

## **The Abnormal Liver Chemistry Profile v 4.1 July 31 2017**

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### **Background**

Liver chemistry profiles are widely used in patients with risk factors for liver disease and can assist with diagnosis and management of these patients in conjunction with an adequate clinical history, examination, and other investigations. However, it is not uncommon to see minor changes in one or more tests in relatively well patients, an issue compounded by the fact that 5-6 tests are normally included in most liver chemistry profiles.

### **Nomenclature**

It should be noted that the standard tests provided in the liver chemistry profile serve a range of different purposes. Whereas albumin can reflect hepatic function, it is also an acute phase protein. Alterations in clotting factors, such as increased prothrombin time, can also reflect hepatic function. Enzyme measurements, however, are not tests of liver function at all.

Hence, terms such as LFT or liver function tests are misnomers and should not be used. The preferred nomenclature would be liver chemistry profile or liver chemistry panel.

### **Scope**

The aim of this guideline is to provide advice on the interpretation and further management of abnormal liver chemistry profile results found in primary care settings and is intended for use in general practice.

A standard liver chemistry profile is also recommended for use in primary care. This should be useful to clinical laboratories. Harmonised reference ranges are also proposed (link with Laboratory Investigation Harmonisation Guidelines – National Laboratory Handbook).

These guidelines apply to adult, non-pregnant patients who are generally clinically stable.

## Key recommendations

### For GPs:

- Please only request liver chemistry profiles in patients who are at risk for liver disease or have suspicious presenting clinical features, rather than include it on all laboratory requests.
- Interpretative guidelines are summarised in the Quick Reference Card (Appendix 1)
- Additional tests such as fractionated bilirubin or alkaline phosphatase isoenzymes are rarely useful and should not be requested without first discussing the clinical issue with your local laboratory

### For Laboratories:

- The standard liver chemistry profile is documented in the Quick Reference Card in Appendix 1, consisting of total bilirubin, total protein, albumin, ALT, GGT, and ALP (6 tests).
- The preferred nomenclature is *liver chemistry panel* or *liver chemistry profile*.

## Epidemiology of Liver Chemistry Profile Testing

In 2016, about 55,000 liver chemistry panels were performed in Tallaght Hospital on patients attending local general practitioners.

## Testing

While it is acknowledged that a significant number of patients presenting to GPs will have some risk of having liver disease, given the prevalence of obesity and habitual alcohol use, it is nevertheless preferable to test only those with such risk or with suspicious presenting features.

### Whom to test:

1. Patients presenting with risk factors for liver disease, including:
  - History of high alcohol intake
  - Obesity, diabetes, metabolic syndrome, dyslipidaemia
  - Hepatotoxic medication use (see list for examples)
  - Family history of iron overload, e.g. haemochromatosis\*
  - Possible exposure to hepatitis viruses (e.g. oral, parenteral, sexual routes)
  - Hepatotoxins, including some herbal preparations

Drug-induced liver injury (DILI), including idiosyncratic reactions, is an increasingly recognised problem, with many drugs and herbal preparations implicated, which may manifest with abnormal liver chemistry tests.

2. Patients presenting with suspicious clinical features, including:

- Jaundice
- Abdominal pain
- Pale stools
- Unexplained itch
- Any features of chronic liver disease (e.g., spiders, palmar erythema)
- Nausea and vomiting
- Fatigue
- Anaemia

Examples of common hepatotoxic drugs in primary care:

- Analgesics (e.g. paracetamol, NSAIDs)
- Statins
- Anticonvulsants (e.g. phenytoin, carbamazepine, valproate)
- Antibiotics (e.g. nitrofurantoin, amoxicillin, isoniazid, co-amoxiclav)
- Isoretinoin
- Methotrexate, azathioprine
- Corticosteroids

*\*Liver chemistry profile is not the first line test to detect haemochromatosis: instead use fasting iron/transferrin saturation.*

### Whom to Re-Test

- When re-testing is required, an interval of 1-3 months is considered adequate in clinically stable patients

### Whom Not to Test

There is no need to test asymptomatic individuals with no risk factors for liver disease, as normal liver chemistry profiles do not exclude liver disease including cirrhosis and may provide false reassurance about present lifestyle.

