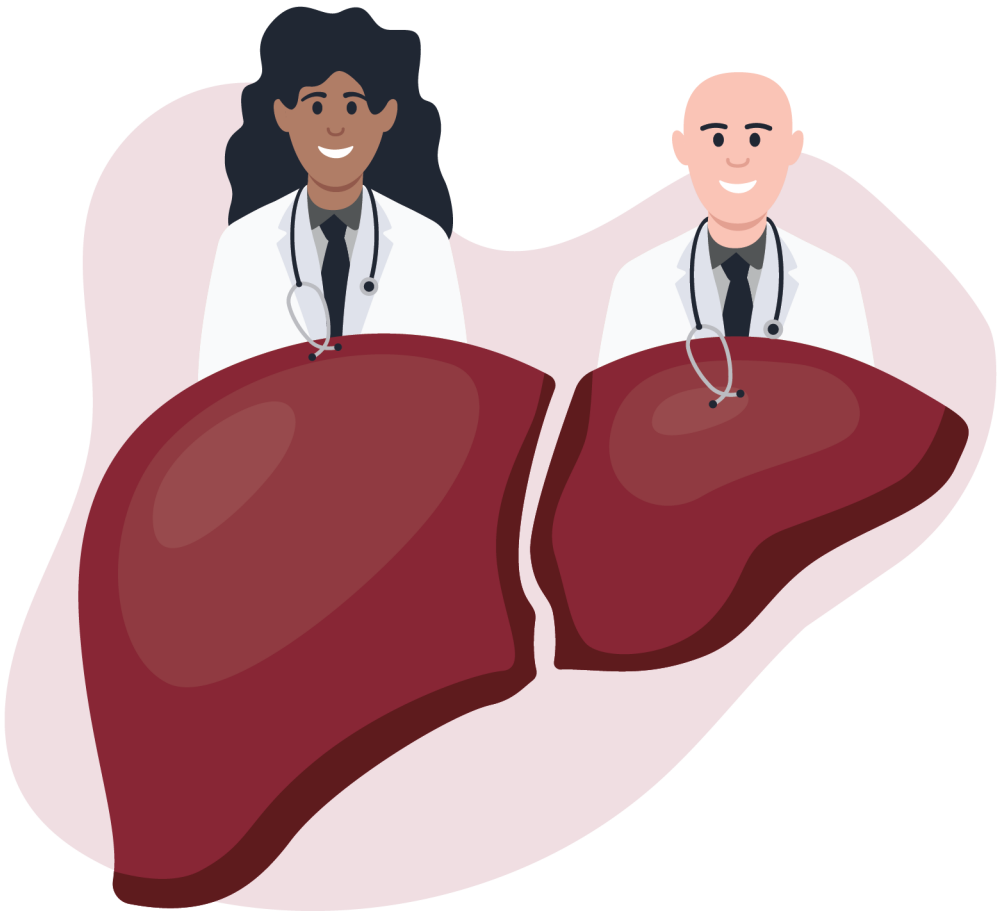
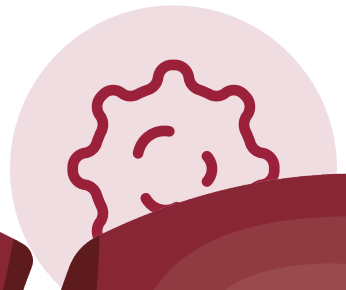


# Understanding Liver Cancers



Liver Cancer Lessons





# ABOUT THE LIVER

The liver is the **second largest** organ in the human body, after the skin. It is football-sized and sits in the upper right part of the abdomen, beneath the diaphragm and above the stomach. The liver performs many **vital** functions within the body, some of which include:

