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Transcript

Non-Alcoholic Fatty Liver Disease (NAFLD)
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Sarah Chart: I would now like to introduce Dr. Ken Cohen, who will be our moderator today. Dr. Cohen is executive director of translational research at Optum Labs and senior national medical director at OptumCare. It is with pleasure that I welcome Dr. Cohen, and I'll hand the call over to you.

Dr. Ken Cohen: Thank you, Sarah. Good morning, everyone. Thanks so much for joining us and welcome to our inaugural OptumCare grand rounds. We're delighted you could join us both today and hopefully for our upcoming grand rounds presentations, which going forward will be on a quarterly cadence. This morning I am so pleased to introduce our speaker, for today's presentation, Dr. Arema Pereira completed medical school at St. John's National Academy of Health Sciences in Bangalore India at age 21. After completing an internal medicine residency at New York Presbyterian Cornell, she pursued an additional hepatitis C fellowship at Cornell before moving to the Pacific Northwest for a gastrointestinal fellowship at the University of Washington. She completed an additional liver transplant fellowship, and currently works as a hepatologist at the Everett Clinic. Dr. Pereira spends her free time traveling with her husband and three children and dabbling in permaculture in their suburban backyard, surrounded by their dog, chickens, bunnies, quails and mason bees. Dr. Pereira, thank you again for being with us today and I will turn the podium over to you.

Dr. Arema Pereira: Thank you for that introduction. Good morning. Let's jump right into this inaugural grand rounds presentation on non-alcoholic fatty liver disease, or NAFLD. A quick glance at our disclosure slide. I have nothing to disclose. NAFLD is the most prevalent liver disease in human history affecting 2 billion people globally and 30% of the U.S. population. NAFLD and primarily it's subset NASH, which is non-alcoholic steatohepatitis is an established risk factor for the leading

causes of death, cancer, both liver and non-liberal related cancer, especially colon cancer, cardiovascular disease, and type 2 diabetes. With projected increasing rates of obesity and type 2 diabetes compounded by an aging population, NAFLD is projected to increase to 100 million people in the U.S. by 2030. International NASH day to raise awareness of this condition interestingly follows one week after national donut day. A 2018 publication in hepatology by Allen et al using Optum Labs' data warehouse claims data showed increased healthcare costs for NAFLD independent of its metabolic comorbidities. This appears to be driven primarily by liver biopsies, imaging and hospitalizations.

Looking at the graph, we can see that there is an increase, right from the time of index diagnosis throughout the five-year span of this study for patients identified as having NAFLD. So NAFLD is clearly a topic that is worthy of our attention to determine who is at risk and how do we best manage resources in this population. Defining non-alcoholic fatty liver disease requires evidence of hepatic steatosis, either on imaging or liver biopsy and excluding secondary causes of hepatic fat accumulation, such as significant alcohol consumption, long term use of steatogenic medications, hepatitis C virus infection, et cetera. We are all familiar with the NAFLD, but if you have been coming across the term MAFLD, and that leaves you well baffled, just know that a search is on for an alternate name to better define the pathophysiology of this disease. NAFLD is divided into bland steatosis or non-alcoholic fatty liver and steatohepatitis or non-alcoholic steatohepatitis called NASH. Steatosis is just fattening the liver with no evidence of hepatocellular injury and no evidence of fibrosis. NASH on the other hand is hepatic steatosis that is accompanied by inflammation, evidence of hepatocyte injury, which is typically ballooning and presence or absence of fibrosis. It's important to note that fibrosis is not required to make a diagnosis of NASH.

Alcohol use is pervasive, and alcohol is an important confounding factor in NAFLD. Looking at the liver society guidelines from across the globe, we can see that the definition of significant alcohol consumption varies. A standard drink contains about 14 grams of pure alcohol, the AASLD or the American Association for the Study of Liver Diseases in their 2018 guidelines defined significant

alcohol consumption at approximately three drinks per day for men and two drinks per day for women. EASL or the European Association for the Study of Liver defines it at a little over two drinks per day for men and approximately one and a half drinks per day for women. The Asia Pacific working party guidelines from 2017 set the lowest threshold of two drinks per day for men and one drink a day for women. These are arbitrary thresholds based on levels above which risk of cirrhosis is higher. Moderate alcohol consumption is associated with decreased improvement in steatosis or resolution of NASH. So, it's really unclear that there is any safe level of alcohol consumption in NAFLD.

