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Gamma-glutamyl Transferase Testing in Adults

Policy Number: AHS – G2173 – Gamma-glutamyl Transferase Testing in Adults	Original Effective Date: 05/15/2022 Current Effective Date: 02/01/2026

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I. Policy Description

Gamma-glutamyl transferase (GGT), also known as gamma-glutamyl transpeptidase (GGTP),[1,2] is an enzyme that has a half-life of between fourteen and twenty-six days and is present in the cell membrane of many different tissue types, including the heart, brain, seminal vesicles, kidneys, bile duct, spleen, and gallbladder.[3,4] GGT is traditionally considered a predictive marker for liver dysfunction, bile duct ailments, and alcohol consumption.[5] However, new research suggests that GGT may be useful as an early predictive marker for several other conditions including heart failure, arterial stiffness, arterial plaque, gestational diabetes, atherosclerosis, several infectious diseases, and numerous types of cancer.[5] Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Related Policies

Policy Number	Policy Title
AHS-G2036	Hepatitis Testing
AHS-G2110	Serum Marker Panels for Hepatic Fibrosis in the Evaluation and Monitoring of Chronic Liver Disease

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

This policy is specific to individuals 18 years of age or older. Criteria below do not apply to individuals less than 18 years of age.

1) For individuals with elevated alkaline phosphatase activity, serum GGT testing no more than once every two weeks **MEETS COVERAGE CRITERIA**.

2) To assess for liver injury, function, and/or disease, serum GGT testing no more than once every two weeks **MEETS COVERAGE CRITERIA** for individuals with at least one of the following conditions:

   a) For individuals with chronic alcohol use.

   b) For individuals on a long-term drug therapy known to have a potential for causing liver toxicity.

   c) For individuals with exposure to hepatotoxins.

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d) For individuals with viral hepatitis, amoebiasis, tuberculosis, psittacosis, or similar infections that may cause hepatic injury.

e) For individuals with primary or secondary malignant neoplasms of the digestive system.

f) For individuals with diabetes mellitus.

g) For individuals with malnutrition.

h) For individuals with disorders of iron and mineral metabolism.

i) For individuals with sarcoidosis.

j) For individuals with amyloidosis.

k) For individuals with lupus.

l) For individuals with hypertension.

m) For individuals with gastrointestinal disease.

n) For individuals with pancreatic disease.

o) To assess liver function subsequent to liver transplantation.

3) For asymptomatic individuals, serum GGT testing during a wellness visit or a general exam without abnormal findings **DOES NOT MEET COVERAGE CRITERIA**.

IV. Table of Terminology

Term	Definition
AACC	American Association of Clinical Chemistry
ACG	American College of Gastroenterology
AF	Atrial fibrillation
ALEH	American Association for the Study of the Liver
ALP	Alkaline phosphatase
ALT	Aminotransferase
ANCA	Anti-Neutrophilic Cytoplasmic Autoantibody
AP	Alkaline phosphatase
APRI	Aspartate aminotransferase-to-platelet ratio index
ASAM	American Society of Addiction Medicine
AST	Aminotransferase
ASV	Average successive variability
BP	Blood pressure
BSG	British Society of Gastroenterology
CAG	Canadian Association of Gastroenterology
CAGE	Cut, Annoyed, Guilty, and Eye-Opener
CBC	Complete blood count
CDT	Carbohydrate-deficient transferrin
CHB	Chronic Hepatitis B

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CHD	Coronary heart disease
CKD	Chronic kidney disease
CLD	Chronic Liver Disease
CLIA ’88	Clinical laboratory improvement amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CSSC	Clinical Services and Standards Committee
CV	Coefficient of variation
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DB	Direct bilirubin
DILI	Drug-induced liver injuries
EASL	European Association for Study of Liver
ESRD	End-stage renal disease
FBC	Full blood count
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
GGT	Gamma-glutamyl transferase
GGTP	Gamma glutamyl transpeptidase
GPR	Gamma-glutamyl transpeptidase-to-platelet ratio
HDL-C	High-density lipoprotein cholesterol
HIBD	High-intensity binge drinking
INR	International normalized ratio
KIM-1	Kidney injury molecule-1
LDT	Laboratory-developed test
LFT	Liver function test
LSM	Liver stiffness measurement
MCV	Mean corpuscular volume
Mets	Metabolic syndrome
MI	Myocardial infarction
MR	Mendelian randomization
NAFLD	Non-alcoholic fatty liver disease
NCD	National coverage determination
NSAIDs	Nonsteroidal anti-inflammatory drugs
PBC	Primary biliary cholangitis
PLT	Platelet
PSCI	Post-stroke cognitive impairment
PT	Prothrombin time
TBL	Total bilirubin
TC	Total cholesterol
TE	Transient elastography
TRG	Triglycerides

