My name is Jai Behari. I'm one of the hepatologists here at UPMC Presbyterian. And it's my pleasure today to speak with you about fatty liver disease. I thank the organizers for giving me this opportunity.

So in today's talk, we'll talk about three major areas. I'll give you some updates, some very significant changes to the terminology and definition for fatty liver disease for 2020 that really takes the power away from specialists and takes the definitions away from a histology and biopsy based diagnosis, and gives it back into the hands of internists, family physicians, and primary care physicians. So these are changes that I think will be very exciting for most internists because this really empowers you to make the diagnosis and define a management plan for the patient before you refer those patients to us.

In the second part, I'll talk a little bit about clinical challenges in the management. There are some really important problems that we face. The good news, of course, is that this is a very exciting a dynamic area of research and development. And chances are that anything I tell you today will probably be obsolete by next year.

In the final part, I will give you a very simple and practical framework for evaluating and managing these patients that hopefully you'll be able to apply today, this afternoon when you're back in your clinics.

So with that, let me give you a little background and some very exciting new changes to the definitions and terminology for fatty liver disease for 2020. But let me start with a fairly typical case. This is an example of a patient that is very commonly referred to me in the fatty liver clinic.

So this is a 70-year-old female who's presenting after an abdominal ultrasound for right upper quadrant pain. She has a history of a BMI of 31, so that's WHO class I obesity. She does not have diabetes but she is on a statin for dyslipidemia. No significant history of alcohol exposure. She has transaminase, as given here. ALT is 35, AST is 22.

And the ultrasound report, which you are reviewing in your clinic, seems to suggest that the liver is echogenic, which the radiologists think may be suggestive of fatty infiltration of the liver. So fairly typical case that you would see in your clinic on any given day.

Now, this is an example of an ultrasound. What exactly is the radiologist looking at that makes them suspect fatty liver disease for these patients? On the left is this patient-- and this is a real patient, by the way, from my clinic-- Where the ultrasound at initial diagnosis showed fatty liver.

And here, if you focus on the red circle here, this is the liver. And in the green circle here is the kidney. And normally, both of them should look the same on the ultrasound. So they should have the same level of echogenicity, or brightness on the echo-- on the ultrasound.

On the right is the same patient who had undergone one of our supervised weight management programs and had a very significant 13% weight loss over that one year when she had the ultrasound again. Same patient, if you compare the red circle on the left with the red circle on the right, you start to see that the echogenicity of the liver now starts to resemble that of the kidneys, which are the two green circles here.

So that's a clue that the radiologist will look at. So next time you see an ultrasound, if you compare an image where the liver and kidney are both in the same field of view, you might be able to even tell yourself if the liver is echogenic, and therefore fatty. And, of course, here making the point that fatty liver is clearly reversible for most of our patients.

The other very common presentation is a CT scan that's done for either kidney stones, abdominal pain, or some other indication. And there again, the radiologists mention the presence of a fatty liver. And this is an example of that from a paper we published a few years ago with my colleague, Dr. Dunn.

And here, you can tell the difference between the liver, which is again the red circle on the left, and the kidney, which is-- I'm sorry, the spleen in this case, which is the green circle on the right. And that's called the liver-spleen attenuation. So if you measure the Hounsfield units on the left side, and you subtract it from the spleen on the right side, if it's less than minus 10, then that suggests the presence of fatty infiltration of the liver. And this is usually measured on a non-contrast CT scan.

So these are common scenarios where patients might be seeing you in clinic after they've been diagnosed with fatty liver quite incidentally or if they had any abnormal liver enzymes or symptoms prior to seeing you.

So what exactly does that mean and what's going on from a histologic perspective, from a microscopic perspective? And this is a fairly typical biopsy from one of my patients in the clinic that is showing the three features of non-alcoholic steatohepatitis. The red arrow points towards a hepatocyte that is suffering from oxidative stress.

And we call that a balloon hepatocyte. So instead of being a nice cuboid, this is sort of a balloon shaped hepatocyte that's in the process of dying and releasing serum transaminases into the bloodstream. The blue arrow points towards a fat globule. So that's steatosis. And that's the most obvious feature on a biopsy. And then the green arrow points towards a focus of inflammation. And if you have all three things present on a biopsy, then we call that NASH.

