Casual Friday Series

The Layers of Liver Disease Part 2

A Biogenetix Clinical Presentation

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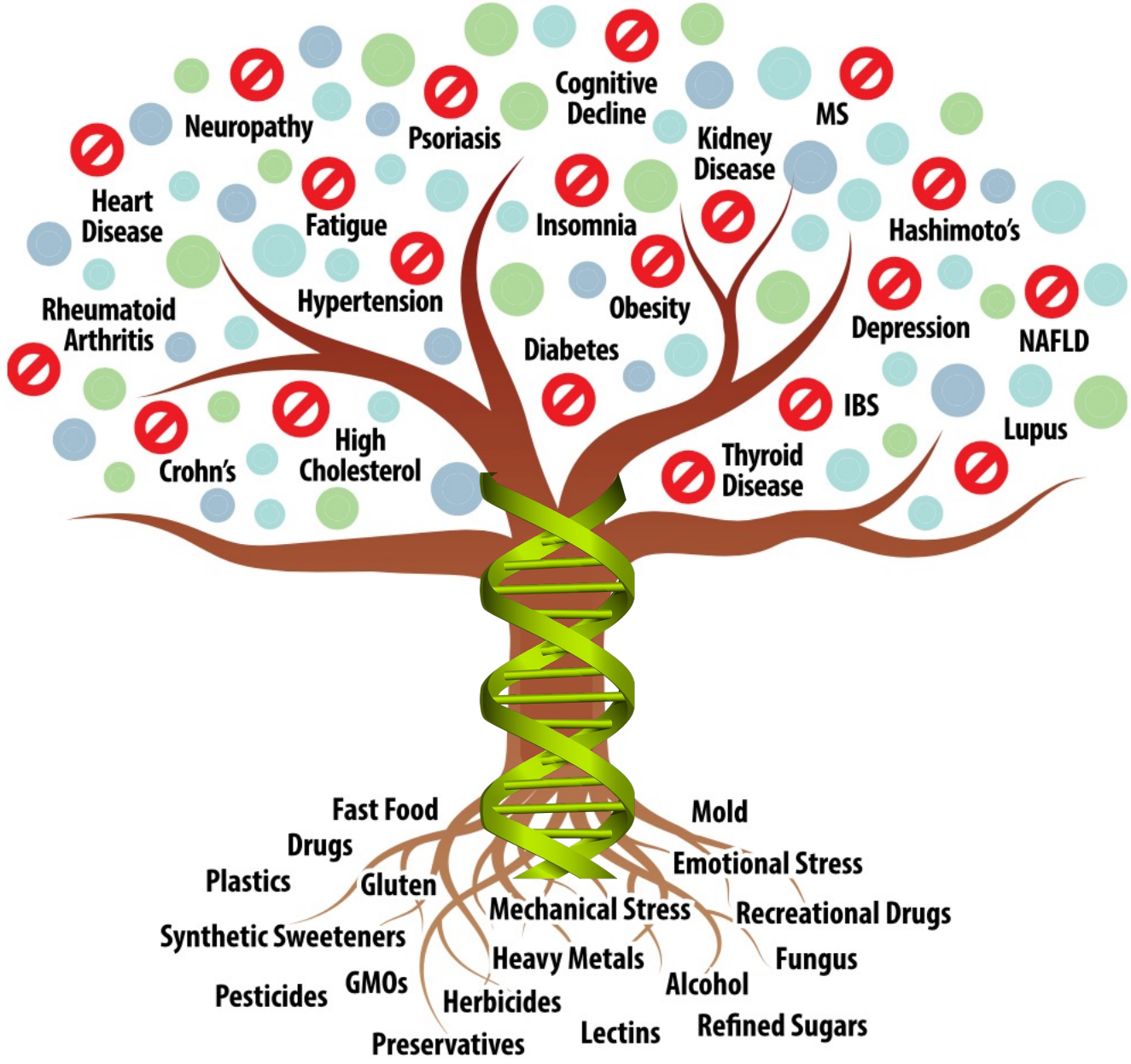
Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

The liver has a significant role in metabolism, regulation of red blood cells (RBCs) and glucose synthesis and storage. The liver function tests typically include alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time (PT), the international normalized ratio (INR) and albumin. These tests can be helpful in determining an area of the liver where damage may be taking place and depending on the pattern of elevation can help organize a differential diagnosis. Elevations in ALT and AST in disproportion to elevations in alkaline phosphatase and bilirubin denotes a hepatocellular disease. Whereas, an elevation in alkaline phosphatase and bilirubin in disproportion to ALT and AST would denote a cholestatic pattern. The actual function of the liver can be graded based on its ability to produce albumin as well as vitamin K dependent clotting factors.

https://www.ncbi.nlm.nih.gov/books/NBK482489/

Viral Hepatitis

Viral illnesses are a common cause of hepatitis and elevation in LFTs. Viral hepatitis B, C, and D can cause chronic hepatitis, while hepatitis A and E cause acute viral hepatitis. Several other viruses, including HIV, Epstein-Barr (EBV), and Cytomegalovirus (CMV), can also cause hepatitis.[11]

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic disease that is characterized by continuing hepatocellular inflammation and necrosis and a tendency to progress to cirrhosis. It is more common in young women than men with a 4:1 ratio. The patient usually presents with high LFTs without apparent cause. These patients can have positive autoantibodies, including antinuclear antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibodies, and antibodies to the liver antigen.

