# Nonalcoholic Fatty Liver Disease: An Important Consideration for Primary Care Providers in Hawai‘i

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## Abstract

*Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. NAFLD is a broad term for both non-alcoholic fatty liver (NAFL), which describes simple fatty liver without inflammation, and non-alcoholic steatohepatitis (NASH), the more severe phenotype with hepatocellular inflammation. The population of Hawai'i is particularly vulnerable to the NAFLD and obesity epidemics due to its large proportions of high-risk ethnic minorities exposed to varying degrees of westernization. Unfortunately, primary care providers (PCPs) often face a lack of awareness on the diagnosis and disease spectrum of NAFLD. Early initiation of treatment for NAFLD is crucial to slow its progression and prevent liver-related morbidity and mortality. This review aims to raise awareness for NAFLD among PCPs in Hawai'i by summarizing the disease's epidemiology, diagnosis, and treatment. The diagnostic workup of NAFLD in the primary care setting involves exclusion of other liver disease etiologies and staging assessment of fibrosis and steatosis through non-invasive means such as serum biomarkers or elastography. Patients with overt signs and symptoms of cirrhosis or a high likelihood of advanced hepatic fibrosis should be referred to liver disease specialists. The role of PCPs in NAFLD management involves facilitating weight loss through therapeutic lifestyle modifications and treatment of comorbid cardiovascular conditions. Evidence-based pharmacologic therapies for NAFLD are available, such as vitamin E and pioglitazone, with more currently in development.*

## Keywords

*Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, primary care, Hawai'i*

## Abbreviations and Acronyms

*AASLD = American Association of Study of Liver Diseases*
*ACE = Angiotensin converting enzyme*
*ALT = Alanine aminotransferase*
*APRI = AST to platelet ratio index*
*ARB = Angiotensin receptor blocker*
*AST = Aspartate aminotransferase*
*BMI = Body mass Index*
*CVD = Cardiovascular disease*
*DM = Diabetes mellitus*
*FIB-4 = Fibrosis-4*
*FXR = Farnesoid X receptor*
*GLP-1 = Glucagon-like peptide 1*
*GREACE trial = Greek Atorvastatin and Coronary Heart Disease Evaluation trial*
*HCC = Hepatocellular carcinoma*
*MetS = Metabolic syndrome*
*(MEC) = Multiethnic/Minority Cohort*
*MRE = Magnetic Resonance Elastography*
*NAFLD = Non-alcoholic fatty liver disease*
*NAFL = Non-alcoholic fatty liver*
*NASH = Non-alcoholic steatohepatitis*
*NHOPI = Native Hawaiians and Other Pacific Islanders*
*NFS = NAFLD Fibrosis Score*
*NPV = Negative predictive value*
*PIVENS trial = Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis trial*
*PCP = Primary care provider*
*PNPLA3 = Patatin-like phospholipase domain-containing 3*
*PPV = Positive predictive value*
*RAS = Renin-angiotensin system*
*TE = Transient elastography*
*US = United States*

## Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to excessive fat accumulation in the liver in the absence of significant alcohol consumption, defined as ≥21 drinks per week in men and ≥14 drinks per week in women, typically in the setting of insulin resistance. NAFLD affects a large proportion of the United States (US) population, and its incidence and prevalence are increasing to an epidemic around the world. NAFLD has 2 distinct phenotypes: simple fatty liver or non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH).[1] NAFL is a condition with hepatic steatosis without inflammation, while NASH refers to steatosis that is accompanied by varying degrees of hepatocyte injury and fibrosis. In this review, we summarize the epidemiology and natural history of NAFLD, appropriate diagnostic workup and management in the primary care setting, and indications for referral to liver disease specialists. Our goal is to strengthen the role of PCPs in combating the growing epidemic of obesity and NAFLD in Hawai‘i.