Processing and storing nutrients

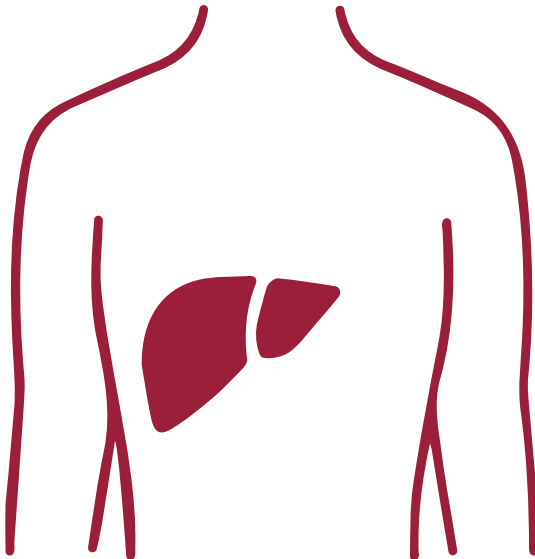
Removing waste from blood

Filtering and removing toxic chemicals

Producing bile to aid with digestion

Producing coagulation factors that stop bleeding

Producing albumin, which helps maintain the blood's volume



When diagnosed at an **early stage**, cancers of the liver can be treated effectively.

# ABOUT LIVER CANCER

## Global Burden of Liver Cancer

Liver cancer has become a global issue, and the number of new liver cancer cases has tripled over the past four decades. Since 2020, liver cancer has been the sixth<sup>1</sup> most common cancer in the world and the third<sup>2</sup> leading cause of cancer death worldwide. According to the World Health Organization, there were more than 905,700 cases of liver cancers and 830,200 deaths from liver cancers globally in 2020.<sup>1</sup> Liver cancer incidence is predicted to increase by 55.0% from 2020 to 2040, with a predicted mortality for 2040 that is 56.4% higher than in 2020.<sup>1</sup>



Liver cancer is the **THIRD<sup>2</sup>** leading cause of cancer death worldwide

The global burden of disease for liver cancer is the highest in East and Southeast Asia as well as Northern Africa, in terms of incidence or new cases and mortality. In 2020, new cases of liver cancer in Asia accounted for 72.5% of the total liver cancer cases in the world, and deaths caused by liver cancer in Asia accounted for 72.4% of the total liver cancer deaths in the world.<sup>5</sup> The incidence and mortality rates of liver cancer are higher among Asian men than in Asian women.<sup>5</sup> Asian men have the fourth highest incidence of liver cancer, with the second highest mortality, while Asian women have the seventh highest incidence of liver cancer, with the mortality ranking sixth.<sup>5</sup> By 2040, China may have the highest prevalence of liver cancer in Asia.<sup>5</sup> Other countries with predicted increase in liver cancer incidence by 2040 include the United Arab Emirates, Qatar, Kuwait and the Syrian Arab Republic; however, the incidence rate in Japan, Georgia, North Korea, Armenia, and China may remain relatively flat.<sup>5</sup>



In 2020, new cases of liver cancer in Asia accounted for **72.5%** of total liver cancer cases in the world



In the United States, the age-adjusted death rate for liver cancer increased by 43% for men and by 40% for women from 2000-2016.<sup>17</sup> The death rate for American men is about two (2.0-2.5) times greater than the rate for women.<sup>17</sup> Comparing all 50 states, the District of Columbia (D.C.) has the highest death rate by liver cancer, while Vermont has the lowest.<sup>17</sup>

# Primary Liver Cancer

Primary liver cancer begins and develops in the liver tissue. This is different from secondary liver cancer, which starts in another part of the body and spreads to the liver through metastasis. Metastasis is the spread of cancer cells from the place where they first formed to another part of the body. The most common types of liver cancer are hepatocellular carcinoma (HCC) and intrahepatic bile duct cancer/cholangiocarcinoma (CCA).