We could spend a lot of time talking about the pathogenesis of NAFLD, but that is not the focus of the talk today. Suffice it to say that there is an excessive input of free fatty acids from adipose tissue into the liver and a diminished hepatic export. This is a complex interaction involving multiple hits between genetic factors, the release of free fatty acids, inflammatory cytokines and adipokines, insulin resistance and oxidative stress appear to be the primary drivers in disease progression and fibrosis. Numerous modifiers for NAFLD have been studied and they are listed out nicely in this table from an article from Kata and Vanilla published in gastroenterology in 2020, they can be broadly divided into comorbidities, genetic factors, microbiome products, nutrition and behavior. Factors in bold in this table are shown to drive NASH progression. Those in black are associated with evolving evidence. Those in red have an established association and those in green are protective.

There is a noticeable variable prevalence of NAFLD among populations. As an example, there is an increased risk of NASH and increased prevalence of fibrosis among Hispanic Americans, origin appears to play a role. Hispanics of Mexican origin have a 33% prevalence of NAFLD. Whereas those of Puerto Rican descent have an 18% and those of Dominican descent have a 16% prevalence of NAFLD. Differences are attributable in part to carriage of a single polymorphism of the PNPLA3 gene. African Americans have higher rates of metabolic syndrome, but NAFLD and NASH is less common compared with Caucasian and Hispanic populations. Again, attributable in

part to PNPLA3 risk allele carriage rates. Given the high prevalence of NAFLD, projected increases in numbers, but associated costs that come with diagnosis, who should be screened? Returning to our liver societies. We can see that they all agree that systematic screening of the general population is not recommended.

AASLD has no screening recommended due to lack of evidence of cost effectiveness to support screening, even in high-risk groups. However, vigilance is suggested. EASL recommends screening in patients with obesity, type 2 diabetes, metabolic syndrome, and those with persistently abnormal liver enzymes. The Asia Pacific society recommends screening in patients with obesity or type 2 diabetes. It is worthwhile to note that lean NAFLD is prevalent in Asia, where almost a quarter of patients with NAFLD are not obese. Common clinical scenario, where patients are referred to liver clinic for NAFLD assessment are incidental hepatic steatosis, a patient who is found to have fattened their liver on a scan that is done for some other reason and or persistently elevated liver enzymes. A group of 11 authors with expertise in evaluating and treating liver diseases and serving as advisors to NASHNET or global centers of excellence network committed to NASH care delivery, proposed questions and recommendations to help primary care providers identify patients at risk of NAFLD and recognize those who will benefit from specialist referral.

The questions they put forth are, does the patient have risk factors for NAFLD? If the answer is yes, does the patients have evidence of NAFLD? If the answer is yes, does the patient have evidence of significant fibrosis by non-invasive tests? We will also touch upon their recommendations throughout the duration of this talk today. Easily identified clinical risk factors that drive NAFLD progression are increased BMI, obesity, metabolic syndrome, type 2 diabetes, and genetic factors. At this time, there is no data to support screening patients with genetic risk, but clinically irrelevant panels may be available in the future.

So, who is at risk of NAFLD? Returning to the recommendations from the Dhanani et al article, the first recommendation is to identify patients at risk for NAFLD based on the presence of one or more

of the following: obesity defined as a body mass index of more than equal to 30 or more than equal to 25 in Asian patients, increased waste circumference more than 35 inches for women, more than 40 inches for men with lower cutoffs for Asian patients, hypoglycemia either a diagnosis of type 2 diabetes or hemoglobin A1C of more than 5.7 or fasting glucose of over 100, fatty liver on imaging. Recall that to make a diagnosis of NAFLD requires exclusion of other conditions that cause fat in the liver. The diseases that we are aware of that commonly result in fatal liver are non-alcoholic fatty liver, alcoholic liver disease, viral hepatitis, autoimmune hepatitis, drug induced liver injury, Wilson's disease, alpha one antitrypsin deficiency and hereditary hemochromatosis.

