Anthem

Clinical UM Guideline

Subject: Outpatient Alpha-Fetoprotein Testing
Guideline #: CG-LAB-26
Status: Reviewed

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Description

This document addresses outpatient alpha-fetoprotein (AFP) testing.

Clinical Indications

Medically Necessary:

Outpatient alpha-fetoprotein testing is considered **medically necessary** for any of the following indications:

A. Screening for neural tube defects in pregnant persons; **or**
B. Evaluation or management of the following conditions:
   1. Carcinoma of unknown primary site; **or**
   2. Germ cell tumors; **or**
   3. Hepatocellular carcinoma (HCC): diagnosed HCC, suspected HCC, or for those at high risk for HCC; **or**
   4. Mediastinal mass; **or**
   5. Ovarian cancer; **or**
   6. Pelvic mass; **or**
   7. Retroperitoneal mass; **or**
   8. Testicular cancer or suspicious testicular mass; **or**
   9. Thymoma or thymic cancer.

Not Medically Necessary:

Outpatient alpha-fetoprotein testing is considered **not medically necessary** when the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this guideline are included below 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.

AFP
When services are Medically Necessary:

CPT	
82105	Alpha-fetoprotein (AFP); serum

ICD-10 Diagnosis	
A52.74	Syphilis of liver and other viscera
B16.0-B17.9	Acute hepatitis B, other acute viral hepatitis
B18.0-B18.9	Chronic viral hepatitis
B66.1	Clonorchiasis
B66.3	Fascioliasis
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic ducts
C37	Malignant neoplasm of thymus
C38.1-C38.3	Malignant neoplasm of mediastinum
C38.8	Malignant neoplasm of overlapping sites of heart, mediastinum and pleura
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C56.1-C56.9	Malignant neoplasm of ovary
C62.00-C62.92	Malignant neoplasm of testis
C75.3	Malignant neoplasm of pineal gland
C76.3	Malignant neoplasm of pelvis
C78.1	Secondary malignant neoplasm of mediastinum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.60-C79.63	Secondary malignant neoplasm of ovary
C79.82	Secondary malignant neoplasm of genital organs
C7A.00	Malignant carcinoid tumor of unspecified site
C7A.090-C7A.098	Malignant carcinoid tumors of other sites
C7B.00-C7B.09	Secondary carcinoid tumors
C80.0-C80.1	Malignant neoplasm without specification of site
D01.5	Carcinoma in situ of liver, gall bladder and bile ducts
D13.4-D13.5	Benign neoplasm of liver, extrahepatic bile ducts
D15.0	Benign neoplasm of thymus
D15.2	Benign neoplasm of mediastinum
D17.79	Benign lipomatous neoplasm of other sites (peritoneum, retroperitoneum)
D20.0-D20.1	Benign neoplasm of soft tissue of retroperitoneum and peritoneum
D37.6	Neoplasm of uncertain behavior of liver, gallbladder and bile ducts
D39.10-D39.12	Neoplasm of uncertain behavior of ovary