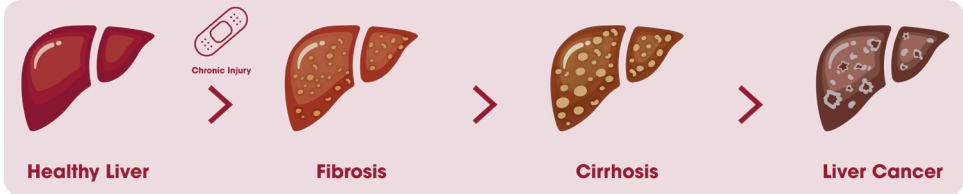


## KEY FACTS

	Hepatocellular Carcinoma (HCC)	Cholangiocarcinoma (CCA)
 <h2>KEY FACTS</h2>	<ul style="list-style-type: none"> <li>Begins in cells of the liver called hepatocytes.</li> <li>Hepatocytes are the main liver cells responsible for:                             <ul style="list-style-type: none"> <li>Secreting bile for digestion.</li> <li>Filtering toxins.</li> <li>Metabolizing carbohydrates, lipids, and proteins.</li> </ul> </li> <li>75-85% of primary liver cancer cases are HCC.<sup>8</sup></li> </ul>	<ul style="list-style-type: none"> <li>Begins in the cells of bile ducts, which are tubes inside and around the liver.                             <ul style="list-style-type: none"> <li>Intrahepatic CCA begins in the bile ducts inside the liver.</li> <li>Extrahepatic CCA begins in the bile ducts outside the liver.</li> </ul> </li> <li>CCA represents 10-15% of all primary liver cancer cases.<sup>9</sup></li> </ul>
 <h2>RISK FACTORS</h2>	<ul style="list-style-type: none"> <li>Men over 60</li> <li>Chronic liver disease</li> <li>Liver scarring due to hepatitis B virus (HBV) or hepatitis C virus (HCV)</li> <li>High alcohol consumption</li> </ul>	<ul style="list-style-type: none"> <li>Men over 60</li> <li>Scarred bile duct tissue</li> <li>Liver infection with parasites (liver flukes)</li> <li>Bile duct problems since birth (congenital)</li> </ul>

# LIVER REGENERATION

The liver has an exceptional capacity to repair itself when injured or damaged. While this regenerative capacity usually lasts a lifetime, continuous damage to the liver over a prolonged time can cause the liver to exhaust its ability to repair itself. Once the liver reaches this state of repair exhaustion, healthy liver cells (hepatocytes) become replaced by scar tissue called fibrosis.



## Continuous damage to the liver can happen two ways:



### 1. DNA damage or scarring of liver tissue

One mechanism of damage is through mutations in the DNA. DNA is the cellular structure that provides genetic material, or instructions for all components and chemical processes in the body, including proper growth and multiplication of cells. Mutations or errors in the DNA lead to changes in these genetic instructions. These changes can damage liver cells and cause them to multiply and grow uncontrollably, which can eventually lead to the formation of a cancerous tumor or liver cancer. Such mutations, specific to liver cancer, can be caused by various risk factors, such as prolonged exposure to aflatoxins,<sup>10</sup> hereditary genetic liver diseases,<sup>11</sup> and viral infections, including chronic HBV and HCV infection,<sup>11</sup> since viruses and chemical toxins can make changes in the DNA.



### 2. Constant scarring of liver tissue

This is commonly caused by excessive alcohol consumption and viral hepatitis infections. Each time the liver gets damaged due to these risk factors, it tries to repair and heal itself. However, scar tissue or fibrosis forms during this repair.

When fibrosis begins to cover large portions of the liver, it reaches a state known as cirrhosis, which makes it difficult for the liver to function properly, can be life-threatening, and is often irreversible or unrepairable.<sup>12</sup> Unrestricted scarring of cells and/or uncontrolled growth of scarred tissue within the liver can increase the risk of developing cancerous tumors, which is why cirrhosis is one of the main risk factors of liver cancer. Therefore, it is important to diagnose cirrhosis early and limit the underlying risk factors to avoid further damage.

# RISK FACTORS

Having a single or even several risk factors does not mean that a person will develop cancer; however, having more than one risk factor substantially increases the likelihood of a person developing liver cancer. Behavioral risk factors, such as alcohol use and smoking, can be changed, while others, such as birth gender, age, and diabetes, cannot. The most prominent risk factors are as follows:



Alcohol consumption



Smoking tobacco



Obesity



Type 2 diabetes



Viral hepatitis (HBV or HCV)



Cirrhosis



Aflatoxin exposure

- Aflatoxin is a poison produced by a fungus that grows on food in moist, warm conditions.<sup>13</sup>
- Aflatoxins can be found in crops of maize, corn, peanuts, cottonseed, rice, and tree nuts.
- Exposure to aflatoxins occurs by eating produce from contaminated crops or eating of meat or dairy products from animals that have been fed with contaminated crops.
- Farmers and other agricultural workers are more exposed to aflatoxins from inhaling dust while handling and processing contaminated crops.