Now, I have to say this is a very tricky diagnosis to make. And even very experienced pathologists will sometimes not agree with each other in terms of the presence or absence of ballooning, which seems to be a very tricky thing to diagnose. It's, of course, quite easy to see steatosis on an average liver biopsy.

And if we stain these slides with a special stain-- this is called a trichrome stain shown here in the blue-- there's a chicken wire pattern of perisinusoidal fibrosis. And these are all the yellow arrows showing you the patchwork or network of fibrosis, or scar tissue being laid down three-dimensionally in the liver. So that's a fairly typical biopsy of a patient with advanced NASH. In this case, was a patient that was stage three out of four fibrosis, which is fairly significant.

So what's the natural history? I think it's important to keep this in mind because you may be seeing patients at any stage of the disease process. And this slide gives you an overview of a healthy liver. So that's the top left here, showing you a histologic specimen from a normal liver and a liver which is normally brown, smooth. The contours are very smooth and the liver is firm and brown.

Once the liver gets fatty, it actually starts to look yellow. Certainly our surgeons see a lot of this during laparoscopic procedures and other intra-abdominal procedures. And in some individuals there is the presence of ballooning, presence of inflammation in addition to the fat. And that's called non-alcoholic steatohepatitis because steato, meaning fat, and then hepatitis is that inflammatory component along with liver cell injury.

And in some individuals, there is progression to fibrosis. So here, again, the trichrome stain in blue, the liver then starts to get a little bit more fibrotic, ultimately giving rise to cirrhosis. And it's important to keep in mind that in many individuals, the fat disappears as the fibrosis progresses.

And so we frequently will see patients in our clinic who have cirrhosis or de-compensated cirrhosis with complications. But they do not have any fat either on their biopsy or at the time of a liver transplant because the fat has gone away by then, leaving just a fibrotic cirrhotic liver behind.

And in about 1% to 2% of cases in patients that have cirrhosis with NASH, there is development of liver cancer. So that is the natural history. But fortunately of course, this progression doesn't happen in every patient. And one of the major clinical challenges that I'll talk to you about is how do you define where the patient is along this whole natural history pathway?

It's also important to keep in mind because this is so important for most internists and primary care practices, is that fatty liver disease is very closely associated with insulin resistance, and the metabolic syndrome, and type 2 diabetes mellitus. And so way back in the early 2000s, this association was recognized. So we've known this for a long time. And it's not surprising that as a greater and greater percentage of our population suffers from obesity and diabetes, there is also a parallel increase in the prevalence of fatty liver disease.

And the reason I highlight this point is that these are the patients that you are seeing years before we are seeing these patients. So if you are seeing a patient that has all of these risk factors, that has obesity, diabetes or insulin resistance, impaired fasting glucose, hypertension, dyslipidemia, sleep apnea, gout, that whole syndrome, definitely keep fatty liver in mind as an additional metabolic complication of their overall disorder.

Now, in terms of the pathogenesis, it's sometimes very easy to fall into the trap and say well, it's all related to lifestyle, it's all related to diet and weight. But the fact remains that NAFLDs are extremely complex disease with a very complex pathogenesis. We certainly see patients that have all the risk factors and have every reason in the world to have advanced liver disease, but do not.

And then there are other patients who completely lack any of these metabolic risk factors yet have very aggressive liver disease. So there's a lot that we need to understand about the underlying pathogenesis and etiology.

But in general, we do understand that inside the liver, there are some abnormalities in triglyceride handling and metabolism, whether it's related to de novo lipogenisis, fatty acid oxidation, or export from the liver, and now, increasingly, some genetic polymorphisms have been identified that are associated with abnormalities of lipid droplet handling within hepatocytes. And that's a very important variant, genetic variant, called PMPLA3.

But it's also obvious that there's a lot going on outside the liver that's contributing to the pathogenesis of NAFLD. Clearly there are some genetic variations and mutations that increase the risk for obesity. And MC4R receptor mutations have been associated with hyperphagia and early obesity.

