Anthem

Clinical UM Guideline

Subject: Gamma Glutamyl Transferase Testing
Guideline #: CG-LAB-29
Status: New

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Description

This document addresses laboratory testing of gamma glutamyl transferase (GGT) in blood.

Clinical Indications

Medically Necessary:

GGT testing using blood is considered **medically necessary** for any of the following indications:

A. To differentiate between sources of elevated alkaline phosphatase activity; **or**
B. To evaluate liver function, injury or disease in individuals with at least one of the following:
   1. Known or suspected hepatobiliary disease; **or**
   2. Alcohol use disorder; **or**
   3. Substance use disorder; **or**
   4. Therapy with medication that has potentially toxic effects on the liver; **or**
   5. Exposure to hepatotoxins; **or**
   6. Infections that may cause liver injury (for example, viral hepatitis, amoebiasis, tuberculosis, and similar infections); **or**
   7. Pancreatic disease; **or**
   8. Gastrointestinal disease; **or**
   9. Liver transplantation; **or**
   10. Primary or secondary malignant neoplasms; **or**
   11. Diseases or conditions known to have liver involvement (for example, diabetes mellitus, sarcoidosis, amyloidosis, disorders of iron and mineral metabolism, lupus, hypertension, heart failure).

Not Medically Necessary:

GGT testing using blood is considered **not medically necessary** when the above criteria are not met.

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.

When services are Medically Necessary:

CPT	
82977	Glutamyltransferase, gamma (GGT)

ICD-10 Diagnosis	
A02.0-A04.9	Other salmonella infections, shigellosis, other bacterial intestinal infections
A06.0-A09	Amebiasis, other protozoal intestinal diseases, viral and other intestinal infections
A15.0-A19.9	Tuberculosis
A20.0-A20.9	Plague
A22.7	Anthrax sepsis
A26.0-A27.9	Erysipeloid, leptospirosis
A30.0-A39.9	Other bacterial diseases
A40.0-A41.9	Streptococcal/other sepsis
A42.0-A42.9	Actinomycosis
A48.0-A49.9	Other bacterial diseases not elsewhere classified/unspecified
A51.0-A53.9	Early/late/other and unspecified syphilis
A69.20-A69.29	Lyme disease
A70	Chlamydia psittaci infections
A75.0-A79.9	Rickettsioses
A95.0-A95.9	Yellow fever
B00.0-B00.9	Herpesviral [herpes simplex] infections
B15.0-B19.9	Viral hepatitis
B20	Human immunodeficiency virus [HIV] disease
B25.0-B27.99	Cytomegaloviral disease, mumps, infectious mononucleosis
B37.0-B37.9	Candidiasis
B39.4	Histoplasmosis capsulati, unspecified
B50.0-B54	Malaria [plasmodium falciparum, vivax, malariae, other]
B57.0-B58.9	Chagas' disease, toxoplasmosis
B65.0-B67.99	Schistosomiasis, other fluke infections, echinococcosis
B97.0-B97.89	Viral agents as the cause of diseases classified elsewhere
C00.0-C96.Z	Malignant neoplasms
D00.00-D09.9	In situ neoplasms
D10.0-D36.9	Benign neoplasms
D3A.00-D3A.8	Benign neuroendocrine tumors