## Racial and Ethnic Distribution of Risk Factors

- Exposure to aflatoxin increases the risk of liver cancer among individuals with chronic HBV or HCV infection and is a prominent risk factor in some locations, such as Asia, sub-Saharan Africa, and Mexico.<sup>7</sup>



- Infection with HBV or HCV, fatty liver disease, alcohol intake, and aflatoxins are among the top attributing risk factors for liver cancer among the Asian and Asian American population.<sup>5</sup>

Asian American men have the **highest** risk of liver cancer of men of all other racial/ethnic groups.<sup>6</sup>

- Long-term and low-level dietary exposure to aflatoxin is a noteworthy risk factor for HCC in Asia.<sup>5</sup>
- In the US, Hispanic men and women have a higher prevalence of type II diabetes and excess body weight compared to non-Hispanic whites, and are thus more likely to develop metabolic-associated liver cancer.<sup>7</sup>

Chronic HBV and HCV infection is the **strongest** risk factor for liver cancer.

- Despite the relatively low prevalence in the US overall, HCV infection majorly impacts liver cancer among Hispanic individuals in Florida.<sup>7</sup>
- Chronic liver disease is among the leading causes of death among Asian Americans.<sup>6</sup>
  - Asian American men have higher incidence and mortality rates for liver cancer as compared to Hispanic, non-Hispanic white, or Asian/Pacific Islander men.<sup>6</sup>
  - Asian American men are 60% more likely to die from liver and IBD cancer, as compared to non-Hispanic White men; whereas, Asian American women are 90% more likely to develop liver and IBD cancer than non-Hispanic White women.<sup>6</sup>



# SYMPTOMS

There are few, if any, signs and symptoms of early- and even intermediate-stage liver cancer. This is partly because there are no pain fibers in the liver. Since the liver lining tissue cannot sense pain, cancer can grow to a large size, only causing pain when it begins to stretch out of the liver. As liver cancer grows in the body, common symptoms that appear include:<sup>11</sup>



Stomach pain  
or pain in the upper  
part of the belly



Progressive  
weight loss



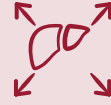
Loss of appetite



Jaundice (yellowing  
of the skin or eyes)



White stools



Abdominal bloating  
due to enlarged liver



A feeling of fullness after  
eating a small meal



Weakness and  
fatigue



Fever



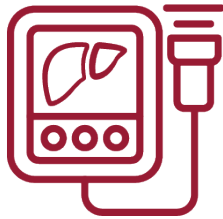
Nausea or vomiting



A lump or heaviness in the belly

# SCREENING

Screening for a condition is done to find the disease early in people at risk. When diagnosed at an early stage, cancers of the liver can be effectively treated. The American Association for the Study of Liver Diseases recommends surveillance for liver cancer in adults with cirrhosis using screening tests every 6 months with ultrasound (with or without the alpha-fetoprotein blood test)<sup>14</sup>. Persons with chronic hepatitis B virus without cirrhosis are also recommended to have liver cancer surveillance, generally above the age of 40 years.<sup>15</sup>



## LEWIS R. ROBERTS MB, CHB, PHD

*Professor of Medicine, Division of Gastroenterology & Hepatology at Mayo Clinic*

“Liver cancer screening is not recommended for the general population because it has not been proven to reduce the risk of dying of liver cancer. However, people with chronic liver conditions are at increased risk of liver cancer and may consider screening, such as people who have:

- HBV infection
- HCV infection
- Nonalcoholic steatohepatitis
- Alcoholic cirrhosis
- Liver cirrhosis from any other causes.”

# STAGING

If liver cancer is suspected after screening, several different types of diagnostic tests are used to gather more information, such as blood tests, imaging tests, and possibly a liver biopsy. If cancer is diagnosed, additional tests will be done to determine if cancer has spread within or beyond the liver. This process is called staging. This additional information helps the healthcare team make recommendations for appropriate treatment. There are two commonly used staging systems for liver cancer in the U.S.

## 1

### Tumor Node Metastasis (TNM)

This system was developed by the American Joint Committee on Cancer (AJCC). It includes stages: I, II, III, IV. The TNM system takes into account the following factors:



- Tumor characteristics (size, number, vascular invasion)
  - Vascular invasion refers to the presence of tumor cells within the blood vessels or lymph vessels.