There's clearly a very important role of adipose tissue and adipokines arising from the adipose tissue. Insulin resistance in pancreas and beta cell failure clearly has a role. And the gut microbiome is getting increasing attention in this field to try to understand what the various mechanisms are.

So the bottom line is we have a long way to go before we understand the fundamental pathogenesis and how different patients have different etiologies and underlying pathophysiologic mechanisms.

But the most exciting thing in my mind is the new terminology for 2020, where non-alcoholic fatty liver disease, which until now was a diagnosis of exclusion and therefore sort of a negative diagnostic criteria, has now been flipped over into a positive diagnostic criteria. And I think it really gives the power back to internists and primary care physicians.

Because, if you see a patient, an adult patient with hepatic steatosis, either detected through imaging or if you have blood biomarkers, for example, if you get a NASH FibroSURE. In any case, if you have a patient that has hepatic steatosis and that person has either overweight or obesity coexisting or they have type 2 diabetes mellitus, you can make a positive diagnosis of metabolic dysfunction associated fatty liver disease, or MAFLD instead of NAFLD.

It's also important to keep in mind that lean or normal BMI individuals can have MAFLD or NAFLD. And in this case, it's the presence of at least two metabolic risk factors, and typically, the factors that you would associate with the metabolic syndrome, so waist circumference, hypertension, dyslipidemia, et cetera, or pre-diabetes.

And it's important here that the definition no longer requires a liver biopsy or histologic evaluation to come up with the diagnosis of NASH. So you don't need to know about hepatocyte ballooning or inflammation. You can see these patients in clinic on a regular day, and very confidently make a positive diagnosis for MAFLD.

So in the rest of my talk, I'll use the words MAFLD and NAFLD interchangeably. I think this is the year where we are transitioning to the new terminology.

Those individuals that come to see us and have cirrhosis with all of the metabolic criteria are now labeled as having MAFLD-associated cirrhosis. So we used to call it NAFLD-associated cirrhosis. And now we're calling it MAFLD-associated cirrhosis. And many individuals, whether or not they have any fat in their liver at this moment in time, if they had a prior liver biopsy or any prior imaging showing the presence of hepatic fat, hepatic steatosis, then they would also be labeled as having MAFLD-associated cirrhosis.

Of course, there's a small percentage of patients that do not fit into this criteria. And we still call them cryptogenic cirrhosis, where we're not quite sure what the underlying etiology is. And the estimates are that perhaps a certain percentage of these patients have autoimmune hepatitis-related burnt out cirrhosis. So they may not have the risk factors for MAFLD or NAFLD.

It's also important to keep in mind that increasingly, since fatty liver disease is so prevalent in our population where obesity and diabetes are so common, it is possible to have more than one reason for having liver injury. It's not necessarily that the patient only has MAFLD.

And so you may have a patient that has all the metabolic risk factors but also consumes a fair amount of alcohol or may have chronic hepatitis B and C. And these individuals are now said to have dual etiology fatty liver disease. And we've known this for a long time, for example, in those individuals who had hepatitis C and alcohol use for example, that the risk of progression to cirrhosis is way higher in those individuals.

Now, how much alcohol is too much I think is very controversial. It's unclear. The current definition suggests three drinks on average per day in males and greater than two drinks per day in females is associated with alcohol-related liver disease, is the primary etiology. And certainly binge drinking, which is more than five drinks in one two-hour session or more than four in females is also part of that process.

But I have to tell you, sometimes it's very tricky to tell these two apart. And so I don't hesitate to diagnose patients as having dual etiology fatty liver disease if they have risk factors, both metabolic as well as significant alcohol use. And it's also certainly possible to have triple or even quadruple etiology fatty liver disease in our population, just given how prevalent these problems are.

So very quickly, to solidify these concepts I have some clinical examples from my clinic a 54-year-old male comes in with a BMI of 40 and had hepatic steatosis on ultrasound. Very straightforward-- the presence of obesity and hepatic steatosis-- with the new definition, you can confidently label as MAFLD.