D40.10-D40.12	Neoplasm of uncertain behavior of testis
D81.82	Activated Phosphoinositide 3-kinase Delta Syndrome [APDS]
E78.2	Mixed hyperlipidemia
E83.00-E83.09	Disorders of copper metabolism
E83.10-E83.19	Disorders of iron metabolism
E88.01	Alpha-1-antitrypsin deficiency
F10.10-F10.99	Alcohol related disorders
J98.59	Other diseases of mediastinum, not elsewhere classified
K70.0	Alcoholic fatty liver
K70.2-K70.31	Alcoholic fibrosis and sclerosis of liver, alcoholic cirrhosis of liver
K73.0-K73.9	Chronic hepatitis, not elsewhere classified
K74.00-K74.02	Hepatic fibrosis
K74.60-K74.69	Other and unspecified cirrhosis of liver
K75.4	Autoimmune hepatitis
K75.81	Nonalcoholic steatohepatitis (NASH)
K75.9	Inflammatory liver disease, unspecified
K76.0	Fatty (change of) liver, not elsewhere classified
K76.81-K76.89	Other specified diseases of liver
N44.1-N44.8	Cyst and other nonimflammatory disorders of testis
N50.3	Cyst of epididymis
N50.811-N50.89	Other specified disorders of male genital organs
N53.12	Painful ejaculation
N53.8-N53.9	Other or unspecified male sexual dysfunction
O09.00-O09.93	Supervision of high risk pregnancy
Q53.10-Q53.9	Undescended testicle
Q76.428	Congenital lordosis, sacral and sacrococcygeal region
R39.83-R39.84	Non-palpable testicle(s)
R91.1-R91.8	Abnormal findings on diagnostic imaging of lung
R93.2	Abnormal findings on diagnostic imaging of liver and biliary tract
R93.5	Abnormal findings on diagnostic imaging of other abdominal regions, including retroperitoneum
R93.811-R93.89	Abnormal findings on diagnostic imaging of testis, other specified body structures
R97.8	Other abnormal tumor markers
Z03.71-Z03.79	Encounter for suspected maternal and fetal conditions ruled out
Z17.0-Z17.1	Estrogen receptor status
Z34.00-Z34.93	Encounter for supervision of normal pregnancy
Z36.0-Z36.9	Encounter for antenatal screening of mother
Z85.05	Personal history of malignant neoplasm of liver
Z85.238-Z85.29	Personal history of other malignant neoplasm of thymus, other respiratory and intrathoracic organs
Z85.43	Personal history of malignant neoplasm of ovary
Z85.47	Personal history of malignant neoplasm of testis
Z86.002-Z86.004	Personal history of in-situ neoplasm of other and unspecified genital organs; oral cavity, esophagus and stomach; other and unspecified digestive organs

When services are Not Medically Necessary:
For the procedure code listed above for all other diagnoses not listed.

AFP-L3
When services are Medically Necessary:

CPT

82107	Alpha-fetoprotein (AFP); AFP-L3 fraction isoform and total AFP (including ratio)

ICD-10 Diagnosis

A52.74	Syphilis of liver and other viscera
B16.0-B17.9	Acute hepatitis B, other acute viral hepatitis
B18.0-B18.9	Chronic viral hepatitis
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic ducts
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D01.5	Carcinoma in situ of liver, gall bladder and bile ducts
D13.4-D13.5	Benign neoplasm of liver, extrahepatic bile ducts
D37.6	Neoplasm of uncertain behavior of liver, gallbladder and bile ducts
E83.10-E83.19	Disorders of iron metabolism
E88.01	Alpha-1-antitrypsin deficiency
F10.10-F10.99	Alcohol related disorders
K70.0	Alcoholic fatty liver
K70.2-K70.31	Alcoholic fibrosis and sclerosis of liver, alcoholic cirrhosis of liver
K73.0-K73.9	Chronic hepatitis, not elsewhere classified
K74.00-K74.02	Hepatic fibrosis
K74.60-K74.69	Other and unspecified cirrhosis of liver
K75.4	Autoimmune hepatitis
K75.81	Nonalcoholic steatohepatitis (NASH)
K75.9	Inflammatory liver disease, unspecified
K76.0	Fatty (change of) liver, not elsewhere classified
K76.81-K76.89	Other specified diseases of liver
R93.2	Abnormal findings on diagnostic imaging of liver and biliary tract
Z85.05	Personal history of malignant neoplasm of liver

When services are Not Medically Necessary:
For the procedure code listed above for all other diagnoses not listed.

Discussion/General Information

AFP is a glycoprotein produced during pregnancy. It's produced initially by the yolk sac and later by the fetal liver and gastrointestinal tract. During pregnancy it can be found in the amniotic fluid and in the pregnant person's blood. AFP concentrations decline after birth.