- Lymph node involvement



- Metastatic disease caused by the spread of tumor cells to other parts of the body

## 2

## Barcelona Clinic Liver Cancer (BCLC)

This system is the most common staging system and only applies to HCC. It includes stages: O, A, B, C, D. The BCLC staging system considers the following factors:



- The Child-Pugh score, which measures normal liver function, especially in people with cirrhosis



- Blood levels of bilirubin (bilirubin causes yellowing of the skin and eyes)



- Blood levels of albumin (a prominent protein produced by a liver that functions normally)



- Prothrombin time (measures how well the liver can make blood clotting factors)



- Fluid (ascites) in the abdomen



- Brain function affected by liver disease



- Tumor characteristics (amount, size)



- Performance status of daily activities

Both staging systems, TNM and BCLC, are evidence-based. Both are commonly used for HCC staging and management, although the BCLC Child-Pugh score is exclusively used with HCC. For CCA, physicians typically use the TNM staging system because the system classifies the cancer stage and defines the extent of the cancer including size, location, and number of tumors.

## The following two systems are used to determine priority for liver transplant in the U.S.:

### Milan Criteria

This system determines if liver transplantation in adults with HCC or cirrhosis is right to cure the disease.

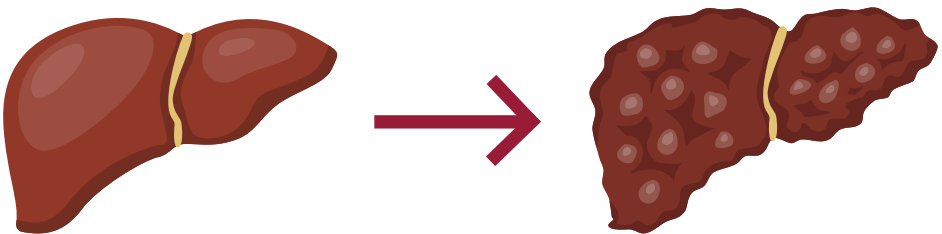
There are four criteria:

1. Single tumor diameter less than 5 cm
2. No more than three tumors, each one not exceeding 3 cm
3. No invasion of tumor cells into the blood or lymphatic vessels (angioinvasion)
4. No extrahepatic (outside of the liver) spread of tumors

### Model for End-Stage Liver Disease

This system, otherwise known as MELD, is a scoring system for assessing the severity of chronic liver disease to determine disease prognosis and prioritize the allocation of liver transplant.

- MELD scores range from 6-40, measured by lab tests performed on serum bilirubin, serum creatine, and the international normalized ratio (INR) for prothrombin time to predict survival.
- Pediatric End-Stage Liver Disease (PELD) score is a similar score, adjusted to be used for children younger than 12 years of age.



# RISK REDUCTION & PREVENTATIVE PRACTICES

The American Cancer Society estimates that up to 70% of liver cancer cases, particularly hepatocellular carcinoma, can be prevented with certain lifestyle changes.<sup>3</sup> These include:



## Vaccination against viral hepatitis

The hepatitis B vaccine is recommended for all infants at birth and adults at increased risk, since there is no treatment available. Universal vaccination of newborns with the HBV vaccine reduces the incidence of HCC.<sup>5</sup>



## Treat of viral hepatitis

Though it has no vaccine, hepatitis C virus can be cured in 95% of cases with direct-acting antiviral medicines.



## Maintain a healthy weight

and avoid obesity if you have fatty liver disease or type 2 diabetes.



## Exercise regularly

and eat a healthy, balanced diet that contains essential vitamins and minerals.



## Avoid excessive alcohol consumption



## Avoid cigarette smoking

Do not smoke or chew products containing tobacco.



## Avoid sharing needles

Practice safe injection practices with sterile needles to prevent the spread of viral hepatitis.



