision-making processes. Ideal biomarkers for HCC are those that would enable clinicians to diagnose this cancer at asymptomatic stages and also, to help and identify better candidates in each tumor stage for appropriate therapeutic modalities. There is still a need for specific biomarkers to improve detection of HCC at early or very early stages, assess specific prognosis and prediction of treatment response.

Supplemental Information

PRACTICE GUIDELINES

European Association for the Study of the Liver – European Organization for Research and Treatment of Cancer (EASL-EORTC)
EASL-EORTC indicate that accurate tumor biomarkers for early detection of HCC need to be developed. Data available with tested biomarkers (i.e., AFP, AFP-L3 and DCP) show that these tests are suboptimal for routine clinical practice

National Comprehensive Cancer Network
According to the National Comprehensive Cancer Network Guidelines for the treatment of hepatocellular carcinoma, serum biomarkers are being studied as diagnostic tools for individuals with suspected HCC. Included in this setting are des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II). The NCCN does not consider DCP optimal in this setting. Although the discussion mentions the HALT-C trial, which determined the combined use of AFP and DCP biomarkers are superior to individual biomarker use in hepatitis C patients who developed HCC, the guidelines do not mention the use of DCP in the algorithm for screening or surveillance.

Government Regulations

National:
There is no National Coverage Determination for des-gamma-carboxy prothrombin (DCP) levels.

Local:
There is no Local Coverage Determination for des-gamma-carboxy prothrombin (DCP)

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Noninvasive Techniques for the Evalution and Monitoring of Patients with Chronic Liver Disease

References

1. Balaceanu, LA. “Biomarkers vs imaging in the early detection of hepatocellular carcinoma and prognosis.” *World J Clin Cases.* 2019 June 26; 7(12): 1367-1382
2. De, J, et al. “A systematic review of des-γ-carboxy prothrombin for the diagnosis of primary hepatocellular carcinoma,” *Medicine (Baltimore)*, 2016, Vol. 95, No.17, pp. e3448, doi: 10.1097/MD.0000000000003448.
3. European Association for the Study of the Liver & the European Organization for Research and Treatment of Cancer. “EASL-EORTC Clinical Pratice Guidelines: Management of hepatocellular carcinoma.” *Journal of Hepatology* 2012 vol. 56 j 908–943.
4. Inagaki, Yoshinori, et al. “Clinical And molecular Insights into the Hepatocellular Carcinoma tumour Marker Des-C-Carboxyprothrombin.” *Liver International*, Vol. 31, No, 1, September 27, 2010, pp. 22-35.
5. Lok, Anna S., et al. “Des-Carboxy Prothrombin and -Fetoprotein as Biomarkers for the Early Detection of Hepatocellular Carcinoma.” *Gastroenterology*. Vol. 138, 2010, pp. 493–502.
6. Mann, Christopher D., et al. “Prognostic molecular markers in hepatocellular carcinoma: A systematic review.” *European Journal of Cancer*, Vol. 43, No. 6, pp. 979-992.
7. Nakamura, Shinichiro, MD, PhD, et al. “Sensitivity and Specificity of Des-Gamma-Carboxy Prothrombin for Diagnosis and Patients with Hepatocellular Carcinomas Varies According to Tumor Size.” *American Journal of Gastroenterology*. Vol. 101, No. 9, 2006, pp. 2038-2043.
8. National Comprehensive Cancer Network. “NCCN Clinical Practice Guidelines in Oncology. Hepatocellular Cancers.” v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed June 4, 2024.
9. Piñero F, Dirchwolf M, Pessôa MG. Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment. Cells. 2020;9(6):1370.
10. Toyoda, Hidenori, et al. “Prognostic Significance of Simultaneous Measurement of Three Tumor Markers with Hepatocellular Carcinoma.” *Clinical Gastroenterology and Hepatology*. Vol. 4, No. 1, pp. 111-117.
11. Volk, Michael L., et al. “Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: A comparison of AFP, DCP, and AFP-L3.” *Cancer Biomarkers: Section A of Disease Markers.* Vol. 3, No. 2, 2007, pp. 79-87.
12. Yoon, Seung Kew. “Recent Advances in Tumor Markers of Human Hepatocellular Carcinoma.” *Intervirology*. Vol. 51, 2008, Supplement 1, pp. 34-41.
13. Zhou, Lin, et al. “Serum tumor markers for detection of hepatocellular carcinoma.” *World Journal of Gastroenterology*. Vol. 12, No. 8, 2006, pp. 1175-1181.
14. Zhu, Rong, et al. “Diagnostic performance of des-γ-carboxy prothrombin for hepatocellular carcinoma: a meta-analysis.” *Gastroenterol Res Pract,* 2014, doi: 10.1155/2014/529314

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 6/4/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/09	6/3/09	4/21/09	Joint policy established
11/1/11	8/16/11	8/16/11	Routine maintenance; references updated
5/1/13	2/19/13	3/4/13	Routine maintenance; references updated
9/1/14	6/20/14	6/23/14	Routine maintenance; references updated
11/1/15	8/24/15	9/14/15	Routine maintenance; references updated
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance
11/1/20	8/18/20		Rationale and references updated
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine maintenance
11/1/23	8/15/23		Routine maintenance (slp) Vendor managed: N/A
11/1/24	8/20/24		Routine maintenance (slp) Vendor Managed: N/A

Next Review Date: 3rd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ONCOPROTEIN DES-GAMMA-CARBOXY PROTHROMBIN (DCP) IMMUNOASSAY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of the policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.