A patient that has a normal BMI, on the other hand, at 24 but does have at least two metabolic disorders, in this case pre-diabetes and dyslipidemia, and has fatty liver, now has MAFLD. But this would be the lean variant of MAFLD. And in our clinic, it's about 5% to 10% of the patients do fall into that category.

A 60-year-old male who had a previous biopsy showing steatohepatitis has class I obesity and drinks four alcoholic drinks per day-- so this is above our threshold-- I would label as having dual etiology fatty liver, both MAFLD plus alcohol-related liver disease. And then a 71-year-old female showing a steatotic nodular liver, concerning for cirrhosis, who has class 2 obesity and diabetes, is a patient that I would label as having MAFLD-associated cirrhosis.

So again, there's no need for a biopsy. There's no need for a specialist referral here. You can confidently make this positive diagnosis based on the new definitions. And I think it really makes a lot of sense. And I like the new consensus guidelines a lot.

So with that background, I'll move on to some real world clinical challenges. Where are we here in 2020? What are some of the things that you need to keep in mind when you're seeing these patients?

So the first important thing to keep in mind is that the prevalence of NAFLD/MAFLD is increasing worldwide. And the US the estimates are pretty staggering. It's about a third of the US population, or about 90 million individuals, have MAFLD. And as you can tell from this map, it's really, truly a global problem. And we're not the only country in the world suffering from this disease.

And also, the smaller-- the pie graphs here show the prevalence of PNPLA3, which is a very important genetic polymorphism, or variant associated with MAFLD. And that seems to be higher in the Hispanic American population. So that seems to increase the risk of having aggressive fatty liver disease, also increasing the risk for alcohol-related cirrhosis, as well as hepatitis C-related cirrhosis and cancer.

So clearly, there are some important genetic variations, as well as ethnic and racial differences that need to be teased out in the future. But the point is, if a third of our population has this condition, you really need to keep this in mind when you're seen these patients in your clinic.

The other thing to keep in mind is that a family history has a very important role in terms of diagnosis and prognosis. And this very interesting study from a few years ago showed that first-degree relatives of patients who had NASH-related cirrhosis had an increased risk of advanced fibrosis. They were completely asymptomatic, undiagnosed patients who underwent an MRI scan and were found to have advanced fibrosis.

So this is a fairly important and high yield history that you could take in your patients. So they do mention a history, a family history of cirrhosis, you have to keep that in mind, particularly in the right metabolic setting.

The other important thing is that there is a very high prevalence of MAFLD/NAFLD in patients that have obesity and type 2 diabetes, which is half our population here in Western Pennsylvania. And these are two graphs showing the increasing prevalence as BMI increases. And so with increasing obesity to class 3 or higher, the prevalence reaches almost 100%. So clearly in patients that are undergoing weight loss surgery, for example, this is almost 90% or higher. Not all of them, though, have fibrosis or cirrhosis. But this is just the presence of fat in the liver with or without inflammation and hepatitis.

Also, in individuals with type 2 diabetes mellitus. The current estimates are 70% of patients that have type 2 diabetes will have MAFLD. So it's very important to keep that in mind because many of these individuals will not have elevated liver enzymes. They may have advanced fibrosis. But they may not have abnormal biochemistries. So this is important to keep in mind.

And currently, the guidelines in Europe are certainly suggesting screening for MAFLD in patients with type 2 diabetes mellitus. And I think in the future, the US guidelines will also change to suggest that certainly some of the other societies, like the Endocrine Societies, et cetera, have a growing awareness regarding screening patients for liver disease.

What's going on in our own population? This is a study we published from my clinic from a few years ago showing the BMI distribution of patients that were referred to us for evaluation of fatty liver disease. We had ruled out alcohol-related disease in most of these patients.

And as you can see from this distribution, that really it's class I obesity that's the most common in our patients. So patients aren't necessarily suffering from severe obesity, but of course, the majority of patients have overweight or obesity as comorbidities. But there are a few individuals that have normal body weight. So in our population, it's about 6%. So that's definitely important to keep in mind. And if they have the metabolic disorders, then you have to keep the presence of MAFLD in mind.