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V. Scientific Background

Gamma-glutamyl transferase (GGT) is a cell surface enzyme found throughout the body. GGT cleaves extracellular glutathione (an antioxidant) and other gamma-glutamyl compounds to increase the availability of amino acids for intracellular glutathione synthesis purposes. GGT also plays an important role in maintaining glutathione homeostasis, as well as in providing defense against oxidative stress.[6] The measurement of circulating GGT is often used as a diagnostic tool for the identification of liver diseases, biliary diseases, and alcohol consumption. This is because GGT is very abundant in the liver; considerable GGT concentrations are also found in the intestine, kidney, prostate, and pancreas.[7] While GGT measurement may not be useful in the diagnosis of specific types of liver disease, it is one of the best predictors of overall liver mortality.[7] Additional research has shown that elevated GGT concentrations in the serum may also be associated with an increased risk of type 2 diabetes, gestational diabetes, hypertension, stroke, coronary heart disease, and cancer.[5] Abnormal GGT levels are also identified in anorexia nervosa, Guillain-Barré syndrome, hyperthyroidism, obesity, dystrophica myotonica,[8] and cigarette smoking.[9] Certain drugs may lead to unusual GGT levels in the blood as well. It has been reported by the AACC (2024) that drugs such as phenytoin, carbamazepine, barbiturates (including phenobarbital), lipid-lowering drugs, antibiotics, antifungal agents, anticoagulants, immunosuppressive medications, antidepressants, hormones, nonsteroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, testosterone, and histamine receptor blockers may cause an increase or decrease in GGT levels. LabCorp (2021) does not recommend ordering a GGT test if the patient is currently taking phenytoin or phenobarbital since these medications may lead to false elevations in GGT.

Gamma-glutamyl transferase measurement may also be a useful secondary measure to assist with liver diagnoses. Alkaline phosphatase (ALP) is an enzyme found throughout the body and is typically identified in the liver or bone. Meanwhile, GGT is not found in bone.[2] Therefore, if elevated ALP levels are detected in a patient, physicians may use a high GGT level to rule out bone disease as the cause of an elevation of ALP; however, if GGT is low or normal, then elevated ALP levels are more likely to be caused by bone disease.[9] This means that elevated GGT levels suggest that elevated ALP levels are of a hepatic origin.[11]

Koenig and Seneff (2015) report that population wide GGT levels have increased steadily in the United States over the last three decades. This may factor into an increased disease risk over time. It has been hypothesized that GGT levels are increasing due to a greater exposure to environmental and endogenous toxins which result in increased levels of oxidative and nitrosative stress.[5] Elevated serum GGT levels are known markers of oxidative stress, which occurs when an imbalance is present between antioxidants and free radicals in the body.[12] Simple lifestyle changes, such as avoiding exposure to toxic chemicals and limiting iron intake, may help to lower GGT levels.

Liver function tests are blood tests typically ordered as a panel rather than solitarily. These tests measure the level of several liver enzymes in serum or plasma samples. The liver enzymes frequently measured to detect liver abnormalities include serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, and bilirubin; other liver tests may incorporate the measurement of GGT, albumin and prothrombin time.[11] Some report that GGT is only occasionally included in a liver function testing panel,[3] while others report that GGT is still a commonly measured serum liver enzyme.[13] Nevertheless, Dillon and Miller (2016) conclude that GGT should be measured on liver functioning test panels “some of the time.” This is likely because GGT measurement is not very specific, and its elevation will typically not help the physician to differentiate between diseases.

GGT and Liver-Related Diseases

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The liver is an organ in the abdomen which detoxifies metabolites, manufactures proteins, and generates biochemicals required for growth and digestion. Many types of liver disease exist, such as hepatitis A, hepatitis B, hepatitis C, cirrhosis, fatty liver disease, and liver cancer to name a few. GGT is elevated in the blood in most diseases that cause damage to the liver, including hepatitis and cirrhosis.[9] Primary biliary cholangitis (PBC), drug-induced liver injury (DILI), alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD) are the main causes of the abnormal GGT in clinic. GGT levels have different characteristics in different liver diseases. For instance, abnormal GGT in PBC and DILI was associated with cholestasis; in ALD, it was associated with both oxidative stress and cholestasis, and in NAFLD, it was associated with oxidative stress.[14]