Now this is not an exhaustive list, a typical lab panel to assess these patients would include a hemogram with special attention paid to hemoglobin and platelet count looking for anemia and thrombocytopenia that can be seen in portal hypertension, a complete metabolic panel paying attention to the sodium as hyponatremia is a poor prognostic indicator in cirrhosis, looking at the liver enzymes, the ASD and the ALT are they elevated? How much are they elevated? What is their pattern of elevation? Looking at the albumin, is there evidence of hepatic synthetic dysfunction and the bilirubin for evidence of biliary obstruction, excluding hepatitis B and hepatitis C, checking thyroid and celiac screen, looking for evidence of ion overload with an ion panel and ferratin, and since the majority of these patients have evidence of hypoglycemia or elevated lipid checking a hemoglobin A1C and lipid panel. Upon referral to hepatology clinic, some of the tests that I commonly assess in people with elevated liver enzymes is an alpha-1 antitrypsin quantification, ceruloplasmin, looking for autoimmune hepatitis with an anti-nuclear antibody, smooth muscle antibody, possibly an SPEP and assessing for PBC with an anti-mitochondrial antibody.

Sometimes a liver biopsy is considered. Confusing lab findings to be aware of in NAFLD are a serum ferritin, which can often be mildly elevated, but does not reflect ion overload. If the ferratin and trans ferritin saturation are elevated exclude genetic hemochromatosis. ALT can be normal in up to 50% of patients with NAFLD. Elevated ASD and ALT levels do not always correlate with the severity of liver damage. An upper limit of normal for ALT for approximately 35 for men and 25 for

women is recommended to guide management decisions. Note that this is typically lower than the upper limit of normal from the lab normal. Serum auto antibodies, such as an anti-nuclear antibody and a smooth muscle antibody are frequently detected often in low titers. This is epiphenomenon and does not impact natural history of NAFLD. However, if they are markedly elevated or accompanied by significant elevation of liver enzymes, more than five times the upper limit of normal then autoimmune hepatitis should be assessed for.

There are three leading causes of death in patients with NAFLD and they are cardiovascular disease, cancer, and liver disease. Presence and severity of fibrosis is currently the best indicator of long-term liver outcomes, liver cancer, cirrhosis, liver transplant. In this diagram presented in an article by Marengo et al, looking at the progression and natural history of NAFLD in adults. We concede that it starts off as simple steatosis, less than 50% of these patients progress – progressed to NASH with mild of fibrosis and an even smaller subset progresses to NASH with severe fibrosis and cirrhosis. This is typically a slow-moving process with fibrosis progression of one stage every six to 15 years in NASH. However, rapid progressors have been described. Prevalence of NAFLD is approximately 30% of the U.S. population. Of this 30%, 20% will have NASH with advanced fibrosis, which is approximately 5% of the general population. Note that there is some decree of reversibility in the earlier stages of fibrosis. But typically, once we get to cirrhosis that is not considered reversible, at least not in the short term. A diagnosis of NASH is made with a liver biopsy, and this is the goal standard. However, it is an invasive test. There are risks involved such as a risk of bleeding, risk of damage to the surrounding structures and a risk of infection. It can be painful. There are costs involved. In addition, sampling errors and histological interpretation can further affect the quality of a liver biopsy.

There are no acceptable, non-invasive modalities to differentiate between bland steatosis and NASH. However, it is the presence and extent of fibrosis that determines liver related outcomes. This table lists the top diagnostic panels selected based on study size an area under the curve of more than 0.8 for detection of advanced fibrosis. The top three prediction scores, the BARD score,

NAFLD fibrosis score and FIB-4 index are clinical prediction scores using the readily available clinical variables that can be calculated at no cost. The lower two, the fiber test and the ELF panel are proprietary panels sender tests that do involve a cost. In addition, the ELF panel is currently only available in Europe.