It's also important to keep in mind that increasingly, given the diverse patient population that we have, that there are different standards for obesity. So if you have patients from Asia, for them 23 BMI should be considered overweight and 27 should be considered obesity, which is different from a European American population, where the numbers are 25 and 30 for class I obesity. So it's clearly possible to have normal weight but have all the risk factors and metabolic dysfunction associated with MAFLD.

And so around the world, there has been an increasing prevalence of fatty liver disease despite no parallel increase in obesity, probably because of genetic differences in the capacity to gain weight. And of course, the upshot of that is that because it's such a huge public health burden, we will see patients in the future with increasingly advanced stages of MAFLD that are going to be a big challenge for us clinically to manage because there will be progression in some, not all, of these patients.

And so the current estimates are perhaps somewhere around 8% to 12% of patients will have steatohepatitis or the progressive form of fatty liver disease. And about a third of those patients that have steatohepatitis will progress through fibrosis and cirrhosis. And of those, 1% to 2% will go on to develop liver cancer.

So this is, of course, a very big deal. And so it's important to keep this in mind because if we identify and intervene early, we can make a difference in the natural history of the disease.

The important take-home message that I really want to emphasize is that the most important prognostic factor that we know of right now for liver-related outcomes-- so that cirrhosis, liver cancer, de-compensation, need for liver transplantation-- is the stage or degree of liver fibrosis. And so someone that has very little fibrosis in the liver is likely going to be OK for a period of time. And if they do have progression, obviously their risk increases.

On the other hand, someone that has very high fibrosis, they are likely to have a much higher risk. And most natural history studies have not found a similar correlation with the degree of fat, for example, or any biochemistries that we test routinely. So just to refresh your sort of background that we stage fibrosis in from 0 to 4, where 0 is normal and 4 is cirrhosis.

And typically, someone that has F0, F1 fibrosis typically is in a low risk category, at least that's how we treat those patients in my clinic. Someone that has F2 fibrosis is sort of in between. It's certainly reversible at that point with lifestyle modification or therapy. And someone that has F3 or F4 fibrosis is classified as having advanced liver fibrosis. And that is a very high risk category with a fairly high risk of progression to hepatic de-compensation requiring liver transplantation or liver cancer in the future.

So it's important to keep in mind where the person is. And I don't think it's important to really know which specific stage a patient is at. But it's OK to say someone is low risk, relatively F0 or F1, or if they're high risk, F3 and F4. And sometimes it's clinically difficult to know if they are in the middle, whether they are low or high risk. So there are a few patients that are sort of indeterminate.

And, of course, the importance of this is that there is a very important impact of fibrosis on survival. These are data from my clinic 899 patients, so a very large cohort in the last 10 years, with biopsy proven NASH. And you can tell that someone that has early stage fibrosis, which we defined as F0 to F2, which is the red line here, and compare that with those who had advanced fibrosis-- I'm sorry, the other way around, the red line is advanced fibrosis, the blue line is the low fibrosis-- you can see that very dramatic difference in survival where patients who have advanced fibrosis are having a significantly lower survival than those individuals who are low risk. So an important take-home message, because much of our diagnostic focus is in stratifying the patients in these two groups.

The other very important clinical challenge as of 2020 is that there is no FDA approved treatment for MAFLD/NAFLD as of 2020. There is a lot of research activities going on. We have currently eight ongoing clinical trials in my clinic. But the prospect of something being FDA approved is not imminent.

The good news, of course, is that there are over 200 clinical trials. By some estimates now, it's over 250 clinical trials. There is almost 100 now in the US. So there is some hope and there's some prospect that we may have some real liver directed pharmacotherapy available in the near future.

So with that background I'm going to move on to the final part of my talk in the next 10 minutes or so, and to give you a very simple, practical framework with the goal that you could apply this framework to your clinic, to your patients today. And of course, with the caveat that the technology and knowledge is changing so rapidly that this may be outdated by next year.

So the first and important step is to suspect MAFLD. Of all the patients that are referred to us in our clinic, I find that there are some very important differences in referral patterns. I find there are some internists and primary care physicians who are referring a lot of patients to us. They recognize MAFLD early, they keep that diagnosis in mind. They certainly do a very thorough evaluation before they refer the patient to us.