Hepatitis C is a viral infection that targets the liver and causes inflammation. An increase in serum GGT levels is seen in approximately 30% of patients with a chronic hepatitis C infection; GGT levels will peak in the second or third week of illness and may remain elevated for up to six weeks.[8] Further, the GGT-to-platelet ratio has been identified as a reliable laboratory marker in the prediction of liver fibrosis stage in patients with a chronic hepatitis B infection; this ratio was more reliable than AST-to-platelet ratio index (APRI) and fibrosis-4 score (FIB-4).[15,16] The FIB-4 score is a non-invasive scoring system based on several laboratory tests to estimate the amount of scarring in the liver. GGT is also acknowledged as a more specific tool for the identification of non-alcoholic fatty liver disease than ALT.[3] Finally, GGT has also been identified as a useful prognostic tool for patients with hepatocellular carcinoma, the most common type of primary liver cancer.[17]

Lothar (2022) notes that acute viral hepatitis A and B are usually self-limiting and that almost all cases of hepatitis A and 95% of cases of hepatitis B are cured. In contrast, about 85% of acute hepatitis C infections proceed into a chronic form. “During the acute phase of hepatitis, the aminotransferases do not allow any conclusion as to whether hepatitis will be cured or develop into a chronic form in individual cases. The ALT and GGT are the last enzymes to return to normal levels. Monitoring is recommended, including measurements every 2 weeks. If the enzyme levels have not normalized within 6 months or show recurrent elevations, a chronic form must be expected. This always applies if no antibodies against HBsAg and HBeAg are produced or if virus persistence is detected.”[18]

GGT and Bile Duct Diseases

The bile ducts are thin tubes that connect the liver to the small intestine. These ducts help to transport bile from the liver and gallbladder to the small intestine; the bile then assists with the digestion of fats in foods. Singh, et al. (2006) report that in 55 patients aged 23 to 45 years, “GGT and ALP levels were normal in patients of chronic cholecystitis with cholelithiasis but significantly high in patients of common bile duct obstruction.”

In a study conducted by Haijer, et al. (2023), 235 patients with chronic extrahepatic cholestasis due to pancreatic cancer, cholangiocarcinoma, or papillary carcinoma were metabolically examined to determine the relationship between high serum GGT activity and cholestatic itch. The findings indicate that there is an inverse association between the two variables meaning that as GGT increases, the prevalence of itch decreases.[19] This justifies GGT testing in routine panels for liver and biliary disorders as evidence suggests that serum GGT activity may not only reflect cholestasis but could potentially correlate with clinical symptoms in patients with chronic extrahepatic cholestasis. In a broader scope, this biomarker can make a case for patient management and routine clinical use for patients with those conditions.[19]

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GGT and Kidney/Renal Diseases

The kidneys filter the body's blood by removing waste and maintaining electrolyte balance. Acute kidney or renal injuries are sudden episodes of kidney damage or failure. Lippi, et al. (2018) showed that, in dogs with acute kidney injury, significantly higher GGT urine levels were identified.

Chronic kidney disease (CKD) occurs when the kidneys are no longer able to filter blood correctly. Several liver enzyme serum levels, including GGT, have been measured in patients with CKD. However, one analysis reported that relevant GGT data were scant and that "those found reported that there were no differences between the patients with or without chronic kidney disease."[21] Noborisaka, et al. (2013) researched elevated serum GGT levels in cigarette smokers and monitored the development of CKD. The authors completed a 6-year retrospective study on 2,603 male workers and concluded that the "elevation of serum GGT in smokers, to a large extent, depends on the associated alcohol consumption. Elevated GGT in smokers plays at least a partial role in the development of CKD, mainly proteinuria, and the underlying mechanisms remain to be elucidated."[22]

In another study, the authors claimed that GGT variability may be able to predict the risk of end-stage renal disease (ESRD). GGT variability was assessed using the average successive variability, standard deviation, and CV of serial measurements of GGT during the five years before the baseline examination. Subjects were divided into four quartiles and those in GGT ASV quartile four were older, more obese, and had higher BP and more comorbidities than those in quartile one. The metabolic variables got worse as the baseline GGT quartile increased. Overall, the implications of GGT levels were statistically significant, especially in women and in ESRD caused by diabetic nephropathy.[23]

GGT and Pancreatic Diseases

The pancreas is in the abdomen and helps to regulate blood sugar and digestion. Several disorders of the pancreas exist, including type 1 diabetes, type 2 diabetes, pancreatic cancer, and pancreatitis. Elevated GGT levels have been used as a prognostic factor to predict survival time in patients with unresectable pancreatic cancer.[24]

Pancreatitis occurs when the pancreas becomes inflamed due to its own digestive chemicals. Elevated GGT levels are often identified in patients with acute and chronic pancreatitis.[1] However, Gori, et al. (2019) recently researched the GGT to urinary creatinine ratio in dogs with acute pancreatitis and found no association with any outcome in the study.