I would draw your attention to the column that is second to last from the right-hand side, labeled NPV or negative predictive value. Looking at those numbers, you can see that this is where these tests really shine in their ability to exclude advanced disease. Looking at the positive predictive value column to the immediate left of that you can see that those numbers are not as strong. With regards to limitations, these tests have a poor predict – positive predictive value, they're inaccurate at extremes of age. They tend to overestimate disease in diabetics and older patients. In addition, a third of patients are classified as indeterminate, often requiring additional testing. The BARD score is derived from BMI, ASD ALT ratio and diabetes. The NAFLD fibrosis score uses age, hypoglycemia, BMI, platelet count, albumin, and an ASD ALT ratio. The FIB-4 index only requires age, ALT ASD and platelet count.

There are complex equations that go into calculating these scores, but fortunately there are free, easy to use online calculators, which allow input of data and a result in score. This can be done by trained medical assistance to decrease primary care provider burden. And in fact, that is the way that we generate these scores in liver clinic with the assistance of our medical assistance, they calculate a FIB-4 index, a NAFLD fibrosis score, and an APRI index for us. The websites we typically use are mdcalc.com, hepatitisc.uw.edu, and gihep.com. We spoke about non-invasive scores and their strength to accurately rule out advanced fibrosis. The most accurate non-invasive method to identify advanced fibrosis is vibration control, transient elastography trademarked fibro scan, and MRE or magnetic resonance elastography. Liver stiffness steadily increases with increase in fibrosis. These non-invasive techniques can be used to measure liver stiffness that correlates with fibrosis. In addition, transient elastography generates a CAP score or a controlled attenuation parameter score to detect sickness against steatosis. And these are especially

accurate when the reading is over 300. MRI derived fat fraction is currently the goal standard for non-invasive quantification and diagnosis of hepatic steatosis. However, given cost and lack of easy access, it is currently most relevant only in clinical trials.

It is important to recognize the limitations of transient elastography and it can overestimate fibrosis in a non-fasting state flare of transaminase with hepatitis, extra hepatic biliary obstruction, and liver congestion. In addition, conditions that increase the distance between skin and liver capsule, such as severe obesity anisocytosis result in the transient elastography failing to provide a result. Now that we have reviewed the non-invasive methods to assess NASH fibrosis, let's look at the liver society guidelines. We can see that all three societies agree that non-invasive tools should be used to stratify patients as low or high risk for advanced fibrosis. The AASLD recommends the NAFLD fibrosis score, FIB-4 and elastography however, no algorithm is provided. EASL recommends the NAFLD fibrosis score and FIB-4 to risk stratify low versus medium high risk for significant fibrosis, and then refer medium high-risk patients to hepatology for further testing.

There's no specific recommendation from the Asia Pacific society. All three societies agree that a liver biopsy remains the gold standard for differentiating between bland steatosis and steatohepatitis, and also staging liver fibrosis. A liver biopsy id recommended if there's suspicion for NAFLD advanced fibrosis or concern for coexisting or competing etiology for chronic liver disease. In clinical practice because of the risks associated with a liver biopsy typically the commonness indication for me to reach for a liver biopsy in these patients would be concerned for coexisting or competing etiology. Returning to the risk stratification and fibrosis assessment recommendations from the Dhanani et al, article for each at-risk patients identified, calculate FIB-4 index score to determine whether the patient has minimal, indeterminate, or likely advanced fibrosis. In the table provided, you can see the cutoffs for each group and that they are further stratified based on age because of the inaccuracies at the extremes of age. Patients with a FIB-4 of less than 1.3 have minimal fibrosis and can be managed by their PCPs. Patients with an indeterminate fibrosis score should have a second non-invasive test, ideally transient elastography

and patients with an elevated score, have a high likelihood of advanced fibrosis and should be referred to hepatology.