But if you do see a patient that has obesity, diabetes, that has metabolic syndrome with or without obesity and diabetes, and irrespective of their liver enzyme status since many patients with MAFLD may not have elevated liver enzymes, it's important to keep the diagnosis in mind. If you don't think about the diagnosis, if you don't think about the liver as a very important component of the metabolic syndrome, then it's possible that you may miss some of these patients.

And every week in clinic, I will see an average of one patient that was known to have fatty liver at least a decade ago but had never been staged or had been risk stratified, and by the time they come to see us, have cirrhosis with or without portal hypertension. So clearly, there has been a missed opportunity in changing the natural history of the disease.

We asked the question recently in collaboration with Dr. Kathleen [INAUDIBLE] in the Department of Medicine, whether in our population we are under undue diagnosing NASH/MAFLD. And these are, of course, based on ICD-9 and 10 codes. And here, we looked at the back network across seven sites, very large number of patients. And we find that there is a very, very small number of patients who are being diagnosed with NASH.

So we think that there is a very large population that's out there that are simply not being identified by our physicians. So it's something to keep in mind as you see these high risk patients in your clinics.

So after that first step of keeping the diagnosis in mind in the right patient population, it's important to, of course, define the etiology. And hopefully, with the 2020 definitions, you'll have the confidence to be able to make this diagnosis. So if you have someone that has obesity, that has diabetes, or the metabolic syndrome, you'll be labeling them as MAFLD.

Always keep in mind that it's sometimes extraordinarily difficult to tell MAFLD and alcohol-related fatty liver disease apart. And so don't hesitate to label those patients as dual etiology fatty liver. Because then your treatment will be focused on two separate problems, not necessarily just one problem.

And certainly, in the old days when we had hepatitis C as a big problem along with alcohol, we not just recommended complete alcohol cessation, but treated the hepatitis C separately. So it does change your management plan pretty significantly. And it's important to define the disease appropriately.

It's also important to keep in mind that if MAFLD is affecting a third of our population, you are going to see patients that have more than one liver disease. And a common diagnostic problem for us is to separate NASH/MAFLD from autoimmune hepatitis. And it's a pretty big challenge, even for liver specialists sometimes. But again, to make the point that what's fatty liver may not be the only problem a person has. So perhaps keep that in mind as you see these patients.

And of course, it's certainly possible to have triple or quadruple etiology fatty liver disease where there is underlying metabolic issues, plus alcohol, plus hep C, plus perhaps a genetic mutation, such as alpha 1 antitrypsin or hemochromatosis. And these patients, of course, are the highest risk patients with a very high risk of developing cirrhosis as well as liver cancer. So perhaps that's the population that you want to target for referral earlier rather than later because they have the higher risk for progression.

So it's important to use these new definitions. And it does give you the power now without requiring a liver biopsy or a specialist evaluation. And so it's important to consider again, like I said in the previous slide, alcoholic liver disease, which is very, very common in our population now. We are certainly seeing a really significant uptick, particularly post-COVID.

There is also still quite a lot of hepatitis B and C in our community. Autoimmune hepatitis, which we all look for, is relatively rare disease in most practices, although not for us in our clinics. But it's a relatively uncommon diagnosis, although we do look for it in our patients. And then there are other rare genetic causes. But do keep this in mind. And these are all simple screening tests that you could do in your clinics before you refer patients to us.

The other common question that I get asked a lot by referring docs is what do autoantibodies mean in this population? And if someone has anti-nuclear antibody or smooth muscle antibody, which are autoimmune markers, whether that necessarily means the patient has autoimmune hepatitis or whether it increases the risk of NASH fibrosis?

And the bottom line here is it's quite common to have low or borderline elevation of ANA and smooth muscle antibodies in our patients, both alcohol-related and non-alcohol-related, or metabolic fatty liver, and does not seem to increase the risk of having either underlying inflammation or fibrosis.

