JAIDEEP BEHARI: Thank you very much. So rather than just going through a bunch of facts about NASH I've designed the doc as a case of fatty liver that presents to you. And just like in real life, we'll go fast. I'm sure you have precisely five seconds to make a decision in clinic, and so I'll have a bunch of questions scattered through the doc, and we'll go through the options.

It'll be obvious to you what the answer is at the end of the talk. And I have quite a few of these questions built in. But if you have any doubts about any of the options please raise your hand, or we can discuss right afterwards, during the break.

So let's start with a patient. This is a fairly typical patient. The details have been changed really slightly here, just to make it more comprehensive. But it's a 57-year-old female, with a history of impaired fasting glucose, hypertension, dyslipidemia

She was doing really well two, three months ago, and then develops this achy right up a quadrant pain. So she had this pain for about three weeks, ended up in the local ER. The blood-work there shows and ALT of 85. ASD was 65. She had a normal [INAUDIBLE], GGT, total bilirubin, albumin. All the other labs were OK. But she had an ultrasound of the abdomen, which shows a heterogeneous liver echotexture, normal gallbladder, and no kidney stones. So the patient was sent home, wasn't admitted. She's feeling OK now, but then she was recommended to follow up in your office for the ultrasound findings, and the high liver enzymes.

So based on this history, what you know so far, would you say that this patient has NAFLD, NAFL, NASH, NASH cirrhosis, or none of the above? So very quickly, in one second, just a show of hands, anyone that thinks this is NAFLD? How many of you think this is NAFL, NAFL? NASH? NASH cirrhosis? Any options? None of the above. OK. No opinions? OK. All right, I didn't have that as an option.

So very quickly, definitions. When I NASH or NAFLD I mean something very specific. And these are the definitions that are proposed by recent guidelines, or guidance, that was proposed by our national society. So when we say NAFLD or nonalcoholic fatty liver disease, it just means the whole spectrum of fatty liver disease. This could be someone that has just fat, with no manifestations, and on the other extreme, someone that has cirrhosis and liver cancer.

Now, someone that has had a biopsy and has no fibrosis, very little inflammation, we use the word NAFL or nonalcoholic fatty liver. So we've left the D out. There's no disease there. It's just a patient that has fatty liver, that's it. It's not causing any biological or medical consequences.

Now, NASH to me has a very specific meaning, and that's a person that has increased fat, which is defined as 5% or more fat in liver cells, along with specific histologic features. And we'll talk about that in a second. And this is the form of disease that can progress to cirrhosis, and all of its manifestations and complications. So NASH is what you're looking for, the buzzwords and biopsies, and in sub-specialist referral letters to you, because that's what can lead patients to trouble down the road. And then NASH cirrhosis, means someone that has NASH, and that has progressed to cirrhosis, and cirrhosis, again has a very histologically specific definition. We'll talk about that, based on some biopsies.

And then sometimes the patients will come to us very late in the process, when they have cirrhosis, but we don't know why they have cirrhosis. There's no diagnostic test for NASH so far, but based on their co-morbid problems, perhaps the presence of obesity and diabetes, we guess that they have had NAFLD in the past. And those are patients that are called cryptogenic cirrhosis. And there, the breakdown is 70% nonalcoholic fatty liver disease, or sometimes, even alcoholic liver disease. And about 30% of these patients have autoimmune hepatitis that's burnt out, and these patients have gone on to develop cirrhosis with no other serologic or other biochemical markers of the original disease.

So this is an example, a patient from my clinic that had a biopsy that has NAFL, or nonalcoholic fatty liver. And I want to point out a few things, of course, you don't have to worry about these histologic details. But just to give you a visual representation of what you are seeing from a clinical perspective. So these are just some specific features of the liver biopsy, because this is called a portal tract. This is a central vein. And these little white globules are where fat globules were within hepatocytes. And when we process these liver biopsies and put them in formalin the fat disappears, leaving behind this white globule. So the pathologists see this right away. And this is what steatosis, or fatty liver, looks like. So when we do a biopsy, that's what it looks like.