### How to test

A completed standard laboratory test request form must be sent with all samples.

### Information required on the referral form

The request form must include detailed patient and clinical information including:

- **Patient demographics**
  - Patient's name

- Patient's date of birth
  - Medical record number
  - Name of referring clinician
  - Name of referring hospital
  - Order number / external laboratory number (if applicable to external agencies only).
- **Request details**
    - Clinical indication for testing (see list above)
    - Details of any medications and herbal, over-the-counter preparations
    - Information about alcohol intake

**Requests received with no clinical details/inadequate clinical justification or with inadequate patient demographics should not be analysed.**

Full clinical information should accompany all requests. In the event a request is received which does not have the required data (above) or does not have adequate clinical details the laboratory may:

- Issue a report to the requesting doctor, requesting additional clinical details and/or advise that the case is discussed with the local Laboratory Medicine Consultant, and advising that the sample will be discarded after 1 week\* if there is no reply
- Store the sample for up to 1 week\* awaiting further communication from the referring clinician
- Samples can be discarded after 1 week\* if the referring clinician has not provided the required details or if it is determined that testing is not indicated.

*\* actual storage time may be determined locally*

## **Interpretation of liver chemistry profile test results**

The following sections cover the common patterns seen, provide an account of individual tests, and outline what to do for selected common abnormal findings.

### **Common patterns of liver cell injury**

There are two common patterns of liver cell injury that can be easily identified in liver chemistry profiles: hepatocellular injury and cholestasis. In hepatocellular damage, the aminotransferase enzymes will be elevated (alanine transaminase, ALT, and aspartate transaminase, AST) predominantly, whereas in cholestasis the hallmark is elevated gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP).

GGT is a sensitive indicator of liver damage. An elevated GGT occurring by itself and without a similar ALP elevation is commonly due to drug therapies and alcohol intake. On the other hand, an isolated elevated ALP with normal GGT is usually non-hepatic (e.g. of bony origin) and may require separate investigation.

Bilirubin may be elevated in both patterns, more so in cholestasis, but is less useful than the hepatobiliary enzymes to differentiate them.

Fractionated (direct/indirect) bilirubin is also rarely useful when other liver chemistry profile tests are elevated as the cause of hyperbilirubinaemia is usually apparent (however, see caveat in the section on isolated raised bilirubin).

The finding of cholestasis would usually require an abdominal/liver ultrasound examination to determine the cause.

ALP isoenzyme analysis is rarely useful and is not recommended. If deemed necessary, the request should be discussed with your local laboratory in advance.

## Interpretation of common liver chemistry test results

### Bilirubin

Bilirubin is a test of hepatic conjugating capacity and also of hepatic excretory function. The usual reference range for plasma bilirubin in adults is  $< 17 \mu\text{mol/L}$ .

When hyperbilirubinaemia is present, it may consist of either unconjugated or conjugated bilirubin predominantly. However, it is unnecessary to measure bilirubin fractions in most cases.

Bilirubin (in its conjugated form only) may also be measured at the point of care in urine, usually with a dipstick, where its presence is always pathological.

Jaundice is usually noticeable when plasma bilirubin exceeds  $35 \mu\text{mol/L}$ . Jaundiced adults sometimes complain of itch but can often be otherwise well.

The following table summarises the causes of hyperbilirubinaemia.

Type of Jaundice	Causes	Type of Bilirubin elevated
<b>Pre-hepatic:</b>	<ul style="list-style-type: none"> <li>• Haemolysis</li> <li>• Ineffective erythropoiesis</li> </ul>	Unconjugated
<b>Hepato-cellular:</b>		
Pre-microsomal	<ul style="list-style-type: none"> <li>• Gilbert's syndrome</li> <li>• Crigler-Najjar syndrome</li> </ul>	Unconjugated
Post-microsomal	<ul style="list-style-type: none"> <li>• Hepatitis</li> <li>• Toxins (organic solvents, alcohol)</li> <li>• Drugs - paracetamol</li> <li>• Cirrhosis</li> <li>• Dubin-Johnson and Rotor syndromes</li> </ul>	Conjugated and unconjugated
<b>Cholestasis:</b>		
Intra-hepatic	<ul style="list-style-type: none"> <li>• Drugs (e.g., chlorpromazine)</li> <li>• Primary biliary cirrhosis</li> <li>• Pregnancy</li> <li>• Cholangitis</li> <li>• Infiltrations of the liver</li> </ul>	Conjugated and unconjugated
Extra-hepatic	<ul style="list-style-type: none"> <li>• Gallstones</li> <li>• Carcinoma of head of pancreas, stricture (e.g. of common bile duct), biliary atresia</li> </ul>	Conjugated and unconjugated

