Gamma-glutamyl Transferase

Policy Number: AHS – G2173 – Gamma-glutamyl Transferase	Prior Policy Name and Number, as applicable:
Effective Date:01/01/2023	

I. Policy Description

Gamma-glutamyl transferase (GGT), also known as gamma-glutamyl transpeptidase (GGTP) (Singh, Tiwary, Patil, Sharma, & Shukla, 2006; Vroon & Israili, 1990), is an enzyme present in the cell membrane of many different tissue types, including the heart, brain, seminal vesicles, kidneys, bile duct, spleen, and gallbladder (Dillon & Miller, 2016). GGT is traditionally considered a predictive marker for liver dysfunction, bile duct ailments, and alcohol consumption (Koenig & Seneff, 2015). 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 (Koenig & Seneff, 2015).

NOTE: This policy is intended only for adult individuals aged 18 years and older.

II. Related Policies

Policy Number	Policy Title
AHS-G2036	Hepatitis C
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. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g.

National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website https://www.cms.gov/medicare-coverage-database/search.aspx or the manual website.

1) Serum GGT testing* (See Note 1) **MEETS COVERAGE CRITERIA** in individuals with elevated alkaline phosphatase activity.

2) Serum GGT testing* (See Note 1) to assess liver injury, function, and/or disease **MEETS COVERAGE CRITERIA** in individuals who meet at least one of the following:
   a) Chronic alcohol or drug ingestion
   b) Long-term drug therapy known to have a potential for causing liver toxicity
   c) Exposure to hepatotoxins
   d) Viral hepatitis, amoebiasis, tuberculosis, psittacosis, or similar infections that may cause hepatic injury
   e) Primary or secondary malignant neoplasms
   f) Diabetes mellitus
   g) Malnutrition
   h) Disorders of iron and mineral metabolism
   i) Sarcoidosis
   j) Amyloidosis
   k) Lupus
   l) Hypertension
   m) Gastrointestinal disease
   n) Pancreatic disease
   o) As part of liver function assessment subsequent to liver transplantation

3) Serum GGT testing **DOES NOT MEET COVERAGE CRITERIA** as part of a wellness check or for general encounters without abnormal findings.

*Note 1: A maximum of one unit of GGT per week will be reimbursed for adult individuals. In accordance with NCD 190.32, "When used to assess liver dysfunction secondary to existing non-hepatobiliary disease with no change in signs, symptoms, or treatment, it is generally not necessary to repeat a GGT determination after a normal result has been obtained unless new indications are present" (CMS, 2019).

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
BA	Biliary atresia
BSG	British Society of Gastroenterology
BSPGHAN	British Society of Paediatric Gastroenterology Hepatology and Nutrition
CAG	Canadian Association of Gastroenterology
CAGE	Cut, Annoyed, Guilty, and Eye
CBC	Complete blood count
CDT	Carbohydrate-deficient transferrin
CHD	Coronary heart disease
CKD	Chronic kidney disease
CLIA ’88	Clinical laboratory improvement amendments of 1988
CMS	Centers for Medicare and Medicaid
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DB	Direct bilirubin
DILI	Drug-induced liver injuries
EASL	European Association for Study of Liver
ECON	Expert Committee on non-alcoholic fatty liver disease
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FBC	Full blood count
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
GGT	Gamma-glutamyl transferase
GGTP	Gamma glutamyl transpeptidase
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
MCV	Mean corpuscular volume
Mets	Metabolic syndrome
MI	Myocardial infarction
MR	Mendelian randomization

NAFLD	Non-alcoholic fatty liver disease
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
NCD	National coverage determination
NSAIDs	Nonsteroidal anti-inflammatory drugs
PT	Prothrombin time
TBL	Total bilirubin
TC	Total cholesterol
TE	Transient elastography
TRG	Triglycerides

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 (Ndrepepa & Kastrati, 2016). 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 (Newsome et al., 2018). 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 (Newsome et al., 2018). 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 (Koenig & Seneff, 2015). Abnormal GGT levels are also identified in anorexia nervosa, Guillain-Barré syndrome, hyperthyroidism, obesity, dystrophica myotonica (Gowda et al., 2009), and cigarette smoking (AACC, 2020). Certain drugs may lead to unusual GGT levels in the blood as well. It has been reported by the AACC (2020) 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 (2019) 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.

GGT 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 (Singh et al., 2006). 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 (AACC, 2020). This means that elevated GGT levels suggest that elevated ALP levels are of a hepatic origin (Kwo, Cohen, & Lim, 2017).