AFP levels are not usually detectable in healthy adults and those who are not pregnant. When the AFP level is elevated in a non-pregnant person, it can be suggestive of a primary liver cancer or a germ cell tumor. Many tissues regain the ability to produce this oncofetal protein if they undergo malignant degeneration. While an elevated AFP is typical of HCC and some benign liver diseases (for example, alcohol abuse, hepatitis, cirrhosis), it can also be seen in gastric and, rarely, in lung, colon, and pancreatic cancers. Cholangiocarcinoma is cancer of the bile ducts. In some instances, those with cholangiocarcinoma may have an elevated AFP.

Screening in Pregnant Persons
Maternal serum alpha-fetoprotein (MSAFP) testing is recommended as part of universal screening for neural tube defects, often when optimal ultrasound images are not obtained. Neural tube defects occur when the neural tube doesn't close properly very early during pregnancy, often before the pregnancy is known. These types of birth defects may include spina bifida (a spinal cord defect) or anencephalopathy (a brain defect). In a 2021 committee opinion by the American College of Obstetricians and Gynecologists, the recommendation is to test pregnant persons in the second trimester of pregnancy for AFP levels. Elevated levels of AFP in a pregnant person is associated with an increased risk of stillbirth.

Carcinoma of unknown primary site
Occult primary tumors (also referred to as cancer of unknown primary [CUP]) are malignant (cancerous) cells found in the body, but without knowing where the malignancy first began to grow. These types of tumors have a wide variety of clinical presentations and knowing where the cancer originated may affect treatment options and clinical management of the condition. Use of tumor marker AFP may help narrow down the site of origin. The National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) in 2024 published guidelines for occult primary. Their recommendation is to measure AFP for those with a possible primary testicular germ cell tumor or retroperitoneal mass. Differentiating metastatic cancer of the liver from primary HCC can be challenging and the measurement of AFP for HCC is also recommended when doing a workup for CUP in the liver.

Germ Cell Tumors
Germ cell tumors develop in germ cells. They most often develop in the ovary or testicle because this is where most germ cells are located. They may contain several different types of tissue. Depending on how the cells look under a microscope, they can be considered mature or immature. Germ cells are the cells in the body which develop into sperm and eggs. However, while being formed in the womb, germ cells can be left behind in other parts of the body, such as the mediastinum or retroperitoneum. Germ cell tumors can be benign or malignant. When germ cell tumors involve the testes, they can further be divided into seminomas and nonseminomatous germ cell tumors. A seminoma germ cell tumor begins in germ cells. They most often occur in the testicle, but can also be found in other areas such as the brain, chest, or abdomen. Seminomas tend to grow and spread slowly Nonseminomatous germ cell tumors also begin the cells that form sperm or eggs. These tumors are usually made up of more than one type of cancer cell. Although they most often occur in the testicles or ovaries, they can also be found in the central nervous system (such as in the pineal gland in the brain), the mediastinum, or the abdomen. In children they can occur in the tailbone and be considered congenital (present from birth). Since germ cell tumors are not the only cancers which produce AFP, an elevated serum AFP may not be diagnostic for germ cell tumors in those individuals with poorly differentiated cancers. Seminomas rarely have an elevated AFP whereas nonseminomatous germ cell tumors have an elevated AFP in the majority of cases.

In a 2021 retrospective review by Fero and colleagues, the authors reported the incidence and clinical factors of elevated AFP in those with pure histologically diagnosed seminomas. There were 18,616 people identified over a 4 year period with diagnosis of germ cell tumor. Of those, 9849 (53%) had histology of seminoma, and 821 (8.3%) of those had an elevated AFP. A 2010 guideline on Uses of Serum Tumor Markers in Adult Males with Germ Cell Tumors, by the American Society of Clinical Oncology (ASCO) recommends evaluation of AFP in individuals suspected of having a testicular germ cell tumor before diagnostic orchiectomy to assist in establishing the diagnosis.

A 2013 study by Massard assessed whether an early decline in serum tumor markers is associated with outcome in the salvage setting. There were 297 participants with either relapsed or progressive disseminated non-seminomatous germ-cell tumors after first-line chemotherapy for metastatic disease. Participants were assigned to either a training set (n=185) or the external validation set (n=112). AFP was assessed at baseline and 6 weeks after chemotherapy. In the training set, a favorable AFP decline resulted in a 2-year progression-free survival (PFS) of 45%. An unfavorable AFP decline resulted in a 2-year PFS of 17%. In the validation set, favorable decline in AFP resulted in 43% PFS with an unfavorable AFP decline resulting in 27% PFS.