## Epidemiology and Natural History of NAFLD

NAFLD is the most prevalent cause of liver disease worldwide, affecting 25% of the global population and between 21% and 31% of the US population.[2,3] The estimated economic cost of NAFLD in the US is $103 billion annually.[4] NAFLD is forecasted to become the leading indication for liver transplantation in the next decade.[4] The risk factors for NAFLD include obesity, diabetes mellitus (DM), dyslipidemia, and hypertension, which are features of Metabolic Syndrome (MetS).[5] As patients with NAFLD often suffer from co-existent cardiovascular disease (CVD) given the risk factors associated with NAFLD, CVD is the primary cause of mortality in NAFLD.[6] The risk of NAFLD increases with older age, being male, and having lower socioeconomic status.[7] High-calorie diets containing excess amounts

of saturated fats, refined carbohydrates, and sugar-sweetened beverages, together with an unhealthy sedentary lifestyle, also increase the risk of NAFLD.[8,9]

Up to 30% of NAFLD cases are associated with NASH, which has an increased risk of hepatic fibrosis. In NASH, compared to NAFL, hepatic fibrosis progresses twice as rapidly (0.07 vs 0.14 stage per year),[7] and cirrhosis develops 10 times more frequently (11% vs 1% over 16 years).[8] Once patients develop fibrosis, their risk of developing hepatocellular carcinoma (HCC) increases, and they may face liver-related morbidity and mortality.[6,10] The incidence of HCC in NAFLD is 0.04% per year in patients without cirrhosis and up to 4% per year in those with cirrhosis.[11]

## Pathogenesis of NAFLD

Hepatic triglyceride accumulation results from imbalanced lipid uptake, synthesis, and lipid oxidation that occurs with caloric excess and insulin resistance. Chronic overeating promotes adipose hypertrophy and insulin resistance, which increases peripheral lipolysis, fatty acid circulation, and fat influx into the liver. Hyperinsulinemia that accompanies insulin resistance promotes triglyceride synthesis and inhibits fatty acid β-oxidation in the liver.[12] Not all individuals with hepatic steatosis develop steatohepatitis and fibrosis. Simple steatosis progresses to steatohepatitis when toxic lipid metabolites cause mitochondrial dysfunction, reactive oxygen species formation, and inflammatory pathway activation.[13]

Recent genome-wide association and twin studies highlight the genetic basis of NAFLD. For instance, hepatic steatosis and fibrosis demonstrate high concordance among monozygotic twins.[14,15] Perhaps the most well-studied genetic factor for NAFLD is the rs738409 polymorphism (I148M variant) of the patatin-like phospholipase domain-containing 3 (PNPLA3) gene,[16] which is associated with 73% higher hepatic fat content and 3-fold increased risk of severe inflammation and fibrosis.[17] PNPLA3 polymorphism has been well described in Hispanic populations;[18] however, it may also play an essential role in the development of NAFLD in non-obese Japanese populations.[19] NAFLD-associated PNPLA3 mutations are typically found in 13% to 19% of Asians, compared to only 4% of whites and 2% of African Americans.[20] This result suggests that Asians may have a higher genetic predisposition to NAFLD irrespective of diet and metabolic profiles, a finding relevant to the population in Hawai‘i.

## NAFLD: A Pressing Problem for Hawai‘i

Hawai‘i has a diverse population with a high proportion of Asians and Native Hawaiians and Other Pacific Islanders (NHOPI). NAFLD appears to be particularly prevalent among Asians exposed to a rapid pace of westernization.[21] Some studies have shown that the prevalence of NAFLD among "westernized" Asian populations approaches 40%.[22] Setiawan, et al, showed that NAFLD is a significantly more common cause of cirrhosis among Japanese Americans (32.3%), Native Hawaiians (31.5%), and Latinos (31.9%) when compared to whites (21.7%) using the Multiethnic/Minority Cohort (MEC).[23] Among non-cirrhotics, NAFLD was responsible for almost 75% of chronic liver diseases in Japanese Americans and Native Hawaiians, compared to 61% of Latinos and 56% of whites. Furthermore, NHOPI are among the highest risk populations for MetS, type 2 DM, and CVD in the US.[24] Overall, this makes NAFLD a legitimate concern for the population in Hawai‘i given the already high risk of MetS.