GGT and Cancer

GGT levels are correlated with a myriad of chronic conditions and diseases. Emerging research suggests a relationship between GGT and certain types of cancers, specifically gastrointestinal. In a 2025 study, Ramandi, et al. (2025) conducted a meta-analysis of various studies that explored varying GGT levels' effects on the incidence of GI cancers and biliary duct cancers. Their findings conclude that higher GGT levels correlate with higher GI cancer incidence, especially in colorectal and hepatic cancers, furthering the need to investigate this biomarker's role in risk assessment for digestive cancers.[26]

Colorectal adenomas are precancerous growths, also known as polyps, that grow on the inner lining of the colon or rectum. Wang, et al. (2024) uncovered a linear relationship between GGT and the prevalence of advanced colorectal adenomas through a retrospective study in China. "Individuals with high GGT levels (≥50 U/L) had a 61% higher risk of advanced colorectal adenoma compared to those

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with low GGT levels (<50 U/L) (OR=1.61 [1.13–2.31]).”[27] This further reaffirms GGT’s potential role as a diagnostic marker for advanced colorectal adenomas.

GGT and Alcohol Consumption

Increased levels of GGT and alcohol consumption are often correlated. Still, this relationship varies between individuals. GGT concentrations may increase with only small amounts of alcohol consumption in some; on the other hand, only about 75% of chronic drinkers will have elevated GGT levels.[9] GGT assays have been widely used as an “index of liver dysfunction and marker of alcohol intake. The half-life of GGT is between 14 and 26 days and after stopping drink it returns to normal level in 4-5 weeks.”[4] Nivukoski, et al. (2019) report that regular alcohol use is associated with increased GGT and ALT levels. Choe, et al. (2019) report that GGT has low sensitivity as a blood biochemical marker of excessive alcohol intake, but the combined use of the CAGE questionnaire (a four-question questionnaire widely used to screen for alcohol problems) and the measurement of serum GGT is a useful tool for alcohol dependence screening.

GGT and Metabolic Syndrome-Related Risk

Metabolic syndromes are a group of conditions which include high blood sugar, high blood pressure (hypertension), obesity, and abnormal cholesterol levels. GGT has been identified as a biomarker for metabolic syndrome risk.[30] Further, Lee, et al. (2019) report that GGT levels are significantly higher in subjects with a metabolic syndrome-related disorder than in healthy individuals. Metabolic syndromes collectively increase an individual’s risk for the development of many diseases, including heart disease, stroke, type 2 diabetes, and neurologic disorders.

Cardiovascular Disease

Cardiovascular disease (CVD), also known as heart disease, encompasses a group of conditions that narrow or block a blood vessel. This may lead to a heart attack, chest pain or stroke. Ndrepepa and Kastrati (2016) previously stated that while more research needs to be conducted, “Ample evidence suggests that elevated GGT activity is associated with increased risk of CVD such as coronary heart disease (CHD), stroke, arterial hypertension, heart failure, cardiac arrhythmias, and all-cause and CVD-related mortality. The evidence is weaker for an association between elevated GGT activity and acute ischemic events and myocardial infarction.” GGT has been widely identified as a biomarker for cardiovascular risk; in particular, high levels of GGT are associated with a greater risk of atherosclerotic cardiovascular disease,[30] and high GGT variability is associated with an increased risk of myocardial infarction and CVD related mortality.[32] GGT and the risk of atherosclerosis and coronary heart disease has been reported by Ndrepepa, et al. (2018) who report that “it remains unknown whether GGT plays a direct role in the pathophysiology of atherosclerosis and CHD or is merely a correlate of coexisting cardiovascular risk factors.” A study by Arasteh, et al. (2018) researched how serum GGT can be used as a predictive biomarker for stenosis severity in patients with coronary artery disease; these authors report a significant association between serum GGT activity and patients with coronary artery disease. GGT is considered an inexpensive and readily available biomarker that may provide more information than current tools on the prediction of coronary plaque burdens and plaque structures in young adults.[35]

Kim, et al. (2020) studied the relationship between GGT with subclinical atherosclerosis and cardiac outcomes in non-alcoholics which suggested elevated GGT is associated with high-risk feature atherosclerosis and poorer cardiac outcomes. “(1) in asymptomatic individuals, elevated serum GGT

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levels were significantly associated with atherosclerotic plaques, especially calcified plaques, even after adjustment for cardiovascular risk factors; (2) high serum GGT levels were an independent predictor of significant coronary atherosclerosis; (3) during a follow-up of median 5.4 years, individuals with high serum GGT levels experienced more cardiac events."[36] Research supports the continued use of GGT testing as a means of identifying cardiovascular risk factors and outcomes.