We have explored the methods to diagnose NASH and NAFLD. Now let's look at the recommendations for management of NAFLD. All three societies recommend lifestyle intervention with a target weight loss goal of seven to 10% of total body weight. This can be achieved with a daily caloric deficit, moderate intensity exercise, preferably in a structured weight loss program. There are currently no approved drugs to treat NAFLD or NASH. However, multiple drugs are in phase III development. In patients with cardiovascular indications, statins can be safely used in patients with NASH and compensated cirrhosis. Looking at vitamin E and pioglitazone, the AASLD recommends that these medications be used only in patients with biopsy proven NASH. Vitamin E at a dose of 800 international units a day can be considered in nondiabetic patients without cirrhosis. Pioglitazone at 30 milligrams per day can be considered in patients with, or without type 2 diabetes.

Numerous treatments have been studied in NAFLD and NASH. We will touch upon the ones with the most data, and they can be broadly divided into weight loss, insulin sensitizers and other diabetes medications like GLP1 receptor agonist and analogs. Weight loss is the cornerstone of NASH management. Vilar-Gomez et al presented this data in a gastroenterology paper published in 2015. This was based on a prospective study of 293 patients with biopsy proven NASH. These patients followed recommended lifestyle changes over 52 weeks. Paired liver biopsies were obtained for – from 261 patients. Over the 52 weeks of lifestyle intervention, when we look at the presented data in the table and focus on the lowest row patients achieving weight loss, we can see that at least 70% of patients did lose some degree of weight. However, it was only under 5% of weight loss. Only 29 patients were able to lose over 10% of their body weight. For these patients, 90% saw resolution of steatohepatitis, 45% saw fibrosis regression, and 100% saw steatosis improvement. The presence of diabetes or BMI over 35, being female, and having a lot of inflammation at baseline on a liver biopsy, decrease the probable improvement in steatosis or

resolution of steatohepatitis. In this study, only one in five patients were able to achieve a weight loss over 7% to significantly improve liver histology. Other studies have shown that weight through lifestyle intervention is unfortunately difficult to sustain.

Exercise helps, the majority of NAFLD patients unfortunately are engaged in minimal physical activity. Exercise does improve hepatic steatosis. The optimal exercise regimen is unclear. Most studies agree it should be multiple times a week targeting at least 150 minutes per week. Best outcomes are seen if exercise is combined with weight loss. Numerous dietary modifications to assist with weight loss in NAFLD have been put forth. They include a Mediterranean diet, caloric control, limitation of processed foods, increasing intake of unsaturated fat, avoidance of high fat foods, such as animal fat and red meat. And for all you coffee lovers out there, an increase in daily consumption of more than two cups of coffee is associated with close to 50% reduction in risk of cirrhosis. This is not specific to NAFLD however. Intake of sugar sweetened beverage should be strongly discouraged in this patient population. To return to recommendations from the Dhanani et al article with regards to treatment and monitoring.

All patients identified with NAFLD should be counseled on lifestyle modification around weight loss and physical activity. Weight is the best therapy for NAFLD. Carbohydrate restriction is the most effective diet. Patients who lose 10% body weight typically will resolve NAFLD. Weight loss usually results in improved ASD ALT and improved metabolic parameters. Exercise reduces hepatic fat but should be recommended in combination with weight loss. Alcohol use should be discouraged. Complete abstinence is recommended, strongly recommended in advanced fibrosis. Looking at surgical interventions to assist with weight loss in a long term follow up of 180 patients with NASH who underwent bariatric surgery in France, resolution of NASH was seen in liver samples from 84% of patients five years later. Reduction of fibrosis is progressive beginning during the first year and continuing through five years. Looking at the presented graphs, starting from the one on the left.

We can see for patients who achieved more than 10 BMI loss, 90.5% of these patients saw resolution of NASH. Looking at the middle graph we can see that by five years post bariatric surgery, 60% of patients had a fibrosis score of zero. That is really impressive and shows that this is a strong management option for patients who are unable to lose weight with diet and exercise. Notice at the top of the middle graph that the little bars in black are those with a score, a fibrosis score of F4 of cirrhosis. You can see that that remains relatively unchanged over the study interval. And that's not surprising because again, cirrhosis is not thought to be reversible, at least not in the short term. AASLD guidance on bariatric surgery is that it should be considered in otherwise eligible obese individuals with NAFLD or NASH, but is not yet an established option to specifically treat NASH in the absence of obesity. For patients with cirrhosis type, safety and efficacy of bariatric surgery is not yet established. Since a number of patients with NAFLD have hypoglycemia or diabetes.