## Diagnosing NAFLD in the Primary Care Office

PCPs are the first points of contact for patients with NAFLD as they often manage comorbid MetS, DM, and obesity. Unfortunately, PCPs may be underdiagnosing NAFLD. One study suggested that even though more than half of PCPs are treating patients with NAFLD, only 50% are aware of the differences between NAFL and NASH.[25] In a study involving patients with comorbid type 2 DM, the prevalence and severity of NAFLD are significantly underestimated by diabetes specialists.[26] Hence, in light of the increasing number of patients with risk factors for NAFLD, PCPs should be able to recognize patients with NAFLD to allow a timely diagnosis.

Suspicion for NAFLD should rise if there are mild to moderate elevations of alanine aminotransferase (ALT) more than aspartate aminotransferase (AST) or findings of hepatic steatosis on imaging. NAFLD may account for up to 25% of abnormal liver chemistries abnormalities in primary care settings.[27] In patients suspected of having NAFLD, it is necessary to rule out other causes of chronic liver diseases. PCPs should assess the amount of alcohol intake and use of potentially hepatotoxic medications, including supplements. Chronic viral hepatitis should be tested with hepatitis B and C serologies, and autoimmune hepatitis should be evaluated by obtaining autoimmune markers, such as an antinuclear antibody, anti-smooth muscle antibody, or immunoglobulins. Assessment of metabolic risk factors with fasting blood glucose, hemoglobin A1C, and lipids are also an important part of workup.

Some patients with NAFLD may have normal liver chemistries, however the magnitude of ALT elevation is a poor predictor of the severity of liver disease in NAFLD.[28,29] A current guideline published by the American Association of Study of Liver Diseases (AASLD) in 2018 recommends against routine screening for NAFLD in high-risk patients given lack of data suggesting cost-effectiveness and long-term benefit of screening.[30] It has also been suggested that ethnic groups at the highest risk for NAFLD, particularly Hispanics, be screened routinely.[31] Screening for NAFLD is likely best done on a case-by-case basis and guided by the overall clinical picture.

The term "lean NAFLD" is defined as NAFLD in patients with a normal body mass index (BMI) of <23 kg/m$^2$ for Asians and <25 kg/m$^2$ for non-Asians.[5] In comparison to obese NASH patients, lean NAFLD patients have less insulin resistance, which suggests a distinct underlying pathophysiology that is yet to be determined.[32] However, even in patients with lean NAFLD who do not have MetS, there tend to be higher rates of hypertension, dyslipidemia, and elevated fasting glucose than in non-NAFLD patients.[32] Recognition of lean NAFLD patients is particularly crucial for PCPs as these patients tend to remain asymptomatic until the development of cirrhosis and hepatic decompensation.[32] Figure 1 describes clinical findings to consider when adding NAFLD to a differential diagnosis in patients presenting to a PCP.

## Staging Fibrosis in the Primary Care Office

Since fibrosis is the most important predictor of poor clinical outcomes in patients with NAFLD,[33,34] effort should be made to screen for fibrosis by PCPs. Liver biopsy remains the gold standard in diagnosing and staging NAFLD. However, PCPs are typically hesitant to obtain liver biopsy without specialist consultation. In diabetic patients with NAFLD, higher age, BMI >30 kg/m$^2$, smoking, and low platelet levels are independent risk factors for liver fibrosis.[35] Occasionally, a combination of clinical findings, such as the presence of ascites, hepatic encephalopathy, jaundice, and thrombocytopenia, may suggest a diagnosis of cirrhosis. Thrombocytopenia (platelet <150,000 per microliter of blood) is the single most predictive laboratory finding for cirrhosis with a positive likelihood ratio of 6.[33]

Several validated predictive models based on routine blood test have been developed. Three common predictive models for advanced fibrosis and cirrhosis are the AST to platelet ratio index (APRI), Fibrosis-4 (FIB-4), and the NAFLD Fibrosis Score (NFS). APRI >2, FIB-4 >3.25, and NFS >0.676 indicate a high likelihood of fibrosis with positive predictive values (PPV) of 60% to 90%; APRI <1, FIB-4 <1.45, and NFS < -1.455 indicate a low likelihood of fibrosis with negative predictive values (NPV) exceeding 85%.[36,37] These non-invasive markers are particularly useful in excluding cirrhosis. Patients with intermediate or high likelihood of fibrosis require further assessment and referral to liver disease specialists.