Hepatic Steatosis and Nonalcoholic Steatohepatitis

Fatty liver disease, aka nonalcoholic steatohepatitis, has gained more attention recently because of its ability to cause chronic hepatic disease as well as hepatocellular carcinoma (HCC). The typical patient with this disease is overweight, has type II diabetes, or has dyslipidemia and no evidence of clinically significant alcohol use. The AST and ALT are usually both elevated with a ratio of 1:1, with other liver function tests being normal.

https://www.ncbi.nlm.nih.gov/books/NBK482489/

Functional Lab Ranges

- Alanine transaminase: 10-26 IU/L
- Aspartate transaminase: 10-26 IU/L
- Alkaline phosphatase: 65-90 IU/L
- Gamma-glutamyltransferase: 10-26 IU/L
- Bilirubin: .5-.8 mg/dL
- Prothrombin time: 10.9 to 12.5 seconds
- Albumin: 4.2-4.7 g/dL

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Functional Lab Patterns

Alcohol Induced Pattern:	AST:ALT 2:1 GGT Elevated Bilirubin +/-
Cholestatic Pattern:	Alk. Phos. Elevated GGT Elevated Bilirubin Elevated

Nonalcoholic Fatty Liver Disease: The Overlooked Complication of Type 2 Diabetes

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The incidence of NAFLD is rising, paralleling that of obesity and diabetes mellitus. There has been extensive research in the area of NAFLD, especially over the past two decades. However, given the lack of highly reliable noninvasive diagnostic methods, the burden of NAFLD probably remains overlooked. By liver ultrasound, studies have demonstrated the prevalence of NAFLD to be 24% in United States, whereas using blood testing alone this is underestimated at just 13% (6). By the gold-standard magnetic resonance imaging and spectroscopy (^{1}H-MRS), the prevalence of NAFLD in the general population is estimated to be 34% (7).

NAFLD often progresses to steatohepatitis (NASH), especially in patients with T2DM. NASH is hallmarked by hepatocellular necrosis, lobular inflammation and often fibrosis. Many studies have now documented that patients with NASH and fibrosis have the worst mortality (9). As fibrosis progresses, cirrhosis develops. This rate of progression to cirrhosis is highly variable and dependent on age, BMI, blood pressure control, presence of T2DM, and degree of steatohepatitis (10). The three most relevant risk factors are obesity (excessive BMI or visceral obesity), T2DM, and presence of moderate to severe fibrosis (11). However, given the high heterogeneity in disease progression one must admit that the precise factors leading to cirrhosis remain unclear.

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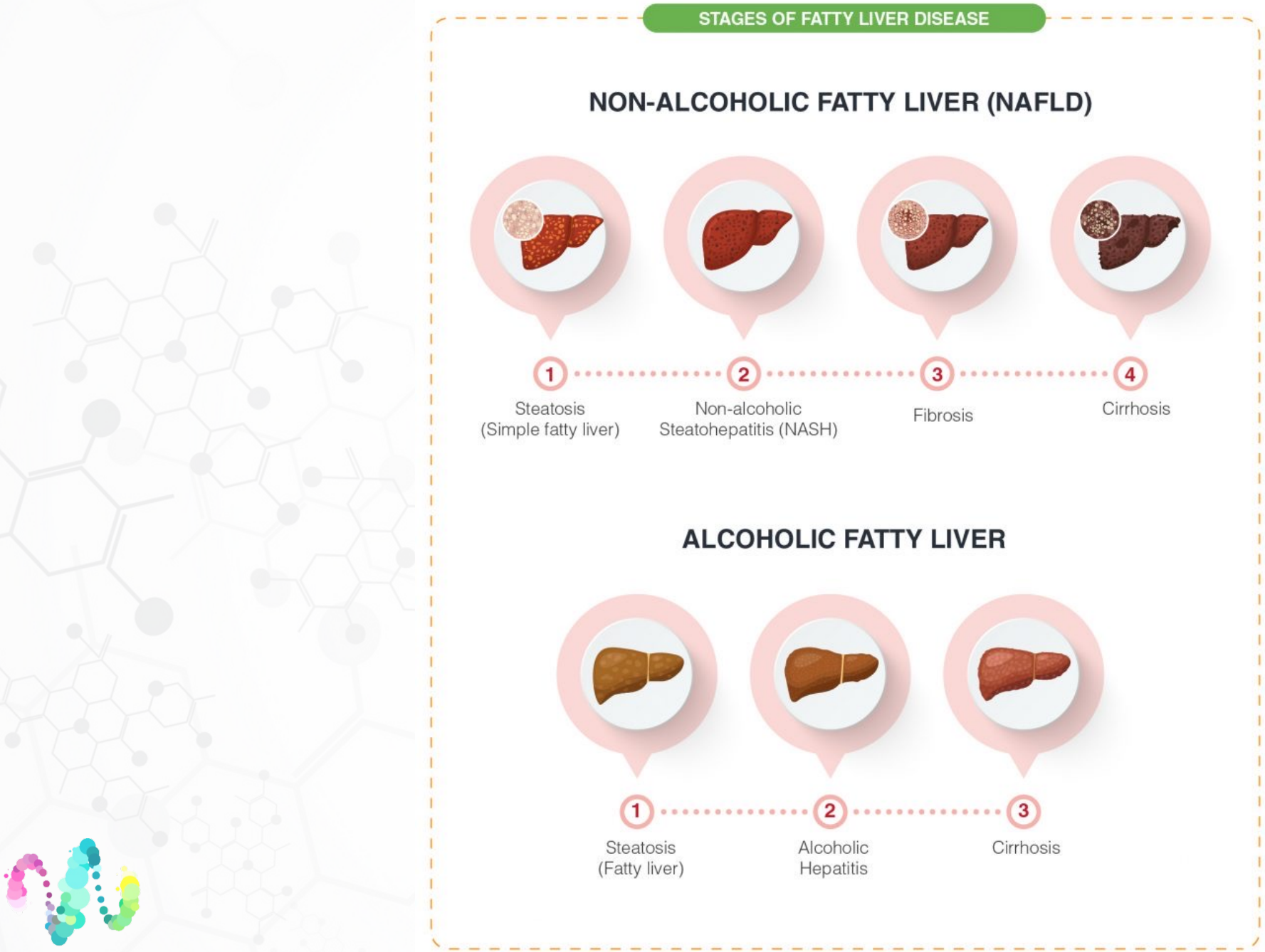