Cerebrovascular Accident

A cerebrovascular accident (CVA) or stroke occurs when a blood vessel leading to the brain ruptures or is blocked by a blood clot. There are three main types of CVAs: transient ischemic attack, ischemic stroke, and hemorrhagic stroke. A transient ischemic attack only lasts a few minutes and occurs because of a temporary blood vessel blockage to part of the brain. An ischemic stroke occurs when an artery in the brain is completely blocked, and a hemorrhagic stroke occurs when a ruptured blood vessel causes bleeding in the brain. Several studies have identified a relationship between GGT levels and both hemorrhagic and ischemic CVAs.[37-39]

Gamma-glutamyl transferase levels have been associated with functional outcomes after an aneurysm and/or stroke. Xu, et al. (2017) state that patients with high GGT levels are more likely to have a poor prognosis after aneurysmal subarachnoid hemorrhage than patients with lower GGT levels, suggesting that serum GGT may be an important prognostic factor for the prediction of aneurysm outcomes. Yang, et al. (2020) also report that high GGT levels were significantly associated with cardioembolic stroke through atrial fibrillation (irregular heartbeat). More, GGT variability has been associated with an increased risk of stroke in the general population,[32] and serum GGT levels have been associated with a greater risk of ischemic or nonembolic stroke in individuals older than 70 years.[39] Serum GGT levels were also found to be significantly elevated in patients who died from an acute ischemic stroke, and high GGT levels were associated with an increased risk of death in male patients with an intracranial arterial calcification.[38]

Type 2 Diabetes

Type 2 diabetes occurs when the body either does not produce enough insulin or resists insulin. Diabetes and GGT levels have been researched by Kaneko, et al. (2019) who state that the simultaneous elevation of GGT and ALT is significantly associated with the development of type 2 diabetes mellitus; confounding factors include alcohol consumption and obesity. Further, when GGT and ALT were included in type 2 diabetes risk prediction, the accuracy of the prediction was improved.[41] Kunutsor, et al. (2014) report that greater circulating GGT levels lead to an increased risk of type 2 diabetes. Higher GGT levels have also been associated with a greater amount of insulin resistance and therefore a higher risk of developing the disease.[30]

Nano, et al. (2017) analyzed 1125 cases of prediabetes and 811 cases of type 2 diabetes. A mendelian randomization (MR) study was performed and the authors found that "MR analyses did not support a causal role of GGT on the risk of prediabetes or diabetes. The association of GGT with diabetes in observational studies is likely to be driven by reverse causation or confounding bias. As such, therapeutics targeted at lowering GGT levels are unlikely to be effective in preventing diabetes."[43] This study is important as the results contradict other related studies. Another bidirectional mendelian randomization study analyzed data from 64,094 individuals with type 2 diabetes and 607,012 control subjects; no association between GGT and type 2 diabetes risk was found.[44] Further, Shibabaw, et al.

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(2019) also report that, based on their study, GGT levels were not significantly higher in type 2 diabetes patients compared to healthy controls (P=0.065).

Neurodegenerative Diseases

Abnormal GGT serum levels have been associated with an increased risk of neurodegenerative disease development. The serum GGT levels and Parkinson disease risk in men and women analyzed by Yoo, et al. (2020) suggest that the top quartile of patients with high serum GGT levels was associated with a lower Parkinson disease risk in men and a higher risk in women (n=20,895 Parkinson disease patients). Another study focused on Alzheimer disease showed that alcohol consumption was associated with an earlier Alzheimer disease age of onset survival and increased GGT blood concentration levels.[47] Alcohol consumption and GGT levels were not associated with late onset Alzheimer disease risk. Further, Hong, et al. (2020) recently reported that GGT variability may lead to an increased risk of all-cause dementia, and Yavuz, et al. (2008) found that GGT levels were increased significantly in Alzheimer disease patients in a cross-sectional study of 132 patients with Alzheimer disease and 158 healthy age-matched controls.

Clinical Utility and Validity

Individuals infected with hepatitis C virus are at an increased risk of developing hepatocellular carcinoma even after a sustained virological response is achieved. A total of 642 patients who had achieved a sustained virological response after a hepatitis C infection participated in this study; 33 participants developed hepatocellular carcinoma.[50] The data showed that "Baseline gamma-glutamyl transferase [GGT] levels strongly correlate with hepatocellular carcinoma development in non-cirrhotic patients with successful hepatitis C virus eradication," suggesting that serum GGT measurement may help to identify specific patients at high risk for developing hepatocellular carcinoma.[50]