Imaging-based assessment of fibrosis and steatosis is becoming an alternate option. Transient elastography (TE, Fibroscan™) and Magnetic Resonance Elastography (MRE) are the main options. TE is usually favored over MRE in the primary care settings because it is less expensive, easy to perform at bedside, and gives results in real-time. TE is more accurate in ruling in

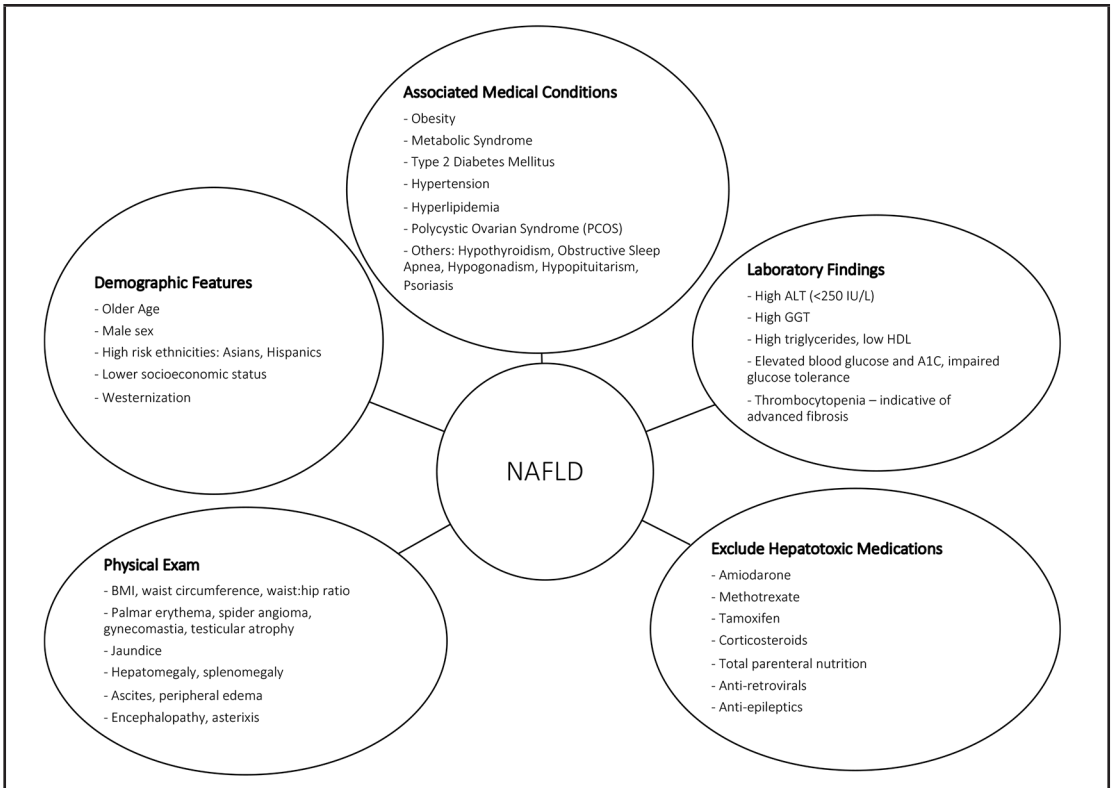


Figure 1. Clinical Considerations in the Insidious Presentation of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