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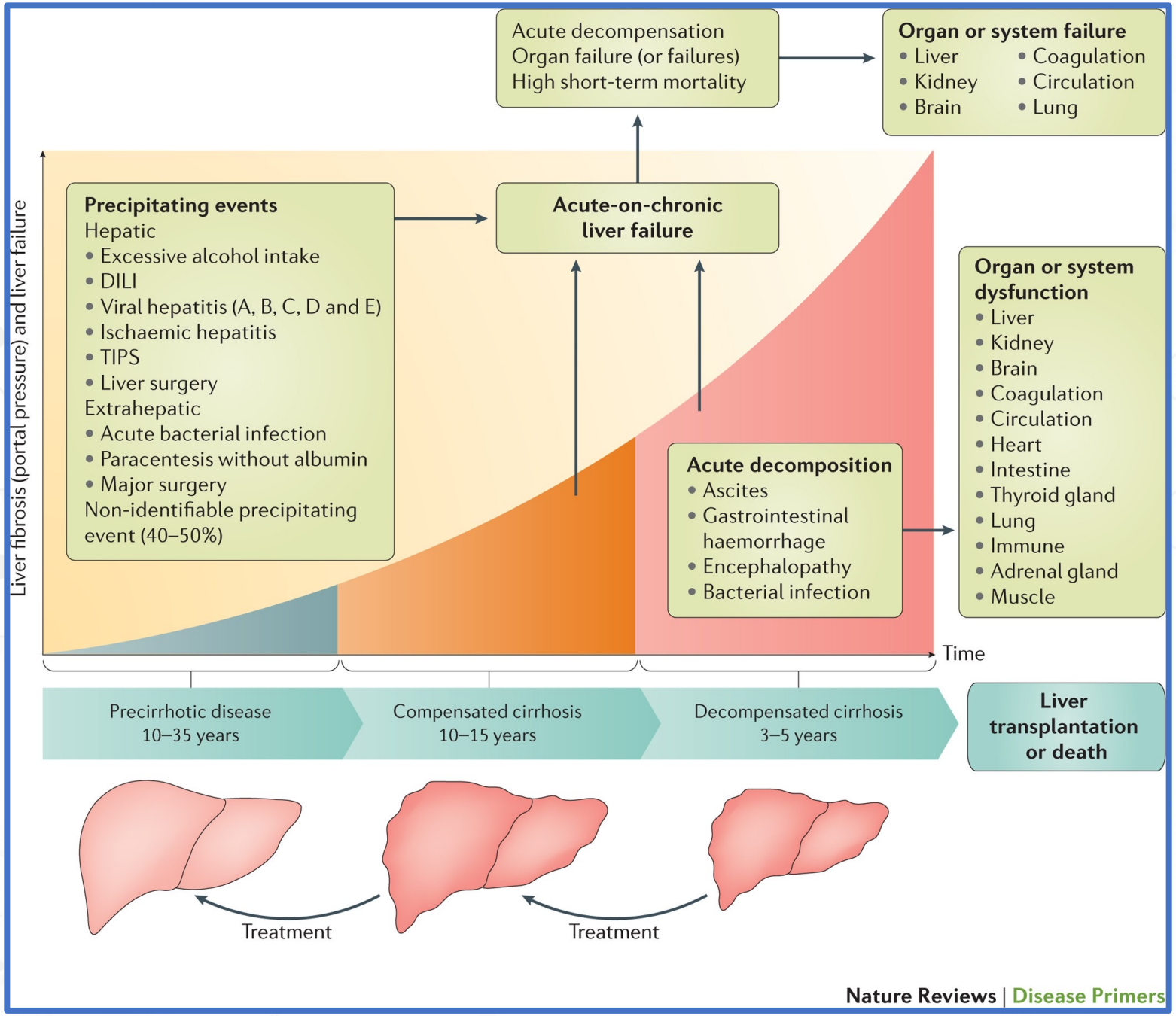