Now the point I want to make here is very simple. If you look at this biopsy slide and had no training in pathology, you could tell that this is mainly pink. There's not much blue there, which is good, because all inflammatory cells-- lymphocytes, neutrophils, et cetera, will have some degree of blue staining. And so this is a pinkish looking slide, which is usually nonalcoholic fatty liver. In contrast, this is an example of a patient that has nonalcoholic steatohepatitis. I've marked a few features here with arrows to tell you what the pathologists are looking for, what we're looking for, during our pathology conferences, for patients who have NASH. This is a feature that's very important to look for, from my perspective at least, and the pathologist perspective, and this was kind of ballooned hepatocyte. It really looks like a balloon. So it's a highly scientific description. That's important for NASH.

Here's again a steatotic hepatocyte. And here's a focus of inflammation in the green arrow. So now you can tell the important features that we're looking for in a patient that has NASH, as opposed to NAFL. But there's another important feature that we're looking for, and that's the degree of fibrosis. And here, the biopsy has been stained with a special kind of stain called a tri-chrome stain, that causes called collagen and to stain blue on biopsy slides. And here you can see this blue, it's almost like a chicken wire pattern of fibrosis, on the liver biopsy, which is seen in nonalcoholic fatty liver disease, as well as alcoholic fatty liver disease.

So what you are doing in clinic, when you're taking a history and seeing the patient for the first time, is highly critical. Because the apologists could not tell based on this biopsy whether this patient has alcoholic or nonalcoholic fatty liver disease. So it's very critical, I think, old fashioned clinical medicine, and taking a good history is very, very important for these patients. And this chicken wire pattern of fibrosis, usually, is indicative of a patient that has NASH, and may get into trouble in the future with this disease.

So based on this presentation, would you say that this patient has adipose tissue dysfunction, and does this patient have obesity and insulin resistance? Does this patient have fatty liver because of development of fatty liver and inflammation? Or are multiple problems involved in the pathogenesis of this patient? So here again, different people look at this problem from different perspectives. Many of you, perhaps, would choose obesity and insulin resistance as the most common driver. But we know now, and then certainly in the fatty liver world, in the hepatology world, the two hit hypothesis was favored for many decades, where the prevailing wisdom was that, first, the patients develop obesity that leads to fatty liver, and something triggers inflammation that then causes progressive for fibrosis. We know now that that's no longer true, and the real pathogenic basis involves multiple steps in an individual. So lots of things need to go wrong. Lifestyle, genetics, environmental triggers, et cetera. Other medications that lead to the development of NASH. So because it's a multi-hit pathogenic process, it's also a difficult problem to treat sometimes.

So here's just a very simple cartoon, showing you what the various pathogenic processes that have been postulated. Clearly, the presence of hyperphagia, or even dietary indiscretion in our extremely poor food environment makes a big difference. The presence of obesity is a very strong risk factor. There are several polymorphisms in genes that have been identified. Insulin resistance is very, very common, not in every patient, but in a large percentage of these patients. And there's a lot of interest now in the role of the gut microbiome and gut dysbiosis in driving the process of insulin resistance and fatty liver disease. Within the liver itself, there are many processes that are going wrong. There are changes in lipid oxidation, and lipoprotein export. There's problems with lipogenesis. And usually there's increased lipogenesis, or production of new fat from incoming carbohydrates in the liver.

So a lot of these patients have a very high refined carbohydrate diet that the liver then converts into lipid. So that the process of de novo lipogenesis is very common in all the studies that have looked at these processes within the liver. And then there are some genes that have been identified, which are associated with liquid droplet formation in the liver. So just to give you an idea, not that you have to remember any of these details, that it's a really complex pathogenesis which is made treatment of this problem very challenging. And that will make sense when we talk about the treatment options that we have right now.

So you learn a little bit more about this patient that's in your clinic now, and you find that she has impaired fasting glucose. She's got dislipidemia hypertension, polycystic ovary syndrome. She developed menopause at the age of 48. She had a sleep study in the past that was negative for sleep apnea, and she has no prior surgeries.

So based on her history, which condition do you think may be associated with her diagnosis of NAFLD? Would you think she has a higher chance of having fibromyalgia, osteoarthritis, psoriasis osteoporosis, or all of the above?