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 (Koenig & Seneff, 2015). Elevated serum GGT levels are known markers of oxidative stress (Yamada et al., 2006), which occurs

when an imbalance is present between antioxidants and free radicals in the body. 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 (Kwo et al., 2017). Some report that GGT is only occasionally included in a liver function testing panel (Dillon & Miller, 2016), while others report that GGT is still a commonly measured serum liver enzyme (Friedman, 2020). 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

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 (AACC, 2020). 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 (Xing et al., 2022).

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 (Gowda et al., 2009). 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) (J. Lee et al., 2018; R. Q. Wang et al., 2016). 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 (Dillon & Miller, 2016). Finally, GGT has also been identified as a useful prognostic tool for patients with hepatocellular carcinoma, the most common type of primary liver cancer (Z. Wang et al., 2014).

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."

Biliary atresia (BA) is a childhood disease characterized by absent, narrow, or blocked bile duct(s). BA is often identified in infants, and high GGT levels are typically detected. Agin et al. (2016) note that GGT elevation is one of the most reliable tests for diagnosing BA. Other researchers have reported that the value of GGT as a diagnostic tool for BA is largely dependent on age. Specifically, "GGT levels contribute to the diagnosis of BA before 120 days. Age must be considered if using GGT levels as a diagnostic test for BA" (Chen, Dong, Shen, Yan, & Zheng, 2016). GGT was found to have the highest diagnostic value

in patients who were between 61-90 days old (sensitivity of 82.8% and specificity of 81.6%), and the lowest diagnostic value in patients who were greater than 121 days old (Chen et al., 2016).

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" (Sette & Almeida Lopes, 2014). Noborisaka, Ishizaki, Yamazaki, Honda, and Yamada (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" (Noborisaka et al., 2013).

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 5 years before the baseline examination. Subjects were divided into 4 quartiles and those in GGT ASV quartile 4 were older, more obese, and had higher BP and more comorbidities than those in quartile 1. 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 (D. Y. Lee et al., 2020).

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 (Engelken, Bettschart, Rahman, Parks, & Garden, 2003).

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 (Vroon & Israili, 1990). 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 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 (AACC, 2020). 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 (Grundy, 2007). Further, M. Y. 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 (Grundy, 2007), and high GGT variability is associated with an increased risk of myocardial infarction and CVD related mortality (Chung et al., 2019). GGT and the risk of atherosclerosis and coronary heart disease has been reported by Ndrepepa, Colleran, and Kastrati (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 (Celik et al., 2014).

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 (Korantzopoulos et al., 2009; Xu et al., 2017; Yao et al., 2019).

GGT 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, Kang, and Lee (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 (Chung et al., 2019), and serum GGT levels have been associated with a greater risk of ischemic or nonembolic stroke in individuals older than 70 years (Korantzopoulos et al., 2009). 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 (Yao et al., 2019).

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 (Kaneko et al., 2019). Kunutsor, Abbasi, and Adler (2014) report that greater circulating GGT levels lead to an increased risk of type 2 diabetes in both males and females. Higher GGT levels have also been associated with a greater amount of insulin resistance and therefore a higher risk of developing the disease (Grundy, 2007).

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" (Nano et al., 2017). 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 (De Silva et al., 2019). Further, Shibabaw, Dessie, Molla, Zerihun, and Ayelign (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. Serum GGT levels and Parkinson disease risk in men and women was studied by Yoo et al. (2020) who found 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 (Andrews, Goate, & Anstey, 2020). 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 (Huang et al., 2014). 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 (Huang et al., 2014).

Dong et al. (2018) researched BA (biliary artresia) in a large cohort of Chinese patients. Data from a total of 1728 newborn infants with obstructive jaundice was collected for this study. The authors note that five predictors including "gender, weight, direct bilirubin (DB), alkaline phosphatase (ALP), and gammaglutamyl transpeptidase (GGT[P]) were significantly different between the BA and non-BA groups ($P < .05$)" (Dong et al., 2018). GGTP may therefore be an efficient tool for BA diagnoses.

The relationship between liver enzymes and the risk of metabolic syndrome have been researched several times. Liu, Zhou, Lu, Wang, and Qiu (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 (Liu et al., 2018). Another study completed by S. 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 (S. Wang et al., 2017).

Ndrepepa, Holdenrieder, 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 3-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)" (Ndrepepa, Holdenrieder, et al., 2018). 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" (Conigrave et al., 2002).

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" (Rosoff et al., 2019). 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" (Rosoff et al., 2019).

A study completed by Jousilahti, Rastenyte, and Tuomilehto (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" (Jousilahti et al., 2000). 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" (Yang et al., 2020).

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" (Hong et al., 2020). 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.

D. Y. Lee et al. (2020) examined the prognostic value of GGT variability in predicting the risk of stroke, myocardial infarction, and mortality in diabetic patients. 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 4 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 1 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" (D. Y. Lee et al., 2020).