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Many factors lead to cardiovascular disease in patients with T2DM and NAFLD. For instance, they have increased intrahepatic triglyceride accumulation and insulin resistance. This is associated with increased hepatic VLDL secretion and a decrease in the peripheral clearance of triglyceride-rich lipoproteins. This results in a proatherogenic profile, which includes hypertriglyceridemia, low HDL-C, and an increase in small, dense LDL particles, plus a state of subclinical inflammation (8).

These patients also often have more severe hepatic insulin resistance leading to progressive deterioration of glycemic control (9). Hepatic insulin resistance is associated with hyperinsulinemia from increased insulin secretion and decreased insulin clearance (3,15). Hyperinsulinemia *per se* has been associated with atherogenesis in animal models of disease and in epidemiological studies. Chronic hyperinsulinemia also causes downregulation of insulin signaling pathways and acquired insulin resistance in short-term clinical studies in humans (11). In this context, hyperglycemia is more severe and also appears to contribute to CVD. Endothelial dysfunction also has been shown to cause increased cardiovascular risk in patients with NAFLD (16). Early left ventricular "diastolic dysfunction" (or heart failure with preserved ejection fraction or HFpEF) has been noted in patients with NAFLD and well controlled T2DM independent of other risk factors (17). Patients with NAFLD are often found to have a significantly worse carotid intima-media thickness with increased atherosclerotic disease when compared with clinically matched patients without NAFLD. This has been correlated in some studies with an advancing degree of steatosis, inflammation, and/or fibrosis (18,19). In NASH with cirrhosis, CVD is the leading cause of mortality (1,8,20).

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The presence of NAFLD and NASH with fibrosis have been recently associated with chronic kidney disease (CKD), and more severe forms of fatty liver disease correlate with worse and progressive stages of CKD. In most studies, CKD has been defined as having an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or increased albuminuria/proteinuria (20,63,64). In a case control study by Targher et al, the severity of liver histology in patients with biopsy-proven NASH was found to be independently associated with the degree of worsening eGFR (65).

A cross-sectional study of Japanese patients with biopsy-proven NAFLD showed an increased prevalence of CKD with worsening liver histology. They found that overall, 14% of patients with NAFLD had evidence of CKD. Of the patients with biopsy proven NASH, 21% had the presence of CKD; and of the patients with NAFLD with no evidence of NASH, only 6% had CKD (64). This was higher than in patients without NAFLD or NASH. The pathophysiology of this association is not well understood, but the increased atherogenicity associated with NAFLD is likely a contributing factor (20). A more recent meta-analysis also showed a higher prevalence of CKD in patients with NASH when compared with patients with NAFLD without NASH, and a higher prevalence of CKD in patients with advanced fibrosis when compared with patients with lower degree of fibrosis (63).

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Normally, there is a close regulation between beta-oxidation, hepatic tricarboxylic acid (TCA) cycle activity, ketogenesis and ATP synthesis. Normally, FFAs influx is efficiently dealt through beta-oxidation. However, in states of chronic overfeeding, beta-oxidation can over time become relatively ineffective, resulting in the accumulation of hepatocyte ceramides and DAGs (as well as acylcarnitines), as seen in states of hepatic steatosis (71,75-77). As summarized in Figure 2, the current working hypothesis in NASH is that overactive hepatic TCA cycle carries the risk of overloading the mitochondrial electron transport chain and hence promoting not only the formation of toxic metabolites but the production of reactive oxygen species (ROS) and other inflammatory mediators. In this setting, it is believed that inflammatory pathways are triggered which then lead to hepatocyte necrosis and chronic inflammation, Kupffer cell activation and recruitment, as well as hepatic stellate cell activation. This disruption of the normal equilibrium between hepatocyte and its microenvironment (i.e., in particular with Kupffer cells and hepatic stellate cells, the latter promoting fibrogenesis) seems to determine the degree of hepatocyte injury and the triggering of downstream pathways that lead to cirrhosis, as reviewed in-depth elsewhere (70). However, while many recent interventions successful in animal models have failed in humans, it is of interest that there is a correlation between successful treatment for NASH in humans (with GLP-1RA or pioglitazone [8]) with studies *in vivo* with such interventions that restore hepatocyte TCA function and reduce intracellular toxic lipids (94, 95), giving support to the hypothesis of increased mitochondrial FFA flux as a potential therapeutic target for patients with NASH.