D37.01-D48.9	Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes
D49.0-D49.9	Neoplasms of uncertain behavior
D57.00-D57.819	Sickle-cell disorders
D65	Disseminated intravascular coagulation [defibrination syndrome]
D68.311-D68.4	Hemorrhagic disorder due to circulating anticoagulants, acquired coagulation factor deficiency
D73.0-D73.9	Diseases of spleen
D81.0-D81.9	Combined immunodeficiencies
D84.0-D86.9	Other immunodeficiencies, sarcoidosis
E08.00-E13.9	Diabetes mellitus
E21.0-E21.3	Hyperparathyroidism
E40-E46	Malnutrition
E55.0-E56.9	Vitamin D, other vitamin deficiencies
E63.0-E64.9	Other nutritional deficiencies, sequelae of malnutrition and other nutritional deficiencies
E66.01-E66.9	Overweight and obesity
E70.0-E88.9	Metabolic disorders
F10.10-F19.99	Mental and behavioral disorders due to psychoactive substance use
F50.00-F50.9	Eating disorders
F55.0-F55.8	Abuse of non-psychoactive substances
G40.001-G40.919	Epilepsy and recurrent seizures
G62.0-G62.1	Drug-induced/alcoholic polyneuropathy
G71.11-G71.19	Myotonic disorders
I10-I1A.0	Hypertensive diseases
I20.0-I25.9	Ischemic heart disease
I27.0-I27.9	Other pulmonary heart diseases
I50.1-I5A	Heart failure, non-ischemic myocardial injury (non-traumatic)
I63.00-I63.9	Cerebral infarction
I80.00-I82.91	Phlebitis and thrombophlebitis, portal vein thrombosis, other venous embolism and thrombosis
I85.00-I85.11	Esophageal varices
J17	Pneumonia in diseases classified elsewhere
J44.0-J44.9	Other chronic obstructive pulmonary disease
K50.00-K52.9	Noninfective enteritis and colitis
K55.011-K59.9	Other diseases of intestines [vascular, paralytic ileus, obstruction, irritable bowel syndrome, other functional disorders]
K63.1-K63.9	Other diseases of intestine
K65.0-K68.9	Disorders of the peritoneum and retroperitoneum
K70.0-K77	Diseases of liver
K80.00-K87	Diseases of gallbladder, biliary tract and pancreas
M04.1-M04.9	Autoinflammatory syndromes
M1A.10X0-M1A.19X1	Lead-induced chronic gout
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M35.00-M35.09	Sjögren syndrome
M83.0-M83.9	Adult osteomalacia
N00.0-N19	Glomerular diseases, renal tubulo-interstitial diseases, acute kidney failure and chronic kidney disease
N25.0-N29	Other disorders of kidney and ureter
N61.20-N61.23	Granulomatous mastitis
O10.011-O16.9	Edema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
O24.011-O25.3	Pre-existing, gestational or unspecified diabetes and malnutrition in pregnancy
O26.611-O26.649	Liver and biliary tract disorders in pregnancy, childbirth and the puerperium
O30.001-O31.8X99	Multiple gestation, complications specific to multiple gestation
O99.210-O99.215	Obesity complicating pregnancy, childbirth and the puerperium
P35.0-P39.9	Infections specific to the perinatal period
P76.0-P78.9	Digestive system disorders of newborn
Q85.00-Q85.09	Neurofibromatosis
R10.0-R11.2	Abdominal and pelvic pain, nausea and vomiting
R16.0-R17	Hepatomegaly and splenomegaly not elsewhere classified, unspecified jaundice
R29.700-R29.742	National Institutes of Health Stroke Scale (NIHSS) score
R40.0-R40.4	Somnolence, stupor and coma
R74.01-R74.9	Abnormal serum enzyme levels
T36.0X1A-T65.94XS	Poisoning by, adverse effects of and underdosing of drugs, medicaments and biological substances; toxic effects of substances chiefly nonmedicinal as to source
T78.00XA-T78.1XXS	Anaphylactic reaction due to food, other adverse food reactions
Z05.0-Z05.9	Encounter for observation and evaluation of newborn for suspected diseases and conditions ruled out
Z08-Z09	Encounter for follow-up examination after completed treatment for malignant neoplasms, for conditions other than malignant neoplasm
Z19.1-Z19.2	Hormone sensitivity malignancy status
Z22.7	Latent tuberculosis
Z48.23	Encounter for aftercare following liver transplant
Z68.23-Z68.45	Body mass index [BMI] 23.0-70 or greater, adult
Z68.53-Z68.54	Body mass index [BMI] pediatric, 85th percentile to greater than or equal to 95th percentile for age
Z79.01-Z79.899	Long term (current) drug therapy
Z85.00-Z87.19	Personal history of malignant neoplasm, certain other diseases and conditions
Z94.4	Liver transplant status

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

Discussion/General Information

Gamma glutamyl transferase (GGT), also known as gamma glutamyl transpeptidase, is an enzyme found throughout the body but predominantly in the liver. It is a cell membrane protein produced in the cells lining the bile duct system in the liver. Normally GGT plays an important role in reducing oxidative stress by facilitating generation of glutathione, a potent antioxidant. GGT also aids in the detoxification of drugs and other xenobiotics in the liver. When the liver is injured, GGT may leak from damaged cells into the bloodstream.

Since the 1960s, measurement of GGT in blood has been used to assess liver function and injury (Brennan, 2022). GGT is commonly measured in either blood serum or plasma. Generally, the higher the level of GGT, the greater the level of damage to the liver. Liver conditions that can cause elevated GGT include hepatitis, cholestasis, and cirrhosis. Hepatitis is often associated with infection by viruses, bacteria or parasites but can also be caused by exposure to liver toxins. The highest levels of GGT are usually seen in patients with cholestasis due to bile duct strictures or stones. Cirrhosis is commonly associated with alcohol use disorder. Even in the absence of cirrhosis, GGT levels tend to be higher in people who regularly drink alcohol, compared with people who drink in moderation or only on occasion. GGT levels may be used to monitor alcohol-drinking habits and follow the evolution of alcoholic liver disease (Neuman, 2020).