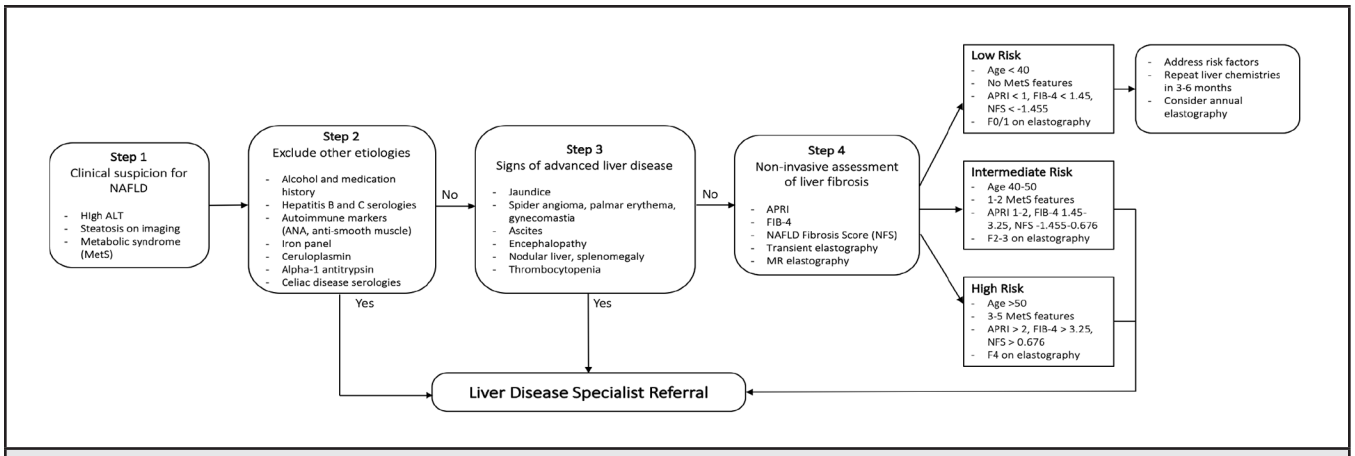


Figure 2. Algorithmic Approach to the Evaluation of Nonalcoholic Fatty Liver Disease in the Primary Care Setting

(PPV >80%) or ruling out (NPV >95%) cirrhosis, compared to diagnosing intermediate stages of fibrosis (diagnostic accuracy 60%).[38] TE is available in select institutions in Hawai'i. Figure 2 describes an algorithm for workup of NAFLD in the primary care settings.

## Treatment of NAFLD in the Primary Care Office

The exact prevalence of NAFLD in Hawai'i is not yet known. The PCP's roles in treating NAFLD include addressing modifiable risk factors through lifestyle changes, treating comorbid cardiovascular conditions, and recognizing indications for referral to liver disease specialists. There are evidence-based pharmacologic treatments that can reverse NASH and fibrosis; however, these are reserved for biopsy-proven NASH, and hence, typically administered by liver disease specialists. While there is a propensity for NAFLD to worsen, there are many modifications the patient and PCP can undertake to slow the progression and even cure the disease.

### Therapeutic Lifestyle Modifications

Weight loss is the best approach to reverse steatosis and steatohepatitis and prevent progression to cirrhosis. Obese or overweight patients should be advised to lose 7%-10% of body weight over several months. A Cuba-based study suggested a loss of ≥10% of body weight led to resolution of NASH in 90% and regression of fibrosis in 45% of patients, while 5% weight reduction can resolve NASH in half of patients.[39] A combination of caloric restriction (30% or 500-1000 kcal reduction per day), moderate-intensity aerobic exercise (150-200 minutes per week over 3-5 sessions), and resistance training is a pragmatic approach towards weight loss.[39,40] Although patients with lean NAFLD have little weight to lose, they should be encouraged to exercise regularly and consider a Mediterranean diet as these interventions are associated with a reduction in visceral and hepatic fat independent of weight loss.[40,41] Patients should be advised limit fructose-containing beverages such as fruit juice.[42] There is some evidence that regular coffee consumption protects against steatosis, steatohepatitis, and fibrosis.[43] Finally, increased meal frequency, increasing calorie intake in the morning, and not skipping breakfast and lunch, may lower risk of NAFLD development.[44]