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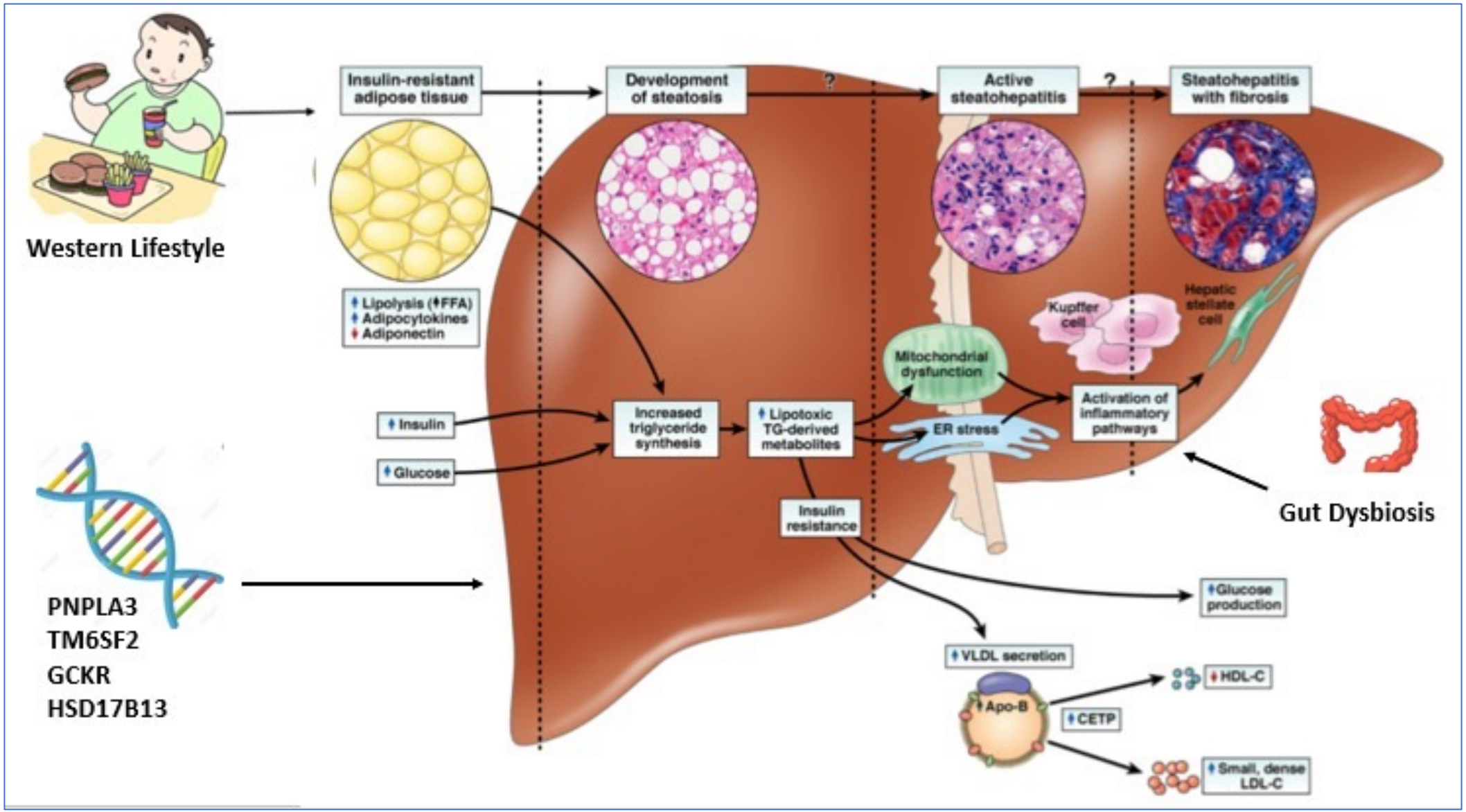