The AASLD put forth guidance on insulin sensitizers Metformin may improve serum aminotransferases and improve insulin resistance. However, there's no significant improvement in liver histology. At this time, it is not recommended for treatment of NASH alone, but Metformin should be considered first line pharmacologic therapy for those with NAFLD and type 2 diabetes. PPAR- gamma agonists like pioglitazone have been shown to improve histology in patients with, or without diabetes, which should be limited in use to those with biopsy proven NASH. Risks and benefits should be discussed with each patient specifically possibility of weight gain, possible bone loss in older women, and the unclear risk of bladder cancer.

Mantovani et al put forth this data in an updated meta-analysis of randomized control trials, looking at GLP1 receptor agonist in NAFLD. Compared to placebo treatment with liraglutide and semaglutide for a median of 26 weeks was associated with significant reduction in hepatic steatosis, improvement in serum liver enzymes, and histologic improvement of NASH without worsening of fibrosis. When we look at table A, it is a forest potent plot and pooled estimates, which shows histologic resolution of NASH. And this did meet statistical significance for liraglutide

and semaglutide. Table B shows that there is a trend in improvement in liver fibrosis. However, this did not meet statistical significance. So, the take home would be that there is improvement in NASH and maybe a trend in improvement in fibrosis, but the improvement in fibrosis is not statistically significant. Returning to treatment and monitoring recommendations. All patients identified with NAFLD should work with their primary care providers to manage medical comorbidities, treat confidence of metabolic syndrome with medication as indicated, statins should be used if indicated, they are not contraindicated in patients with liver disease, in patients with NAFLD with elevated liver enzymes or in patients with NAFLD and cirrhosis.

However, in the presence of decompensated hepatic cirrhosis, they should be used with caution. Antihypertensive agents as indicated avoiding agents like beta blockers as first-line treatment, as they can promote weight gain. preferred medications for diabetes include Metformin, SGLT2 inhibitors and GLP1 agonists. Pioglitazone may cause weight gain but may benefit patients with NAFLD. Insulin and sulfonylurea should be avoided as they have been shown to be associated with progression in NAFLD. Consider bariatric surgery referral in those with a clinical indication. At each clinic visit obtain smoking status and a detailed alcohol history. Smoking is a known risk factor for the development of hepatic fibrosis and liver cancer. Advice on keeping alcohol consumption to a minimum should be encouraged and complete alcohol abstinence strongly recommended in all patients with advanced fibrosis. Any alcohol use in that patient population has been shown to result in a dramatic increase in liver cancer risk.

It is worth spending a little bit of time looking at the PIVENS trial since the bulk of our vitamin E and pioglitazone data arises from this trial. Pioglitazone versus vitamin E versus placebo for the treatment of nondiabetic patients with NASH was a large multicenter randomized control trial of 247 patients in total, randomized to vitamin E at 800 international units per day, or pioglitazone at 30 milligrams per day, or placebo. Primary endpoint was histological improvement in NASH on liver biopsies. A P value of 0.025 was set as statistically significant. When we look at the table, we can see vitamin E versus placebo did meet its primary. Pioglitazone versus placebo showed

improvement in histology changes when it came to NASH, but did not meet statistically significant. Looking at the components that went into the score steatosis, lobular inflammation, hepatocellular ballooning, both vitamin E and pioglitazone were clearly statistically significant when it came to improvement in histology. However, looking at fibrosis, neither of them was able to result in any significant improvement. The take home from this is that NASH can resolve, but fibrosis stays the same.

AASLD guidance on vitamin E is the dose of 800 international units per day in nondiabetic patients with biopsy proven NASH can be considered. It is not recommended to treat NAFLD without biopsy proven NASH. Risks and benefits should be discussed with each patient as lingering concerns remain about the long-term safety of vitamin E. Vitamin D deficiency is present in 55% of patients with biopsy proven NAFLD. Vitamin D has also been shown to be protective against inflammation. So, repletion of vitamin D seems to be an easy intervention in this patient population.