So the reason I put this question in here is that sometimes we see these patients referred to us, and certainly in your practices you'll see them all the time, is because they may not present as fatty liver. They may have one of these other associated problems, and so you have to sometimes suspect underlying fatty liver that the patient may be completely asymptomatic, and have normal liver enzymes. So these are some of the conditions that are very closely associated with fatty liver disease. And they are established associations with obesity, diabetes--type 2 diabetes, dyslipidemia the metabolic syndrome and polycystic ovaries. But there's also a growing body of literature strongly associating NAFLD with hypothyroidism, with sleep apnea, and with some other endocrine problems, as well as surgical issues.

But for the purposes of this question, the right answer is psoriasis. And there's many theories about it, but the one which I find particularly attractive is that, even with cirrhosis, there is a state of low grade chronic inflammation, and then the liver has an important role in that process, and perhaps maybe also subject to that chronic persistent inflammatory state in the body. So these are things to think about when you see these patients, because they may present with one of the other problems as their primary manifestation.

So you'd get more history from your patient. And she says that her mother was diagnosed with cirrhosis at the age of 65, and then ultimately died at the age of 70, and didn't drink a drop of alcohol. Her father is alive at 79. He just has hypertension, otherwise doing well. And she has a sister who's 50, who has diabetes, and has been diagnosed with high liver tests. And this, I can tell you, is a fairly typical family history for the patients that are referred to me in the fatty liver clinic. So then the patient says that she's really worried that she has an increased risk of dying from her liver disease because of her family history. So what would you tell her about the genetics, or the familial risk that she may have of fatty liver disease? And believe me, this is a very, very common question that I get asked, so I'm sure you're getting asked these questions in your clinics too.

Would you tell her that she has no increased risk of liver disease, compared with the general population? That the presence of a family history of liver disease and cirrhosis increases her risk of fatty liver, but not NASH by 25%? Does it increase her risk of having scarring or NASH with fibrosis over tenfold, or does she have an increased risk of developing HCC?

How many of you think it's A, that, there's no increased risk? Anyone think that she does have an increased risk? OK, so that's exactly right. But the increase in risk is shockingly high. And this is a paper that was published in a very prestigious journal just a few months ago, showing that patients who have a first degree relative with NASH related cirrhosis has somewhere between 12 to 15 times higher risk of having advanced fibrosis on a liver biopsy. So this is really a huge problem, and there are no recommendations at this point on screening family members if one person has been diagnosed with cirrhosis. That may change in the future, there's a very large study going on at UCSD, looking at patients who have diabetes and fatty liver. So those recommendations may change in the future. But this is clearly a very sobering result although it hasn't been replicated, certainly I know from my clinic that this is pretty close to the truth. So we have to be very cautious in those patients who've had a family member diagnosed with NASH related cirrhosis, or even cryptogenic cirrhosis, because someone diagnosed with cirrhosis, let's say in the '70s or '80s, may not have had the formal diagnosis of NAFLD.

Then the patient asks whether her genes may be playing a role in her liver disease. So what would you say? Would you say that there's never been any genetic associations found? Would you say that all the NAFLD associated polymorphisms are associated with an increased risk of diabetes? So there's no direct risk, but it's an indirect risk, related to the presence of diabetes? And would you tell her that a gene has been identified that actually increases her risk of cirrhosis, with or without NAFLD? And whether you would recommend any genetic testing for her at this stage, perhaps a referral to a genetic counselor? Would anyone refer this patient for genetic testing, or to a genetic counselor, at this point? OK. How many of you think there is an increase, or there's a gene that can predict the presence of cirrhosis in a patient with NAFLD?

So the answer is actually interesting. It turns out there have been a whole bunch of studies showing that approximately 25% to 30% of the pathogenesis of NAFLD can be explained on the basis of genetics or heredity. And many consortia have looked at very, very large numbers of patients, and they all kind of come up with 20% to 30% number. And so it's kind of interesting that, in general, we are missing a bunch of this. The heritability is missing. We don't know what the mechanisms are. And so at this point, there is no recommendation to do any genetic testing for NASH, even though we know what these genes are, that increase the risk. We just don't know how to incorporate them in clinical practice, because a patient may have the high risk genetic profile, but may not have any signs of the disease. So it's a complex gene environment interaction, and there's no recommendation at this point to do any genetic testing for these patients.