So really, it's more a question of looking at the patient in the right context. And in most patients that have very mild elevation, normal IgG, level no strong history of autoimmunity, I usually do not act upon these antibodies. We will see some patients occasionally that have very high transaminase, a strong family or personal history of autoimmunity and positive antibodies, in which case the only way to tell the two apart is to do a liver biopsy.

And we are certainly looking at this in our population right now but. I do not have an answer for you at this point. The step-- the next step then is to figure out what fibrosis stage the patient is at. And here, I would strongly recommend using a non-invasive test because it's something that you can do very easily. Right now we have all the tools and technologies available.

And as I mentioned a few minutes ago, the most important histologic finding that's associated with liver-related outcomes is the presence of liver fibrosis. So a couple of tests that you could do very easily at point of care using simple biochemistries is FIB-4. And I'll tell you a little bit more about that. The other one is called NAFLD Fibrosis Score. Most of these are available through our medical calculator apps on our smartphones.

You can also use a NASH Fibrosure panel, which I am not a big fan of because of some pretty significant error rates. I have less confidence and comfort level with that. And then we use Fibroscans a lot. We also have ultrasound elastography and MR elastography available.

So there are many different non-invasive tests available. Typically, they have high negative predictive values. So you can confidently rule out the presence of advanced fibrosis or cirrhosis, but not necessarily rule in early stage disease. And I like FIB-4. I'll talk to you a little bit more about that. But these are several serum-based risk stratification tools that are available to us.

The one that I like a lot is called FIB-4. It's available online, on calculators. It's available on smartphone apps. You can very easily use-- calculate this based on age, platelet count, and AST over square root of the ALT level. If you have a patient with less than 1.45 FIB-4 score, a very high negative predictive value for the absence of advanced fibrosis.

On the other hand, a high score of greater than 3.25 typically would mean a very high positive predictive value with high specificity, with a relatively lower positive predictive value for advanced fibrosis. But certainly gives you the idea that you need to risk stratify those patients further. Very simple tool that I highly encourage all of you to apply today in your clinics.

We do have Fibroscan available in the US since 2015. Access is still a little difficult, coverage from insurance is spotty. But it gives us two important numbers. In the blue is a semi-quantitative fat score. In the orange is a semi-quantitative liver fibrosis score. And typically, any score above 7, I start to pay very close attention. Below 7, typically we worry less about those patients. And once the scores are in the double digits-- 11, 12, 13, 16-- we really start to think about cirrhosis or advanced fibrosis for those patients. And certainly, this is something you can order through our clinic in Montefiore Hospital.

Something that's available now in Presby, Mercy, and McGee Hospital is ultrasound elastography. It's called 2d Shear Wave Elastography. So I know a lot of you are very comfortable ordering an abdominal ultrasound for these patients. But think about adding on an elastography to your ultrasound. And that gives you a very easy way to risk stratify patients. And most reports will give you, at the bottom, a scale with interpretation of how much fibrosis the patient has.

We also have MR elastography and proton density fat fraction, which is a way to quantify liver fat. And this is available here at Presby. Sometimes if there is a discrepancy between different tests, I will move to an MR elastography before getting a liver biopsy for some patients.

Here is an example of a patient that got a biopsy during a cholecystectomy, had very low fibrosis. This was part of a study. We did 2D elastography which was very low at 5.7. MR elastography was low. So this is a very easy way for you to rule out advanced fibrosis and avoid referral or treatment for these patients at these pharmacotherapy, because they are in a low risk category.

So this is my proposed simplified diagnostic workflow. If you suspect that the person has fatty liver disease or MAFLD, I think some basic workup to rule out other etiologies is very helpful. You can do an ultrasound with or without Shear Wave Elastogaphy. Certainly, I recommend you use either NAFLD Fibrosis Score or FIB-4.

And if the patient is very low risk, it's OK not to refer those patients to us. On the other hand, if the patient is very high risk with high scores, high liver stiffness measurements, it's probably worth referring those patients to us for further screening for other diseases, as well as possible therapy. And it's the patients who are indeterminate and have all the risk factors that I usually consider a liver biopsy so we can get them into treatment very quickly.