HCC
HCC is a primary malignancy of the liver and the most common form of liver cancer. Diagnosis may be difficult and often requires multiple testing modalities. Those with disorders of the liver (for example, cirrhosis, hepatitis B and C, and alcohol abuse) are at higher risk of developing HCC. Hepatitis C virus is a viral infection which causes inflammation of the liver. It can cause serious liver damage. AFP can be elevated in those with active hepatitis C virus. AFP is the most common serum marker used for HCC and can also be elevated in those with HCC.

In addition to AFP, the AFP-L3% assay is intended for use in the assessment of risk for the development of HCC in those individuals with chronic liver diseases. In a 2007 study, Leerapun and colleagues reported the diagnostic utility and performance characteristics of the AFP-L3% assay. In this retrospective review there were 272 individuals included; 166 had HCC and 106 had benign liver disease (chronic liver disease = 77, benign liver mass = 29). The individuals who had total AFP of 10-200 ng/ml, the AFP-L3% cut-off of less than 10% showed a sensitivity of 71% and a specificity of 63% in diagnosing HCC. For those who had an AFP-L3% greater than 35, the sensitivity was 33% with specificity of 100% for diagnosing HCC. The AFP-L3% assay could be used in combination with AFP to confirm the diagnosis of HCC.

The NCCN published guidelines in 2023 for hepatocellular carcinoma. They recommend AFP testing for those individuals considered to be at high risk for HCC. For those with and without cirrhosis, risk factors include hepatitis B, hepatitis C, alcohol abuse, genetic hemochromatosis, non-alcoholic fatty liver disease, stage 4 primary biliary cholangitis, or alpha-1-antitrypsin deficiency. The NCCN recommendations are based on the 2018 practice guidance for the Diagnosis, Staging, and Management of Hepatocellular Carcinoma published by the American Association for the Study of Liver Diseases. Recent approval for gene therapy for hemophilia b labeling advises regular alpha-fetoprotein testing for those with hepatocellular carcinogenicity.

Mediastinal Mass and Thymoma or Thymic Cancer
The mediastinum is the area in the middle of the chest which separates the lungs. A mass in this area could be caused from the thymus gland, Thymomas or thymic cancer are a type of cancer that affects the thymus. The 2024 NCCN guideline for thymomas and thymic cancers recommends AFP testing as the initial evaluation of a mediastinal mass.

Ovarian Cancer

In the 2023 NCCN clinical practice guideline for ovarian cancer, they recommend tumor markers (including AFP) as part of a preoperative workup as they can be elevated with certain less common ovarian cancers. AFP is commonly used to monitor for germ cell tumor recurrence.

Pelvic Mass
The 2023 NCCN guideline for ovarian cancer also recommends those under the age of 35 with a pelvic mass should have an AFP test to assess for germ cell tumors. AFP can be elevated in individuals with certain less common ovarian cancers and can correlate with disease course. Also, high levels of AFP can be correlated with a higher likelihood of malignancy. For those with germ cell tumors, elevated AFP levels and poor decline in serum AFP levels following treatment may be associated with worse outcomes.

Retroperitoneal Mass
The retroperitoneum is the area in the back of the abdomen behind the peritoneum. The peritoneum is the tissue which lines the abdominal wall and covers organs in the abdomen. Organs in the retroperitoneum include the adrenal glands, aorta, kidneys, esophagus, ureters, pancreas, rectum, and parts of the stomach and colon. A mass in the retroperitoneal area can affect any of the organs listed. A 2010 guideline on Uses of Serum Tumor Markers in Adult Males with Germ Cell Tumors, by the American Society of Clinical Oncology (ASCO) recommends evaluation of AFP in individuals who present with retroperitoneal tumor. An elevated serum AFP may be considered sufficient for diagnosis of germ cell tumor and may stratify risk and guide treatment.