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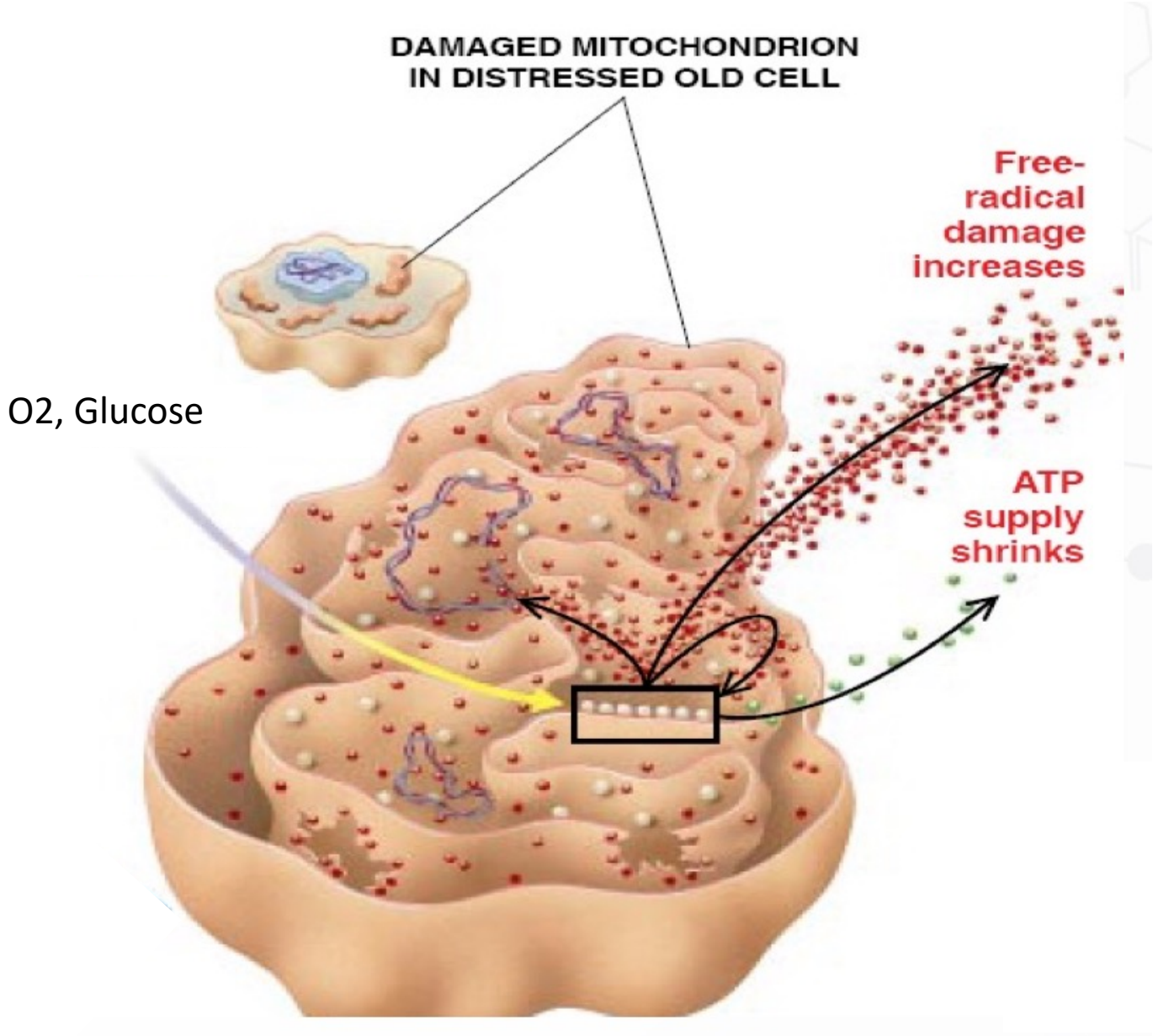

O2, Glucose

Source: Weindrich_SciAm_1996

Table 3.

Biomarkers Available for use in Diagnosis of Advanced Fibrosis (Stages 3 or 4). Modified from reference (8)

Test	Parameters included	number	PPV	NPV	Patients unable to be classified "grey zone"
NAFLD fibrosis score	Age, BMI, diabetes, AST/ALT ratio, platelets, albumin	733	82%	88%	24%
Fibrotest	Age, sex, total bilirubin, GGT, a2-macroglobulin, apolipoprotein A1, haptoglobin	267	60%	98%	32%
†FIB-4 index	Age, AST and ALT, platelets	541	80%	90%	30%