GGT is very sensitive for the diagnosis of liver injury, although it has poor specificity in identifying particular causes. GGT is abnormally high in the majority of individuals with liver disease irrespective of pathogenesis. However, other extra-hepatic diseases and conditions can also contribute to elevated GGT such as pancreatitis, diabetes mellitus, obesity, malnutrition, hypertension, stroke, and chronic obstructive pulmonary disease (Brennan, 2022; Koenig, 2015; Neuman, 2020).

GGT is associated with the metabolic syndrome (MetS) and is often elevated in individuals with nonalcoholic fatty liver disease (NAFLD) (Neuman, 2020). MetS consists of obesity, hypertension, impaired glucose tolerance and hyperlipidemia; NAFLD is the hepatic manifestation of MetS. Additional organ systems are involved in NAFLD related to other components of MetS including kidney, gastrointestinal, and cardiovascular systems. Elevated GGT can be associated with risk to all of these systems including chronic kidney disease, end stage renal disease, chronic intestinal disorders, coronary heart disease and chronic heart failure (Ess, 2011; Lee, 2020; Ndrepepa, 2018; Neuman, 2020; Shen, 2017; Voss, 2021).

Primary and secondary forms of liver cancer can be associated with increased GGT (Whitfield, 2001). In healthy adults, an elevated serum GGT is associated with a higher risk of many cancers, especially liver cancer (Strasak, 2008; Mok, 2016). Elevated GGT may also be an indicator of an increased risk of other cancers including prostate, breast, esophageal and colorectal (Choi, 2017; Hong, 2020; Van Hemelrijck, 2011). There is evidence that GGT is a prognostic biomarker in individuals with cancer, with elevated serum GGT predicting worse outcomes (Ma, 2014; Takemura, 2021; Yin, 2013).

GGT is used as a biomarker to monitor liver function after transplant. Early elevated serum GGT after liver transplantation is associated with improved survival (Alkozai, 2014). Trends in GGT levels have been reported to be useful in detection of rejection of transplanted livers (Hickman, 1994).

Increased GGT can be an indicator of drug-induced liver injury (Weber, 2021). Anticonvulsant drugs such as phenytoin, phenobarbitone, carbamazepine and valproic acid are associated with elevated GGT. Other types of drugs such as the diuretic furosemide, the gastric acid reducer cimetidine, anti-acne medication isotretinoin, and barbiturates can likewise elevate GGT (Brennan, 2022). The commonly used pain reliever acetaminophen can cause liver toxicity and increase GGT levels as well (Ahlers, 2011; McClain, 1999). Some drugs used recreationally or by people with substance use disorder can also lead to liver injury and increased liver enzymes, including cannabis, kratom, cocaine and anabolic steroids (Fernandes, 2019; Silva, 1991; Solimini, 2017; Watkins, 2021).

Exposure to a wide range of environmental chemicals such as the fungicide hexachlorobenzene and the insecticide DDT can produce increased serum GGT (Whitfield, 2001). Heavy metals including lead, mercury, cadmium and copper can prompt significant increases in GGT (Yorita Christensen, 2013). Studies of people exposed to polychlorinated biphenyls (PCBs) have reported increases in GGT that are suggestive of liver damage.

Since the GGT test alone cannot diagnose a specific cause of liver disease, it is usually performed in conjunction with other liver function tests. The British Society of Gastroenterology recommends that “Initial investigation for potential liver disease should include bilirubin, albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT), together with a full blood count if not already performed within the previous 12 months. (level 2b, grade B)” (Newsome, 2018).

Bone disease and liver disease can both lead to elevated levels of ALP. A GGT test along with an ALP test can help distinguish between these disorders. High levels of both enzymes together likely indicate liver disease, while high levels of ALP and low or normal GGT indicate a probable bone disorder. The 2017 guideline of the American College of Gastroenterology for Evaluation of Abnormal Liver Chemistries (Kwo, 2017) states that “To confirm hepatic origin of alkaline phosphatase, the canalicular enzyme GGT may be measured. An elevated GGT suggests that the alkaline phosphatase elevation is of hepatic origin.”

Definitions

Canalicular: Pertaining to the thin capillaries that carry bile in the liver.

Cirrhosis: Scarring of the liver.

Cholestasis: Reduced or stopped bile flow usually due to bile duct obstruction.

Glutathione: A tripeptide made from the amino acids glycine, cysteine and glutamic acid that is found in all mammalian tissues and is responsible for oxidative stress mitigation.

Hepatitis: Inflammation of the liver.

Hepatobiliary: Pertaining to the liver, bile ducts, or gallbladder.

Xenobiotic: A chemical substance that is foreign to the body such as pesticides, food additives, industrial chemicals and environmental pollutants.

References

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
	12/06/2023	Revised References section.
	09/27/2023	Updated Coding section with 10/01/2023 ICD-10-CM changes; added I1A.0 to end of range and O26.649 to end of range.
New	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.