## Drink coffee

There is increasing evidence that drinking at least 2 cups of coffee a day reduces the progression of liver disease in patients and is associated with lower incidences of fibrosis, cirrhosis, and liver cancer, particularly HCC.<sup>16</sup>



## Reduce exposure to aflatoxins

According to the NCI, you can reduce your aflatoxin exposure by discarding moldy nuts and selecting nuts and nut butters from major commercial brands, especially peanuts.<sup>13</sup>

# REFERENCES

1. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol*. 2022;77(6):1598-1606. doi:10.1016/j.jhep.2022.08.021
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021; 71: 209-249. <https://doi.org/10.3322/caac.21660>
3. American Cancer Society. *Cancer Facts & Figures 2024*. Atlanta: American Cancer Society; 2024. 2024-cancer-facts-and-figures-acf.pdf
4. Key Statistics About Liver Cancer. American Cancer Society. 2024. Revised 17 January 2024. Key Statistics About Liver Cancer | American Cancer Society
5. Liu Y, Liu L. Changes in the Epidemiology of Hepatocellular Carcinoma in Asia. *Cancers (Basel)*. 2022;14(18):4473. Published 2022 Sep 15. doi:10.3390/cancers14184473
6. Chronic Liver Disease and Asian Americans. Office of Minority Health. U.S. Department of Health and Human Services. Chronic Liver Disease and Asian Americans | Office of Minority Health ([hhs.gov](https://hhs.gov))
7. American Cancer Society. *Cancer Facts & Figures for Hispanic/Latino People 2021-2023*. Atlanta: American Cancer Society, Inc. 2021 hispanic-latino-2021-2023-cancer-facts-and-figures.pdf
8. Rawla P, Sunkara T, Muralidharan P, Raj JP. Update in global trends and aetiology of hepatocellular carcinoma. *Contemp Oncol (Pozn)*. 2018;22(3):141-150. doi:10.5114/wo.2018.78941
9. Sarcognato S, Sacchi D, Fassan M, et al. Cholangiocarcinoma. *Pathologica*. 2021;113(3):158-169. doi:10.32074/1591-951X-252
10. R.J. Verma (2004) Aflatoxin Cause DNA Damage, *International Journal of Human Genetics*, 4:4, 231-236, DOI: 10.1080/09723757.2004.11885899
11. Liver Cancer. Mayo Clinic. 2024. Published 28 April 2023. Liver cancer - Symptoms and causes - Mayo Clinic
12. Liver Cancer. Mayo Clinic. 2024. Published 11 February 2023. Cirrhosis - Symptoms and causes - Mayo Clinic
13. Aflatoxins. National Cancer Institute. 2022. Updated 5 December 2022. Aflatoxins - Cancer-Causing Substances - NCI
14. Heimbach JK. Overview of the Updated AASLD Guidelines for the Management of HCC. *Gastroenterol Hepatol (N Y)*. 2017 Dec;13(12):751-753. PMID: 29339953; PMCID: PMC5763563
15. Who Should Be Screened? Hepatitis B Foundation. 2024. Who Should Be Screened? » Hepatitis B Foundation ([hepb.org](https://hepb.org))
16. Wadhawan M, Anand AC. Coffee and Liver Disease. *J Clin Exp Hepatol*. 2016;6(1):40-46. doi:10.1016/j.jceh.2016.02.003
17. Xu JQ. Trends in liver cancer mortality among adults aged 25 and over in the United States, 2000–2016. *NCHS Data Brief*, no 314. Hyattsville, MD: National Center for Health Statistics. 2018.

## Resources

Global Liver Institute [www.globalliver.org](http://www.globalliver.org)

Liver Central [www.livercentral.org](http://www.livercentral.org)

National Cancer Institute [www.cancer.gov](http://www.cancer.gov)

American Cancer Society [www.cancer.org](http://www.cancer.org)

Cholangiocarcinoma Foundation [www.cholangiocarcinoma.org](http://www.cholangiocarcinoma.org)

## About Global Liver Institute

Global Liver Institute (GLI) is a 501(c)3 nonprofit organization founded in the belief that liver health must take its place on the global public health agenda commensurate with the prevalence and impact of liver illness. GLI promotes innovation, encourages collaboration, and supports the scaling of optimal approaches to help eradicate liver diseases. Operating globally, GLI is committed to solving the problems that matter to liver patients and equipping advocates to improve the lives of individuals and families impacted by liver disease. GLI holds Platinum Transparency with Candid/GuideStar, is a member of the National Health Council, and serves as a Healthy People 2030 Champion. Follow GLI on [Facebook](#), [Instagram](#), [LinkedIn](#), and [YouTube](#) or visit [www.globalliver.org](http://www.globalliver.org).