Further research has demonstrated the utility of GGT as a diagnostic tool, especially regarding hepatitis. Hu, et al. (2017) Investigated the value of the gamma-glutamyltraspeptidase (GGT)-to-platelet (PLT) ratio (GPR) in diagnosing hepatic fibrosis in patients with chronic hepatitis B (CHB) using 390 untreated CHB participants. "The GPR, as a serum diagnostic index of liver fibrosis, is more accurate, sensitive, and easy to use than the FIB-4 and APRI (aspartate aminotransferase to platelet ratio index), and the GPR can significantly improve the sensitivity and specificity of hepatic fibrosis diagnosis in CHB when combined with the FIB-4 or APRI," indicating that serum GGT is an efficient laboratory practice over traditional methodologies.[51]

The relationship between liver enzymes and the risk of metabolic syndrome has been researched several times. Liu, et al. (2018) completed a large cross-sectional study with 1444 elderly participants to determine the association between liver enzymes and the risk of metabolic syndrome. The authors noted that "The prevalence of MetS [metabolic syndrome] and its components increased remarkably with increasing quartiles of alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) but not with aspartate aminotransferase (AST) in the elderly," showing that these liver enzymes as positively associated with metabolic syndrome development in elderly populations.[52] Another study completed by Wang, et al. (2017) assessed liver function and metabolic syndrome. This study enrolled 32,768 ostensibly healthy participants. Regarding GGT, the authors note that the metabolic syndrome risk "significantly increased … in high quartiles for both genders," suggesting that high GGT levels are a risk factor for the development of metabolic syndromes.[53]

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Ndrepepa, et al. (2018) compared GGT and ALP to see which was a better prognostic marker for mortality in patients with coronary heart disease. A total of 3768 patients with coronary heart disease participated in this three year study. The median value of GGT was 36.2 U/L and the median value of ALP was 69.3 U/L; "Overall, there were 304 deaths: 195 deaths occurred in patients with GGT >median (n = 1882) and 109 deaths occurred in patients with GGT ≤median (n = 1886) … According to ALP activity, 186 deaths occurred in patients with ALP >median (n = 1883) and 118 deaths occurred in patients with ALP ≤median (n = 1885)."[54] The authors conclude that GGT is a stronger prognostic marker for all-cause mortality in patients with coronary heart disease than ALP.

Conigrave, et al. (2002) completed a large, multicenter study with 1863 participants from five countries. This study aimed to measure carbohydrate-deficient transferrin (CDT) and GGT as markers of alcohol consumption. The authors concluded that "CDT was [a] little better than GGT in detecting high- or intermediate-risk alcohol consumption in this large, multicenter, predominantly community-based sample. As the two tests are relatively independent of each other, their combination is likely to provide better performance than either test alone. Test interpretation should take account sex, age, and body mass index."[55]

Rosoff, et al. (2019) studied the association between lipid and liver function enzymes and high-intensity binge drinking (HIBD). This cross-sectional study included 1519 participants. Binge drinking was defined according to the National Institute on Alcohol Abuse and Alcoholism. GGT was one of several enzymes measured (others included high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, total cholesterol (TC), triglycerides (TRG), ALT and AST). The authors state that "HIBD was associated with increased levels of HDL-C, TC, TRG, ALT, AST, and GGT."[56] Further, the authors also note that the largest increases associated with HIBD was found based on GGT levels, suggesting that "GGT may be most sensitive to HIBD."[56]

A study completed by Jousilahti, et al. (2000) researched the relationship between serum GGT levels, self-reported alcohol consumption and the risk of stroke. A total of 14,874 participants took part in this study over five years. The authors report that "serum GGT concentration was associated with the risk of total and ischemic stroke in both genders. There was also a significant association among men between GGT and the risk of intracerebral hemorrhage and among women between GGT and the risk of subarachnoid hemorrhage."[57] Further, a relationship was not found regarding self-reported alcohol and any type of stroke.

Yang, et al. (2020) studied the effects of GGT on stroke occurrence mediated by atrial fibrillation (AF). A total of 880 patients with acute ischemic stroke participated in this study, and AF was identified in 132 of the patients. The authors found that high GGT levels were not associated with large-artery atherosclerosis stroke but were associated with cardioembolic stroke. "The GGT level was significantly associated with cardioembolic stroke via AF. The results obtained in the present study may explain why GGT is associated with stroke."[40]

Hong, et al. (2020) completed a study to determine if there was a relationship between GGT variability and dementia risk in diabetes mellitus patients. This study included 37,983 diabetic patients who were diagnosed with dementia over a 6.12-year follow-up period. "In the fully adjusted model, the group with the highest quartile of GGT variability had a 19% increased risk of all-cause dementia when compared with the lowest quartile group."[48] The authors conclude by stating that in patients with diabetes mellitus, a high amount of GGT variability increased the risk of dementia regardless of other factors such as baseline GGT level.