Mujawar et al. (2020) studied the use of salivary gamma-glutamyl transpeptidase as a biomarker in oral squamous cell carcinoma and precancerous lesions. 75 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 30U/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 (Mujawar et al., 2020).

Liao et al. (2022) studied the association of GTT levels with the occurrence of post-stroke cognitive impairment (PSCI). 1,957 participants with a minor ischemic stroke or transient ischemic attack were measured for GTT and they were categorized into 4 quartiles based on baseline GTT levels. Of the 1,957 participants, 671 (34.29%) patients experienced PSCI at 3 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" (Li, Liao, Pan, Xiang, & Zhang, 2022).

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
- 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" (Kwo et al., 2017).

British Society of Gastroenterology (BSG)

The BSG's guidelines on the management of abnormal liver blood tests state 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 et al., 2018).

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" (Andrade et al., 2019).

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" (Thursz et al., 2018). 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])" (Thursz et al., 2018).

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" (Castera et al., 2015). The guidelines provide a list of several serum biomarkers including GGT.

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

An expert committee for the ESPGHAN published guidelines for the diagnosis and treatment of nonalcoholic fatty liver disease in children (0-18 years). These guidelines include a section on additional testing to consider for chronic liver diseases. Regarding screening labs, the ESPGHAN recommends considering testing for "CBC [complete blood count] with differential, AST, bilirubin (total, conjugated), alkaline phosphatase, GGT, INR [international normalized ratio], albumin, total protein, [and] hemoglobin A1c" (Vos et al., 2017).

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)

The NASPGHAN and ESPGHAN published joint guidelines for the evaluation of cholestatic jaundice in infants. While the background of these guidelines does mention GGTP, the official society recommendations do not mention the measurement of GGTP for the evaluation of cholestatic jaundice in infants. The NASPGHAN and ESPGHAN do recommend that "Any formula-fed infant noted to be jaundiced after 2 weeks of age should be evaluated for cholestasis with measurement of total and conjugated (direct) serum bilirubin (1A). Depending upon local practice, breast-fed babies that appear otherwise well may be followed clinically until 3 weeks of age, at which time if they appear icteric should then undergo serum evaluation of total and conjugated (direct) serum bilirubin" (Fawaz et al., 2017).

The background of the article states that "During the evaluation of the infant with cholestasis, laboratory investigations will help define the etiology, the severity of the liver disease and detect treatable conditions. A critical and important initial blood test is the measurement of serum conjugated (direct) bilirubin (DB), which, if elevated, is a reliable laboratory indicator of cholestasis at this age. Accompanying evaluation of DB levels are standard biochemical and synthetic liver tests to assess the severity of the liver disease to include TB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGTP), prothrombin time (PT) with the international normalized ratio (INR), glucose, and albumin" (Fawaz et al., 2017).

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

The NASPGHAN published guidelines in 2004 for the evaluation of cholestatic jaundice in infants. These guidelines state that "GGTP [gamma-glutamyl transpeptidase] and lipoprotein X are not routinely recommended in the evaluation of cholestasis in young infants" (Moyer et al., 2004). More, this article states that "Gamma glutamyl transpeptidase (GGT[P]) has been used in the past to distinguish biliary atresia from neonatal hepatitis, but wide variability in levels makes interpretation of test results difficult. Especially in the older infant with cholestasis, a very low GGT level may be useful to exclude obstruction and, in conjunction with an elevated alkaline phosphatase level, suggests genetic and metabolic causes of intracellular cholestasis. The degree of elevation of GGT is not useful in discriminating the etiology of the cholestasis" (Moyer et al., 2004).

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 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)" (Minuk, 1998).

American Society of Addiction Medicine

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. When using a urine test, GGT is recommended as the marker of heavy alcohol consumption (ASAM, 2020).

British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN)

BSPGHAN released guidelines on diagnosis of non-alcoholic fatty liver disease (NAFLD). BSPGHAN recommends GGT as a first line liver function assessments including other such as ALT, AST, ALP, split bilirubin, FBC, coagulation screen, albumin, fasting lipid profile, immunoglobulin and complement levels, autoimmune profile including ANCA, anti-transglutaminase antibodies, thyroid function tests, A1AT levels, copper and caeruloplasmin, and Hepatitis A, B, C, and E serology. BSPGHAN also recommends assessing for GGT at each clinic follow up (BSPGHAN, 2020).

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: http://www.cms.gov/medicare-coverage-database/overview-and-quick-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.

VIII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

Code Number	Code Description
82977	Glutamyltransferase, gamma (GGT)

IX. Evidence-based Scientific References

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X. Revision History

Revision Date	Summary of Changes
01/01/2023	Initial Effective Date