Testicular Cancer or Suspicious Testicular Mass
In 2019 the American Urological Association (AUA) published their guidelines on the Diagnosis and Treatment of Early Stage Testicular Cancer. They recommend testing for elevated AFP for individuals with a solid mass in the testis suspicious for cancer (moderate recommendation, grade C). The AUA 2024 amendment document does not address AFP testing.

According to the NCCN 2023 guideline for testicular cancer, a mildly elevated, non-rising AFP may not be indicative of a germ cell tumor and should not be used as the sole indication to treat. However, tumor markers (including AFP) can help determine the prognosis and assess treatment outcomes in those with testicular germ cell tumors.

Definitions

Germ cell tumor: Tumors which form from germ cells, they are embryonic cells that develop into reproductive organs.

Hepatocellular carcinoma: The most common type of liver cancer.

Neural tube: Forms the early brain and spine. When it does not close properly, neural tube defects can occur.

Thymus gland: A small organ in the upper chest which is part of the lymphatic system.

References

Peer Reviewed Publications:

1. Dong N, Gu H, Liu D, et al. Complement factors and alpha-fetoprotein as biomarkers for noninvasive prenatal diagnosis of neural tube defects. Ann N Y Acad Sci. 2020;1478(1):75-91.
2. Fero KE, Lec PM, Sharma V, et al. When is a seminoma not a seminoma? The incidence, risk factors and management of patients with testicular seminoma with discordant elevated serum alpha-fetoprotein. Urology. 2021; 157:188-196.
3. Leerapun A, Suravarapu SV, Bida JP, et al. The utility of Lens culinaris agglutinin-reactive alpha-fetoprotein in the diagnosis of hepatocellular carcinoma: evaluation in a United States referral population. Clin Gastroenterol Hepatol. 2007; 5(3):394-402.
4. Massard C, Kramar A, Beyer J, et al. Tumor marker kinetics predict outcome in patients with relapsed disseminated non-seminomatous germ-cell tumors. Ann Oncol. 2013; 24(2):322-328.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Agency for Healthcare Research and Quality. Imaging techniques for the surveillance, diagnosis, and staging of hepatocellular carcinoma. Evidence-based Practice Center Systematic Review Protocol. 2013 July. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/liver-cancer_research-protocol.pdf. Accessed on January 10, 2024.
2. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. Indications for outpatient antenatal fetal surveillance: ACOG Committee Opinion, Number 828. Obstetrics and gynecology. 2021; 137(6):e177-e197.
3. Gilligan TD, Seidenfeld J, Basch EM, et al. American Society of Clinical Oncology clinical practice guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol. 2010; 28(20):3388-404.
4. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Practice Guideline Hepatology. 2018; 68(2):723-750.
5. NCCN Clinical Practice Guidelines in Oncology®. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. January 10, 2024.
    - Hepatocellular Carcinoma (V2.2023). Revised September 14, 2023.
    - Occult Primary (V1.2024). Revised September 6, 2023.
    - Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (V2. 2023). Revised June 2, 2023.
    - Testicular Cancer (V1.2023). Revised January 26, 2023.
    - Thymomas and Thymic Carcinomas (V1.2023). Revised November 21, 2023.
6. Stephenson A, Bass EB, Bixler RB et al. Diagnosis and treatment of early stage testicular cancer: AUA guideline amendment 2023. J Urol 2024; 2(111):20-25.
7. Stephenson A, Eggener SE, Bass EB, et al. Diagnosis and treatment of early stage testicular cancer: AUA guideline. J Urol. 2019; 202:272-281.

Websites for Additional Information

1. National Cancer Institute. Alpha-fetoprotein. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/alpha-fetoprotein. Accessed on January 10, 2024.
2. National Cancer Institute. Teratoma. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/teratoma. Accessed on February 16, 2024.

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AFP

History

Status	Date	Action
Reviewed	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Discussion/General Information, References, and Websites for Additional Information sections. Revised Coding section, added 82107 with related diagnosis codes.
New	02/16/2023	MPTAC review. Initial document development.