## **Albumin and total protein**

Low plasma albumin is an indicator of reduced of hepatic synthetic function but is also lowered in acute inflammation of any cause. Hypoalbuminaemia occurs in chronic liver disease.

Gamma globulins may be increased in chronic liver disease due to polyclonal hypergammaglobulinaemia. This may manifest as a raised total protein, but note that dehydration is the most likely reason for a raised total protein. The possibility of myeloma should be considered in appropriate patients, and serum and urine protein electrophoresis requested.

Specific immunoglobulin measurements, though not first line tests, can also assist with differential diagnosis. For example IgA is increased in alcoholic hepatitis/cirrhosis, IgG in chronic active hepatitis and IgM in primary biliary cirrhosis and acute viral hepatitis.

## **Transaminases (ALT and AST)**

Measurement of one transaminase is satisfactory for most clinical situations, and most laboratories provide ALT. Although AST is more sensitive than ALT for alcohol-related liver disease, GGT is the most sensitive for alcohol. ALT and GGT are therefore recommended for detection for most primary care presentations, when measured together as part of a liver chemistry panel.

The aminotransferase (transaminase) enzymes, AST and ALT, are raised in hepatocellular damage. AST is found in mitochondria and cytoplasm whereas ALT is confined to the cytoplasm. Conditions causing cell membrane rupture (e.g. viral hepatitis) tend to affect ALT predominantly. ALT is present in higher concentration than AST and has a longer half-life.

However, conditions that damage the whole cell (e.g. alcohol, hypoxic shock, focal tumour deposits, or nodular cirrhosis) tend to affect AST predominantly.

## **ALP and GGT**

Both ALP and GGT are grossly elevated in cholestasis, such as in biliary obstruction due to gallstones, primary biliary cirrhosis, or carcinoma of the head of the pancreas. Both are often raised in hepatitis when there is a cholestatic phase.

Alkaline phosphatase (ALP) is also moderately raised in hepatocellular damage, probably reflecting minor degrees of cholestasis present.

GGT is raised in alcoholic liver damage due to increased synthesis (enzyme induction), and also in focal lesions such as metastatic carcinoma and cirrhosis. GGT elevation often parallels the elevation in alkaline phosphatase in liver disease with a significant biliary component. Minor elevations of ALP and GGT are common in patients with NAFLD.

Ultrasound examination is very useful to detect cholestasis where dilated bile ducts may be seen. Absence of urobilinogen in urine (measured with a dipstick) and absence of stercobilin pigment in faeces (pale stools) are also features of biliary obstruction.

## **Isolated abnormalities: What to do?**

### **Isolated Raised ALP**

- Significant isolated elevation of ALP (e.g. > 100% ULN) is usually due to bone pathology such as Paget's disease or osteomalacia rather than hepatic/biliary pathology
- Minor isolated elevations in ALP up to 50% above the upper reference limit occur commonly (especially in the elderly) and may be repeated within 3 months looking for an increase
- Isolated elevated ALP is often seen in young adults/adolescents due to long bone growth and is normal. Most laboratories will provide an age-specific reference range.
- Increasing values, or elevations > 50% ULN should be discussed with the local laboratory specialist or considered for referral.
- Mild and stably elevated ALP up to 50% ULN is often seen in the elderly. This may be of bony or hepatic origin but does not require further investigation in the absence of relevant clinical findings.

### Isolated raised GGT

- Assuming the ALP is completely normal, alcohol, drugs, other toxins, and steatosis should be considered as likely causes
- Note that cirrhosis may be present with normal liver chemistry panel tests: raised GGT may indicate habitual alcohol consumption in this context.