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Lee, et al. (2020) examined the prognostic value of GGT variability in predicting the risk of stroke, myocardial infarction, and mortality in diabetic patients. A total of 698,937 patients greater than 40 years of age, with a history of diabetes, and without a history of stroke, MI, liver cirrhosis, or chronic hepatitis were included in the study. GGT variability was assessed as the average successive variability (ASV) of serial GGT measurements during the five years before the baseline examination. Subjects were stratified according to quartiles of baseline GGT and GGT ASV. The lower quartile contained subjects with lower GGT levels. According to the results, subjects in GGT ASV quartile four were more obese were more likely to have hypertension, dyslipidemia, or chronic kidney disease, and had a higher risk for stroke, MI, and mortality. On the other hand, subjects in quartile one were older, and had a higher prevalence of chronic kidney disease but a lower prevalence of hypertension and obesity. The authors conclude that GGT variability is associated with a higher risk of stroke, MI, and mortality; therefore, "it is important to identify the factors that contribute to increased GGT variability to extend the lives of patients with diabetes."[23]

Mujawar, et al. (2020) studied the use of salivary gamma-glutamyl transpeptidase as a biomarker in oral squamous cell carcinoma and precancerous lesions. Seventy-five patients with precancerous lesions or oral squamous cell carcinoma were enrolled in the study and assessed for GGT levels. Healthy participants had a GGT between 4 to 30 U/L, those with precancerous lesions had GGT between 39 to 65 U/L, and those with oral squamous cell carcinoma had GGT levels between 53 and 86 U/L. The authors conclude that it can be a reliable biomolecular marker in early detection and prevention of oral cancer that could be routinely employed in dental clinics.[58]

Li, et al. (2022) studied the association of GGT levels with the occurrence of post-stroke cognitive impairment (PSCI). A total of 1,957 participants with a minor ischemic stroke or transient ischemic attack were measured for GGT and they were categorized into four quartiles based on baseline GGT levels. Of the 1,957 participants, 671 (34.29%) patients experienced PSCI at three months of follow-up. The highest GGT level quartile group exhibited a lower risk of PSCI. The authors conclude that "serum GGT levels are inversely associated with the risk of PSCI, with extremely low levels being viable risk factors for PSCI."[59]

VI. Guidelines and Recommendations

American College of Gastroenterology (ACG)

Guidelines from the ACG recommend the following:

- "Before initiation of evaluation of abnormal liver chemistries, one should repeat the lab panel and/or perform a clarifying test (e.g., GGT if serum alkaline phosphate is elevated) to confirm that the liver chemistry is actually abnormal. (Strong recommendation, very low level of evidence).
- An elevation of alkaline phosphatase should be confirmed with an elevation in GGT. Given its lack of specificity for liver disease, GGT should not be used as a screening test for underlying liver disease in the absence of other abnormal liver chemistries. (Strong recommendation, very low level of evidence).
- An elevated alkaline phosphatase level of hepatic origin may be confirmed by elevation of gamma-glutamyl transferase (GGT) or fractionation of alkaline phosphatase
- Measurement of GGT may represent a complementary test to identify patterns of alcoholism or alcohol abuse, although GGT by itself is not helpful in establishing a diagnosis of alcoholic liver disease

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- If the alkaline phosphatase is elevated in the presence of other elevated liver chemistries, confirmation of hepatic origin is not required. With isolated alkaline phosphatase elevation, confirmation with GGT, or fractionation of alkaline phosphatase isoenzymes can be used to help differentiate liver alkaline phosphatase from non-liver sources. However, GGT elevation is not specific for cholestatic liver disease, and can be elevated in >50% of alcoholic patients without obvious evidence of liver disease. GGT can also be elevated in patients with pancreatic disease, myocardial infarction, renal failure, emphysema, diabetes, and in patients taking certain medications such as phenytoin and barbiturates. Given its lack of specificity for liver disease, GGT should not be used as a screening test for underlying liver disease in the absence of abnormal liver chemistries
- Those who present with an elevation in alkaline phosphatase with normal AST, ALT, and bilirubin levels should have their alkaline phosphatase elevation confirmed with a GGT level and if elevated an ultrasound of the liver should be ordered."[11]

European Association for Study of Liver (EASL)

The EASL published clinical practice guidelines for drug-induced liver injuries (DILI). These guidelines state that "ALT, ALP and TBL [total bilirubin] are the standard analytes to define liver damage and liver dysfunction in DILI. AST [aspartate aminotransferase] values can be used to reliably substitute ALT in calculating the pattern of injury when the latter is unavailable at DILI recognition, whereas GGT is less reliable as an ALP substitute. Grade C."[60]