Bariatric surgery may be offered to eligible patients with NAFLD who fail to lose weight with therapeutic lifestyle modifications. Indications for bariatric surgery include BMI >40 kg/m$^2$ or BMI >35 kg/m$^2$ in the presence of obesity-related comorbidities, which include NAFLD. Prospective studies have demonstrated NASH resolution and improvement of fibrosis at 1 year following bariatric surgery.[45]

Light to moderate alcohol consumption in NAFLD is controversial. Epidemiologic studies suggest that light to moderate drinkers may have lower risk of simple fatty liver, NASH, and fibrosis compared to non-drinkers.[46] However, well-designed prospective studies show that lifetime alcohol abstinence more frequently resulted in NASH resolution, alcohol binges promote fibrosis progression, and any alcohol use increased HCC risk in the NASH cirrhotic.[47,48] Hence, cirrhotic patients should abstain from all alcohol use, lifetime alcohol abstainers should not start alcohol use, and non-cirrhotic light drinkers may continue drinking as long as they avoid binges.

## Treatment of Associated Comorbidities

### Diabetes

Type 2 DM is present in about 20% of patients with NAFLD.[1] It is known that the NHOPI population has a high prevalence of type 2 DM.[49] Insulin resistance is a key component in the pathogenesis of NAFLD and severe steatosis is more frequent in patients with high levels of insulin resistance, even in the absence

of overt DM.[13,45] Among antidiabetic agents, thiazolidinediones and GLP-1 agonists have been shown to improve steatohepatitis and reduce progression to fibrosis. In contrast, metformin, sulfonylureas, DDP-4 inhibitors, and insulin have not been shown to improve liver chemistries and histology. Optimal glycemic control is also associated with improvements in steatosis and fibrosis;[50] therefore, NAFLD patients should maintain good glycemic control, irrespective of anti-diabetic agent.

### Hypertension

Patients with NASH are twice as likely to die from CVD compared to the general population (15.5% vs 7.5% over mean follow-up of 13.7 years).[33] It is well established that there is a high prevalence of hypertension in the NHOPI population.[51] Indeed, hypertension coexists in about 40% of patients with NAFLD.[1] Up to 30 % of lean, non-diabetic patients with hypertension develop NAFLD.[52] Blockers of the renin-angiotensin system (RAS), such as angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors, may be preferable in hypertensive patients with NAFLD due to the high prevalence of comorbid DM and the proven renal protective benefits of ARBs and ACE inhibitors in diabetic patients. Additionally, RAS inhibition may have direct hepatoprotective effects by decreasing hepatic inflammation, lowering fibrosis stage, and slowing fibrosis progression.[53] However, caution should be made once patients develop decompensated liver disease as the use of ACE inhibitors or ARBs may increase the risk of renal impairment. In addition, NAFLD patients should be offered assistance on smoking cessation due to its effects on blood pressure and negative associations between smoking and hepatic fibrosis.[54] Recognition and treatment of sleep apnea in NAFLD patients is also necessary to appropriately treat hypertension.

### Dyslipidemia

Up to 70% of patients with NAFLD have comorbid dyslipidemia.[1] The lipid profile in NAFLD is proatherogenic, characterized by high triglycerides, elevated very low-density lipoprotein, and low high-density lipoproteins.[55] Despite the efficacy of statins in CVD, clinicians may hesitate to prescribe statins in patients with elevated transaminases, as in NAFLD, due to perceived hepatotoxicity. However, in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) trial, statins were safely used in patients with moderately elevated ALT, presumably NAFLD, and reduced risk of CV events by 70%.[56] Indeed, liver-related adverse events due to statins occurred in <1% of patients, but more importantly, significant improvements in liver chemistries were observed with statin therapy. Asymptomatic transaminase elevations are relatively common with statin use, but severe hepatotoxicity is rare in clinical practice.[57] Statins are likely safe in compensated cirrhosis but should be avoided in decompensated cirrhosis. Some experts recommend that dyslipidemia in NAFLD should be treated with a combination of statins and ezetimibe.[58]