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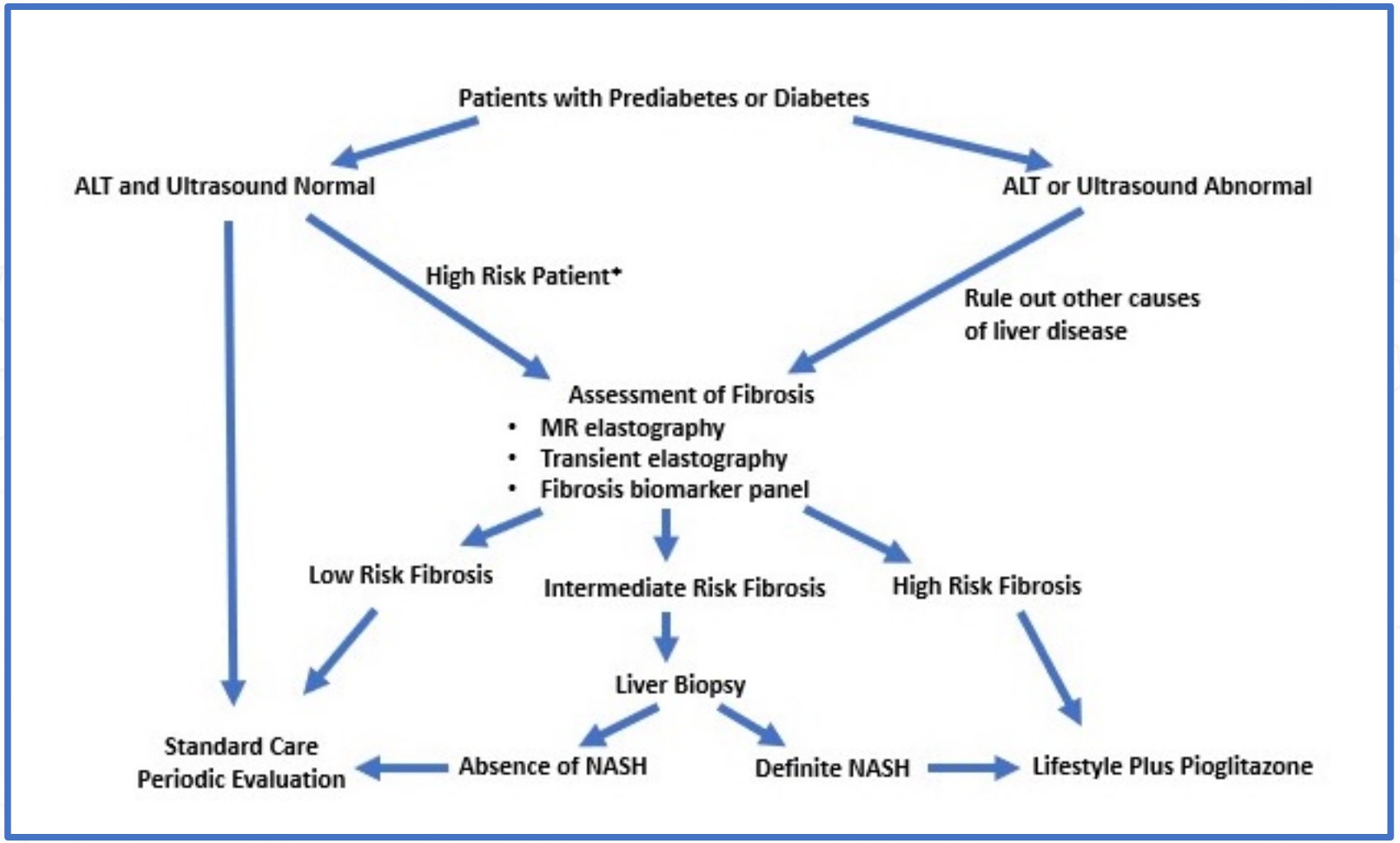