Here's a very simplified flow that you can apply today in your clinic. Definitely, I encourage you to use FIB-4. Please consider shear wave elastography or a Fibroscan if you have access to it. If they are concordant, you can risk stratify the patient confidently. If they are discordant, absolutely OK to consider MR elastography before you move on to a liver biopsy-- so very straightforward, three-step process for risk stratification.

Typically, it's the advance stages of MAFLD that I consider to be appropriate for referral. If they are early stage, I think it's perfectly OK for you to treat those patients in your own clinics.

Step five is to focus on lifestyle modification. These are all very straightforward and common sense approaches, diet improvements, smoking cessation, alcohol cessation, improved physical activity, and weight management. This is bread and butter for all internists and primary care practices.

There is very limited data on optimum diet. But I certainly recommend a Mediterranean style diet with a fairly high degree of evidence to support that. And there is some evidence that coffee consumption is helpful. So if you're taking away alcohol and tobacco from your patients, feel free to give them back coffee because that seems to be very helpful for the liver.

Weight loss is very effective but very difficult to treat for most patients. And in this slide, if you can have a patient lose 10% of their weight, there is a almost complete resolution of steatosis. There is a very significant improvement in steatohepatitis as well as fibrosis regression. Because as you can see in the bottom, very few of our patients are able to successfully lose weight. But certainly, if that's something you can convince your patient to do or treat them for is very, very helpful. And there is, of course, improvement in liver histology with weight loss.

For the appropriate patients, bariatric surgery can be very helpful. There is lots of evidence that bariatric surgery is under-utilized. So if you do have patients that are in the appropriate group with high obesity of 35 or higher with comorbidities, or 40 and higher with or without comorbidities, please consider bariatric surgery and referral for these patients because it does improve NASH and, in some cases, fibrosis.

Exercise is, of course, helpful. Current recommendations are 150 minutes per week. These are data showing an improvement with 250 minutes per week, which is difficult for most of my patients to achieve.

An example of what can happen with lifestyle change-- on the left a patient with advanced fibrosis in October of 2017 in my clinic who lost weight, made lifestyle changes, started exercise. And you can see that the fibrosis, at least based on elastography, went from reds, or F4, to yellows, or F3. So these are real changes. And you can make a difference to your patients by emphasizing lifestyle modification.

Step six is to consider pharmacotherapy for patients that have F2 or F3 fibrosis. The two medicines that we use off label, since there's nothing that's FDA-approved, is vitamin E for patients that do not have cirrhosis and diabetes. But if you do have a patient that has diabetes, you could consider Actos or Pioglitazone at 45 milligrams daily.

A lot of interest in GLP 1 receptor agonists and SGL2 inhibitors. So if you do have patients with diabetes who are on insulin and can be transitioned to these agents, that's definitely worth a shot.

Many clinical trials going on around the world. As I said before, most of them fall into the three categories of lipid metabolism, targeting inflammation, and fibrosis targeting. We currently have nine clinical trials going on, which span the entire spectrum. So please consider referring your patients if you do have motivated patients that may be interested in these approaches.

And finally, never forget the comorbid problems. That's really the domain for internists and primary physicians rather than hepatologists. But these are all important considerations, diabetes and the metabolic syndrome.

Important take-home message, statins are safe. Please do not stop them unless the patient has de-compensated cirrhosis and because of their underlying cardiovascular comorbidity. And if you are seeing a patient who's on metformin, there is some evidence that it decreases the risk of de-compensation and liver cancer. So please continue if you can, unless the patient has de-compensated cirrhosis.

And finally, if the patient has cirrhosis, it's important to screen for HCC with six monthly ultrasound and alpha fetoprotein. And definitely refer for an endoscopy for screening for esophageal varices.

So to summarize NAFLD/MAFLD and NASH are very commonly encountered in clinical practice. Please keep this diagnosis in mind. The new definition gives you a lot of power to make this diagnosis in a positive manner for your patients. Keep in mind, the diagnosis staging and management is very challenging. It's very rapidly evolving. And the guidelines are changing almost every year at this point.

But I've given you a very simple step-wise approach for risk stratification and management that I hope you can apply today in your clinics for effective management of these patients. Thank you very much.