### “Transaminitis”

- Minor elevation in ALT (or AST) with a normal GGT are common and may indicate underlying liver diseases such as non-alcoholic steato-hepatitis (NASH) or alcohol-related disease. They are more often transient and benign, and may be related to intercurrent illness, medication use or strenuous exercise.
- Less frequent causes of transaminitis include viral hepatitis C, autoimmune hepatitis, haemochromatosis, alpha-1 antitrypsin deficiency, Wilson's disease, coeliac disease, haemolysis, myopathy, or hyperthyroidism.
- Consider NASH/NAFLD in patients with diabetes, obesity or metabolic syndrome. Check a fasting glucose and Hba1c for detection of type 2 diabetes mellitus.
- Consider alcoholic liver disease, though the GGT is usually elevated as well as the transaminases.
- The lipid profile may commonly show dyslipidaemia in these patients.
- Transaminases 2-5 times ULN commonly seen in chronic viral hepatitis, steatohepatitis.
- Transaminases rarely >10 times ULN in alcoholic hepatitis.
- Transaminases >20 times ULN, think of acute viral infection, ischaemic hepatitis, drug toxicity, paracetamol toxicity.

### Isolated raised bilirubin

- The most common differential diagnoses of isolated hyperbilirubinaemia are Gilbert's syndrome and haemolysis. Liver disease is unlikely.
- Isolated hyperbilirubinaemia is mostly due to Gilbert's syndrome, a benign condition characterised by fasting unconjugated hyperbilirubinaemia. Bilirubin levels are either normal or at least 50% lower in the non-fasting state. A typical patient with Gilbert's syndrome might notice mild jaundice during a prolonged fast or during intercurrent illness.
- The rest of the liver chemistry profile (including GGT) is normal in Gilbert's syndrome.
- The most important differential diagnosis to exclude is haemolysis. FBC and reticulocytes count should be checked to look for haemolysis. RDW (red cell distribution width) will be increased in haemolysis due to different cell sizes; reticulocytes are larger than mature red blood cells. Serum haptoglobin will be reduced

and serum LDH raised if haemolysis is the cause of hyperbilirubinaemia. Schistocytes might be seen on blood film. .

- The finding of raised fasting total bilirubin (usually not more than 50 µmol/L), with a non-fasting bilirubin 50% lower than the fasting value, along with the remainder of the liver chemistry panel tests being normal, with normal FBC and normal reticulocyte count is sufficient in most cases to confirm Gilbert's syndrome and exclude haemolysis.
- Confirmation of the presence of unconjugated hyperbilirubinaemia by measuring fractionated bilirubin on one occasion is reasonable in Gilbert's syndrome and can also help to elucidate the aetiology of isolated hyperbilirubinaemia.
- Specialist molecular genetic testing for the common UGT1A1\*28 mutation is available at one Irish laboratory but should not be routinely requested without prior discussion with your local laboratory consultant.

## Additional Laboratory Testing

### Worthwhile Additional Tests in the Primary Care Setting:

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*Think of haemochromatosis!*

*Check a fasting iron and transferrin saturation.*

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In primary care, the following additional tests may be helpful to clarify abnormal liver panel tests:

- Serology for hepatitis A, B and C, as well as Epstein-Barr virus (EBV)
- The finding of elevated serum iron, elevated transferrin saturation (or low TIBC), or elevated serum ferritin suggests haemochromatosis. This is the most common treatable genetic disorder in Irish adults and should always be checked for if there are abnormal liver chemistry tests. Early detection prevents cirrhosis in these patients.
  - Patients with suspected hereditary haemochromatosis are often homozygous for the C282Y mutation and should be discussed with the local laboratory to arrange genetic testing in appropriate circumstances.
- Immunoglobulins (IgA is increased in alcoholic hepatitis/cirrhosis, IgG is raised in chronic active hepatitis and IgM is raised in primary biliary cirrhosis and acute viral hepatitis).
- Prothrombin time is prolonged in chronic liver disease.
- Lipid profile

There may be clues to the presence of liver disease in other laboratory tests done:

- The FBC may show macrocytosis or thrombocytopenia
- Low urea in chronic liver disease
- Prolonged PT, increased INR
- Low cholesterol might be due to reduced hepatic synthesis in chronic liver disease

### Tests Not Worth Doing Routinely in Primary Care Settings



The following tests are rarely contributory, and should not be routinely requested without prior discussion with your local laboratory.