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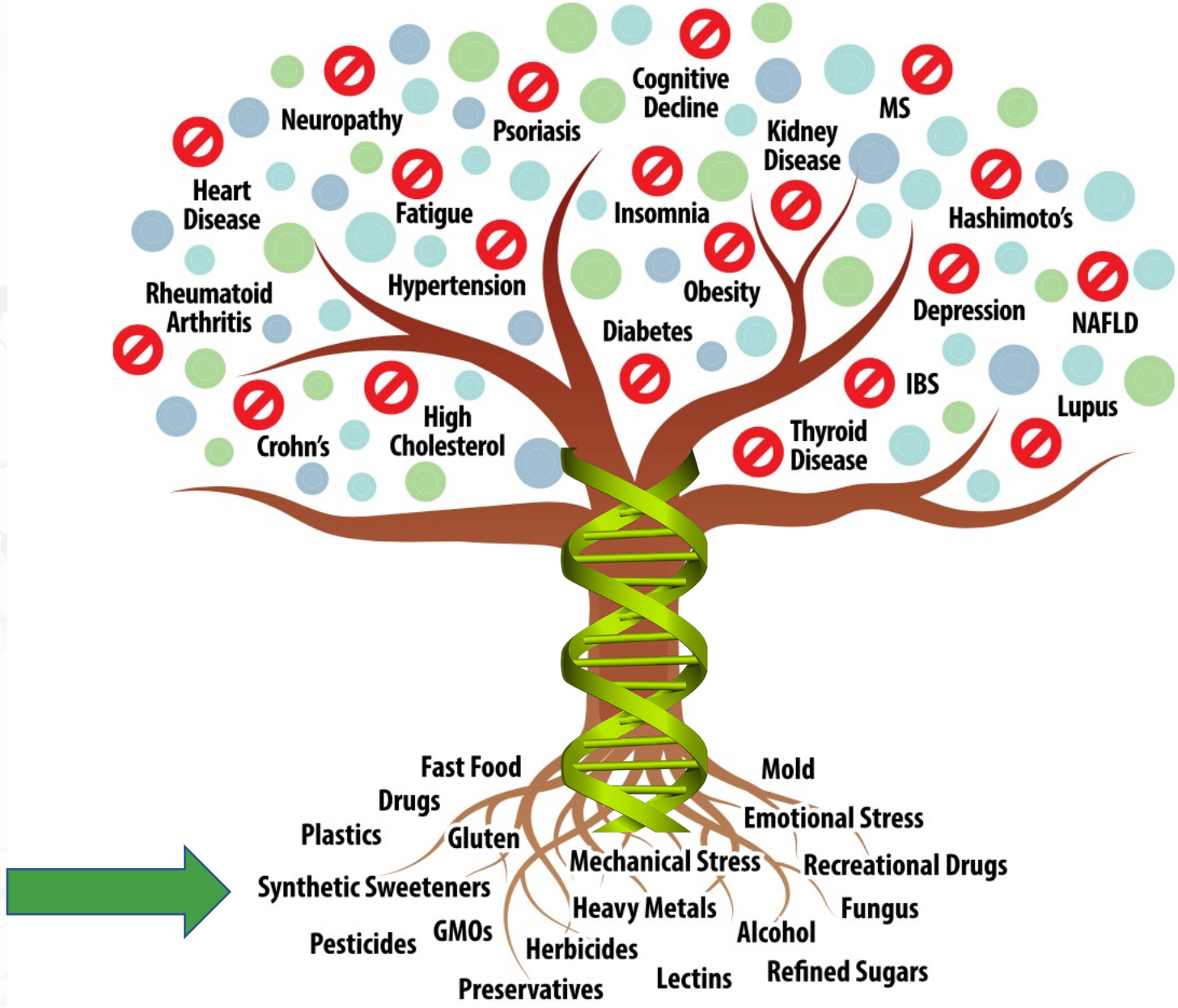
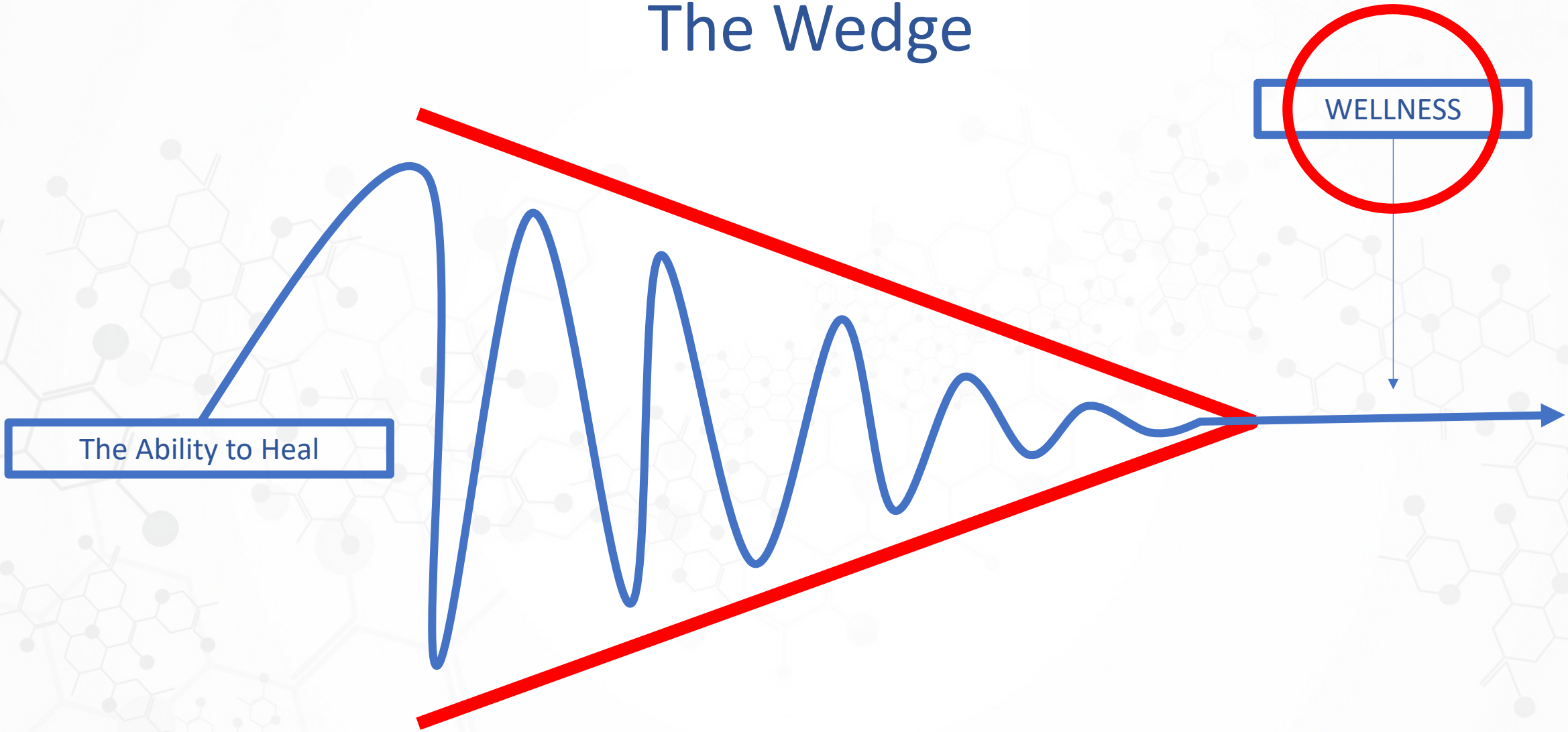

Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

The Wedge



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