The EASL also published clinical practice guidelines for the management of alcohol-related liver disease (ALD). These guidelines state that "As the measurement of GGT, ALT, AST and MCV [mean corpuscular volume] is easy and inexpensive, they remain the most frequently used markers for early detection of ALD. However, all these laboratory values are only indirect markers for ALD, with low sensitivity and specificity... No single marker or combination of markers can differentiate between different causes of liver disease."[61] The authors also note that "Screening investigations should not only include liver function tests (LFTs), i.e. gamma glutamyl transpeptidase (GGT[P]), serum ALT and serum AST, but also performance of a test to detect liver fibrosis (e.g. TE [transient elastography])."[61]

In a 2021 update, the EASL asserted that "In patients with elevated liver stiffness and biochemical evidence of hepatic inflammation (AST or GGT >2xULN), LSM by TE should be repeated after at least 1 week of alcohol abstinence or reduced drinking **(LoE 3; strong recommendation).**"[62]

European Association for Study of Liver (EASL) and Latin American Association for the Study of the Liver (ALEH)

Guidelines from the EASL and ALEH state that "Serum biomarkers can be used in clinical practice due to their high applicability (>95%) and good interlaboratory reproducibility. However, they should be preferably obtained in fasting patients (particularly those including hyaluronic acid) and following the manufacturer's recommendations for the patented tests."[63] The guidelines provide a list of several serum biomarkers including GGT.

Canadian Association of Gastroenterology (CAG)

The CAG practice guidelines for the evaluation of abnormal liver enzyme tests state that GGT may be used as a second-line biochemical test. Specifically, the guidelines state that "All patients with at least

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one abnormal liver screening test (abnormal ALT, AST or ALP) should have the following liver biochemical tests performed: gamma-glutamyl transferase (GGT), albumin, bilirubin (including direct if the total bilirubin is elevated) and either prothrombin time (PT) or international normalized ratio (INR). These tests can be performed as initial screening tests if it is inconvenient for the patient to return to the physician's office within a reasonable period of time (weeks or months depending on the severity of the enzyme abnormalities)."[64]

American Society of Addiction Medicine (ASAM)

The ASAM released clinical practice guidelines on the use of laboratory tests which measure impairment of hepatic functioning. ASAM recommends measurement of GGT and ALT to identify recent heavy alcohol use and risk for alcohol withdrawal, and notes that when conducting a urine test, GGT is recommended as the marker of heavy alcohol consumption.[65]

Clinical Services and Standards Committee (CSSC) of the British Society of Gastroenterology (BSG)

The Clinical Services and Standards Committee of the British Society of Gastroenterology was commissioned to produce guidelines for the management of abnormal liver blood tests. They recommend that the "Initial investigation for potential liver disease should include bilirubin, albumin, ALT, ALP and GGT, together with a full blood count if not already performed within the previous 12 months. (level 2b, grade B)." They note that "If there is clear indication of a specific clinical risk—for example, in high-risk groups such as injecting drug users, migrants from high prevalence areas or prisoners, then some aspects of second-line testing can be undertaken simultaneously. In many patients with liver damage an assessment of liver fibrosis is critical in making decisions about referral and management." They go further to explain that in adults, "clues to the level of liver fibrosis can be gleaned from the use of non-invasive algorithms such as the AST to ALT ratio" such that an AST:ALT greater than one indicated advanced fibrosis or cirrhosis, but warns that "non-invasive markers have not been sufficiently validated in children to be routinely applied in clinical practice."[7]

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
82977	Glutamyltransferase, gamma (GGT)

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
02/01/2026	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Added "of the digestive system." to CC2.e., now reads: "e) For individuals with primary or secondary malignant neoplasms of the digestive system."
01/01/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following changes were made for clarity and consistency: Coverage is limited to GGT testing in adults. For clarity, this results in a title change from "Gamma-glutamyl Transferase" to "Gamma-glutamyl Transferase Testing in Adults" As this policy is specific to adults (individuals 18+), a disclaimer was added to Section III and CC1 and 2 were simplified to remove references to age restrictions. The beginning of Section III now reads: "This policy is specific to individuals 18 years of age or older. Criteria below do not apply to individuals less than 18 years of age. 1) For individuals with elevated alkaline phosphatase activity, serum GGT testing no more than once every two weeks MEETS COVERAGE CRITERIA. 2) To assess for liver injury, function, and/or disease, serum GGT testing no more than once every two weeks MEETS COVERAGE CRITERIA for individuals with at least one of the following conditions:"
09/01/2023	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: All CCs edited for clarity and consistency. Removal of drug ingestion from CC2a, now just says "For individuals with chronic alcohol use." Removal of Note 1, frequency replaced in CC1 and CC2 with "no more than once every two weeks"
01/01/2023	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review did not necessitate any modification to the coverage criteria.
05/15/2022	Initial Policy Implementation

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