## Evidence-Based Pharmacologic Therapy

Pharmacologic treatments that target the primary liver disease in NAFLD are reserved for patients with biopsy-proven NASH since liver-related morbidity and mortality generally occur only in the setting of steatohepatitis and fibrosis. In the Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis (PIVENS) trial, non-diabetics with biopsy-proven NASH received vitamin E 800 IU/day, pioglitazone 30 mg daily or placebo for 96 weeks.[21] In the PIVENS trial, vitamin E and pioglitazone significantly improved histologic findings such as steatosis and inflammation, as well as liver enzymes compared to placebo. However, no improvement was seen in fibrosis. Long-term pioglitazone is associated with weight gain, which appears counterproductive to patients who are being advised to lose weight. Nevertheless, weight gain from pioglitazone is modest, 3 kg on average over 3 years, and likely mitigated by continued adherence to lifestyle interventions.[21] It is important to note that the use of pioglitazone increases the risk of heart failure and is contraindicated in patients with New York Heart Association Class III and IV disease. The safety of long-term use of vitamin E is unclear. A large trial found an increased risk of prostate cancer in patients who receive long-term vitamin E supplementation.[43] To date, there is no data on the efficacy and safety of vitamin E on diabetics or cirrhotic NASH patients.

In a phase II clinical trial, liraglutide was associated with greater NASH resolution and slower progression of hepatic fibrosis.[59] Compared to pioglitazone, Glucagon-like peptide 1 (GLP-1) inhibitors have the added benefits of weight loss, cardiovascular, and renal protection.[57] Obeticholic acid is a potent farnesoid X receptor (FXR) agonist that has also been shown to improve liver histology in NASH patients in a phase II trial.[60] However, minorities common in Hawai‘i may have different pathogenetic pathways for NAFLD and are unfortunately underrepresented in current drug trials.

## Referral to Liver Disease Specialists

Currently, there is no consensus guideline to when to refer NAFLD patients to a liver specialist. In general, NAFLD patients with stigmata of chronic liver disease, decompensated cirrhosis characterized by the presence of ascites, bleeding esophageal varices, hepatic encephalopathy, and jaundice should be promptly referred to liver disease specialists. Patients with an intermediate or high likelihood of cirrhosis on non-invasive testing, such as scoring systems and elastography, should also be referred. For asymptomatic NAFLD patients with a low risk of fibrosis on non-invasive testing who present with mild elevation of transaminases or steatosis on imaging studies, a trial of weight loss through lifestyle interventions in the primary care setting is reasonable before referral to a specialist. The algorithm in Figure 2 can help guide clinical judgment. In addition, currently only limited institutions in Hawai‘i offer TE; therefore, it may be reasonable for PCPs in Hawai‘i to refer to liver disease specialists for TE to avoid invasive liver biopsy.

## Summary

NAFLD is a prevalent and increasing health problem due to the worldwide obesity epidemic. Hawai'i has a unique population composed of a high proportion of NHOPI and Asians who are exposed to western diets and lifestyles that increase the risk of NAFLD. Unfortunately, underdiagnosis and lack of awareness of NAFLD remain important issues among PCPs, who commonly are the first points of contact for NAFLD patients. PCPs in Hawai'i should maintain a high index of suspicion for NAFLD in at-risk patients who have elevated transaminases or incidental findings of steatosis on imaging. Workup of other etiologies of liver disease and non-invasive staging of hepatic fibrosis and steatosis may be done in the primary care setting. The leading roles of PCPs in managing NAFLD are facilitating weight loss and treating comorbid conditions. PCPs should promptly refer patients with signs and symptoms of cirrhosis or a high likelihood of hepatic fibrosis to liver disease specialists.

## Conflict of Interest

None of the authors identify a conflict of interest.

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