After looking at every algorithm that I could get my hands on, a proposed algorithm to identify patients at risk of fibrosis progression in NAFLD would be to identify patients at risk of NAFLD with one or more of the following obesity, increased waste circumference, hypoglycemia, or fatty liver on ultrasound. If liver enzymes are elevated, assess for other causes of liver disease, consider the panel of blood tests that we spoke about before. Determine risk of advanced fibrosis by using easy, free online calculators to calculate a FIB-4 or NAFLD fibrosis score. This would triage patients into low-risk intermediate or indeterminate risk and advanced risk of fibrosis. patients at low risk can be managed in primary care with a focus on weight loss and exercise, vaccination to hepatitis A and B, management of metabolic syndrome, choosing appropriate medications for diabetes, hypertension, hyperlipidemia, advising stopping smoking and avoiding alcohol and consideration of bariatric surgery when clinically indicated. This risk can be reassessed every two years with recalculation of the fibrosis score. For patients with an indeterminate or intermediate FIB-4 or NAFLD fibrosis score, an additional tests such as transient elastography would be recommended. This would, again, subdivide patients into low fibrosis, medium or advanced

fibrosis. Patients with medium or advanced fibrosis could be managed alone with hepatology clinic to assess for other liver diseases, consideration of liver biopsy, management of advanced fibrosis, such as liver cancer screening, portal hypertension, variceal surveillance, and consideration of clinical trials.

In conclusion, NAFLD is an epidemic with a rising mortality and healthcare cost. Given that NAFLD affects one third of the population with projected increases in this number, management pathways are needed to identify those at highest risk of fibrosis progression. Non-invasive tests for fibro are a cost-effective method of stratifying patients into low and high-risk groups. Weight loss remains a crucial part of NASH management and no current FDA approved medications are available. Our primary care providers are overburdened. So, the addition of ancillary staff to assist with dietary and lifestyle changes are essential to the effective management of these patients. And for those looking for additional reading on NAFLD, the top two resources listed were ones that helped guide and shape the format of this talk today. The lower two resources with the papers that were most heavily for this presentation. With that, I thank you for your attention today and turn this talk back over to Dr. Cohen.

Dr. Ken Cohen: Thank you, Dr. Pereira. That was, just a wonderful and comprehensive overview of this incredibly important topic. And while Dr. Pereira was speaking, I did some quick math, I think all of us following this talk can begin to understand that this is in fact an epidemic, but just putting some numbers around that, given the fact that about 30% of the population has NAFLD and about 5% of those will progress to cirrhosis. That would mean in the average primary care practice, which takes care of about 2000 patients per PCP. You would ultimately wind up with 40 patients in your practice with cirrhosis directly related to NAFLD. We currently are not seeing anywhere near that magnitude. And it gives you an idea of what this burgeoning epidemic might look like in the next one to two decades. So, I wanted to just shift slides for a moment and highlight the fact that we have been trying our best to provide education around fatty liver and NAFLD and progression to NASH and cirrhosis.

And I wanted to review the educational pieces that are already in place. As part of our algorithm process, we are developing an algorithm that will align completely with the one that Dr. Pereira just showed. It will be externally vetted through a hepatologist not associated with OptumCare. And once that process is through, and it's been ratified by the PEC we'll make it available on Xyleme, and everybody will have access to it. And as I mentioned, it will align perfectly with what Dr. Pereira just showed you. We have a patient infographic available as part of the Optumcare materials that will direct patients to some factoids about NAFLD, and on our GI specialty module this topic is also covered, presenting some of the literature that was just shared with you. And then, looking at our forum for evidence-based medicine, three times in the past three years, we've had articles specifically related to this.

The first was an overall review in 2018. In March of last year, we highlighted an important paper showing that diabetics in particular, have a high rate of advanced liver fibrosis, which is often unrecognized and then most recently in July of last year, looking at an article that showed that steatosis that without elevated liver enzyme still has a significant risk of cirrhosis and hepatocellular carcinoma. So, important educational materials with more to follow.