- ALP isoenzyme analysis (as described earlier)
- Fractionated Bilirubin (see caveat as described under isolated raised bilirubin)

### **Additional Testing as part of specialist clinical assessment:**

The following investigations are not first-line and are only appropriate as part of a specialist clinical assessment pathway that has been agreed and resourced between the local laboratory, participating hospital clinicians and general practitioners:

- Emergency serum paracetamol measurements in patients sent to the Emergency Department with paracetamol overdose and suspected hepatic necrosis.
- Caeruloplasmin which may be low in the rare Wilson's disease (copper accumulation causing hepatolenticular degeneration) but is also affected by any acute inflammation.
- Low plasma alpha-1 antitrypsin (AAT) may point to the rare condition alpha-1 antitrypsin deficiency but is also affected by any acute inflammation.
- Measuring both transaminases is unnecessary except as part of a funded clinical pharmaceutical trial where it is required by the pharmaceutical company. The ratio of AST to ALT is usually 1:1. It is greater than 1 in alcoholic hepatitis, cirrhosis, or tumour metastases, and usually less than 1 in viral hepatitis. It may be useful in specialist care when risk factors for several conditions are present and the aetiology of a mild acute hepatitis is unclear.
- Alpha-fetoprotein (AFP) for monitoring of known cirrhosis
- LDH is now only measured in suspected haemolytic states, or suspected haematological malignancy or lymphoma. However, LDH (predominantly LD-4 and LD-5 isoenzymes) is often elevated in hepatocellular damage.
- Autoantibody testing

## **Implications for ICT Systems**

### **Laboratory Test Requesting Ordering Modules in Primary Care**

It is recommended that user-friendly GP ordering for liver chemistry profiles in patients at risk for liver disease are established at the point of ordering in GP information systems. The information required for requesting is as stated above, and a user-friendly screen should be developed to allow the GP to select one or more of the relevant clinical indications and to indicate relevant drug therapy. This will require discussion with GP system suppliers.

### **Laboratory Test Requesting Modules in Hospital-based CPOE Systems**

The national MedLIS aims to provide an order-entry system. It is recommended that user-friendly screens for ordering Liver Chemistry Profiles are developed and implemented at the point of ordering. The information required for requesting is as stated above, and a user-friendly screen should be developed to allow hospital-based clinicians to select one or more of the relevant clinical indications and to indicate relevant drug therapy.

## National Laboratory Information System (MedLIS)

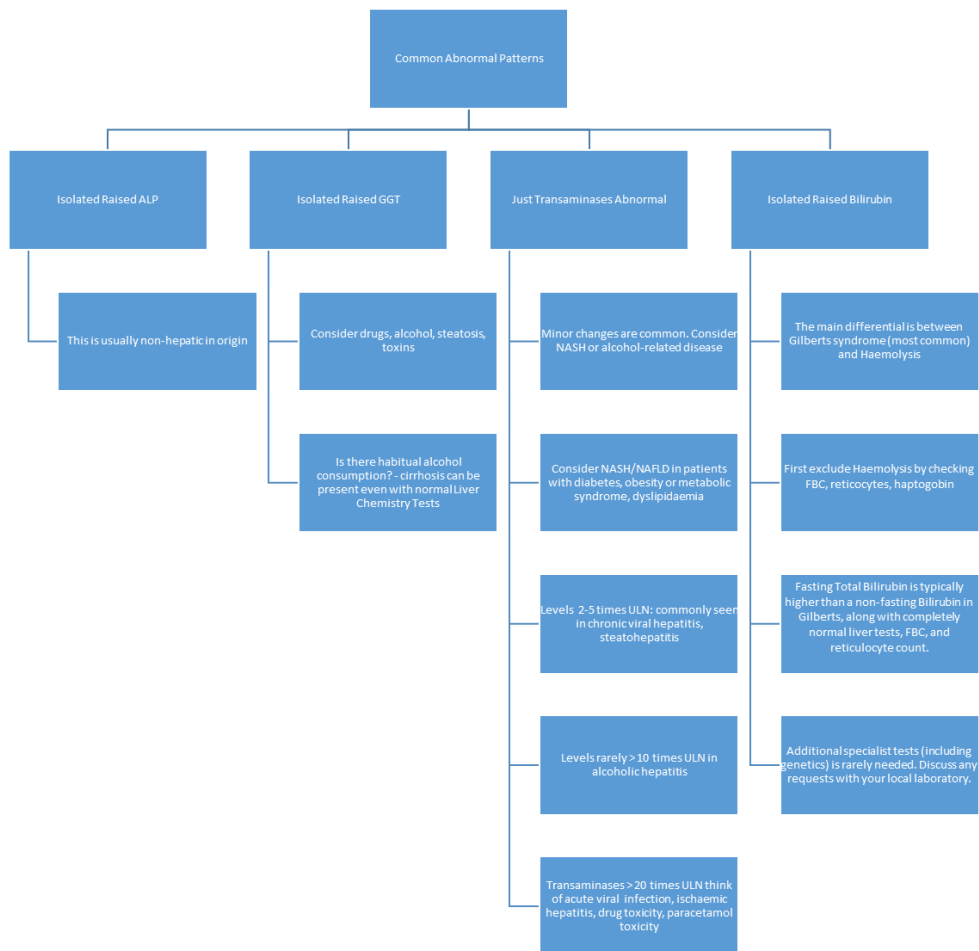
The recommendations given for Primary Care and Hospital-based CPOE systems would apply to circumstances where MedLIS will be providing the CPOE functionality (e.g. where its test ordering module is implemented throughout the hospital)

A pre-laboratory module in MedLIS should check for (1) absence of any clinical details; (2) repeat testing; (3) correct indication for liver chemistry profiles, and generate an alert and an appropriate laboratory report as described above.

## Key References

1. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: evaluation of abnormal liver chemistries. *American Journal of Gastroenterology* 2017;112:18-35
2. [Abnormal Liver Chemistry](#) – evaluation and interpretation. Guidelines and Protocols Advisory Committee, British Columbia, Canada, 2011.
3. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG Clinical Guideline: The Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. *American Journal of Gastroenterology* 2014; 109, 950-966

## Appendix: Quick Reference Card Side 1 (Algorithm)



## Appendix: Quick Reference Card Side 2 (Liver Chemistry Panel Tests)

Test	Harmonised Reference Values	Description and Source	Common Abnormalities
Total Protein (TP)	60-80 g/L	Main constituents are albumin, globulins, and immunoglobulins	High in dehydration, polyclonal hypergammaglobulinaemia (e.g. in liver disease), myeloma
Albumin (Alb)	35-50 g/L	Marker of Hepatic synthesis, and a negative acute phase responder	Low in liver disease Low in acute and chronic inflammation High in dehydration or the "well-nourished"
Total Bilirubin (TBili)	Up to 17 umol/L	Marker of hepatic synthetic function and excretory ability	
Alanine Transaminase (ALT)	20-40	Cytoplasmic Enzyme found in the Liver (5000) but also in many other tissues: kidney (2000), heart (900) muscle (800), pancreas (700), spleen (600), Lung (500), RBC (30)  [where plasma =1]	Commonly raised in hepatocellular injury due to NAFLD, viral hepatitis, etc
Aspartate Transaminase (AST)	20-40	Cytoplasmic and Mitochondrial Enzyme found in the liver (9000) but also in many other tissues: heart (9000), muscle (8000), kidney (8000), pancreas (5000), spleen (2000), lung (800), RBC (200)  [where plasma =1]	Hepatocellular damage (especially alcohol) – more sensitive than ALT but GGT is best  Also raised in severe haemolysis, muscle trauma and disease, hypothyroidism, MI
Alkaline Phosphatase (ALP)	30-130	Bone (made by osteoblasts)  Liver (made by hepatocytes adjacent to the bile canaliculi)  Also: Intestine, Placenta, kidney	Bone disease with increased osteoblastic activity (e.g. osteomalacia, fracture, Pagets disease, bone cancers - osteogenic sarcoma)  Liver disease, especially with biliary involvement;  biliary obstruction - especially extrahepatic
Gamma-Glutamyl Transferase (GGT)	10-50 M 10-40 F	Liver (produced by hepatocytes adjacent to bile canaliculi, epithelial cells of bile ducts), kidney, pancreas	Liver disease (especially with biliary involvement), alcoholism, drug induction