But there's two interesting genes that I just want to mention to you, because you will hear about these over and over again in the future. Because they have a very interesting clinical manifestation. One of them is called PNPLA3. And it's very interesting because it increases the risk of NASH and NASH cirrhosis, but it's independent of metabolic syndrome. And I can't tell you the number of patients in my clinic who have cirrhosis from NASH, but have no diabetes, no dyslipidemia and no hypertension, and first came to us because they had a complication of cirrhosis. And they bring 30 years of primary care records with them. They have never had an abnormal liver injury test, ever in their lives. So this is a very interesting sub phenotype, and we just don't know, at this point, how to screen for these patients, or how to identify the high risk populations. What's interesting about PNPLA3, also, is that it also increases the risk of alcoholic liver disease and cirrhosis, as well as Hepatitis C. So this just generally seems to increase the risk of progressive fibrosis in the liver. And what's disheartening, though, is when they've done studies and told patients their genetic risk and asked them to change their lifestyle, they found it made no difference to patients. So it's a little bit disheartening, and we still don't know how to incorporate this into our clinical practice. So we're not testing for this routinely, outside of a clinical study.

The other very interesting genetic polymorphism is a gene called TM6SF2. And why that's very interesting is that it increases the risk of NASH cirrhosis, but decreases the risk of cardiovascular disease. And the reason is that it's very important for export of lipoproteins and lipids from the liver, and so the liver takes all the brunt from a poor lifestyle, or a poor diet, but the heart seems to be protected, because the liver is not pumping out these inflammatory lipids. So these are two different polymorphisms which confer different clinical phenotypes. And again, we're not to the point yet where we test for these genes regularity. But that might change the future.

So you get some more information about your patient. She tells you she's never smoked or used drugs. She drinks about six to seven alcoholic beverages, usually to a glass of wine with dinner, and then she has two cups of coffee in the morning. So this is by far the second most important question, a common question I get asked in clinic, which is, what are your thoughts about alcohol and coffee and someone that has fatty liver disease? Would you tell this patient to continue both? There's neither a risk nor benefit? Would you say stop both? Would you say continue the coffee, stop the alcohol? Or vise versa? Or, would you say to continue the coffee, but, you can't say anything about the alcohol?

So these are common questions, and this is probably the second most common question for me. So it turns out that coffee consumption actually decreases, or is associated with, decreased risk of fibrosis in patients who have NASH. So these are biopsy proven NASH patients. If they drink two or more cups of caffeinated coffee, not decaffeinated coffee, then they tend to have a lower risk of having fibrosis. There is some data just starting to emerge, but has not been confirmed, very large study epidemiologic studies quite yet. So if my patients are drinking alcohol, I certainly encourage them-- I'm sorry, coffee-- I encourage them to continue. But if they are not drinking coffee, I'm not sure we are at the point yet, where we have to tell them to start drinking coffee. But at least that's something. So you're taking away everything from them, the donuts and the muffins and the alcohol, at least you can give them back some Starbucks. So that, I think, is a reasonable compromise.

In the case of alcohol, the guidelines aren't quite clear at this point. The current guidance that just came out a few weeks ago, actually, suggests that heavy quantities of alcohol should be avoided, although the definition of heavy is very murky right now. Currently it's 21 standard drinks for men, and 14 for women, which I think may be on the higher side, because so many of our patients share other risk factors, and are on so many different medications. So I'm a little uncomfortable with that definition. But that's what the society guidelines suggest at this point.

And there's also a growing realization of a new condition, which has hasn't quite made it into textbooks yet, but you will start to see more and more of this, and certainly here at the University of Pittsburgh, we're taking the lead on this, because we have so many of these patients who have both metabolic risk factors, and are heavy drinkers. And we've come up with a name, called dual etiology fatty liver disease we call it DAFLD, instead of NAFLD, and DASH, of NASH. You'll see more and more of these patients, so just be aware, because sometimes you can't tell them apart, and certainly, I have more than 100 patients in my clinic, I have no idea whether they have primary alcoholic liver disease or nonalcoholic fatty liver disease.

So then you do a physical exam for this patient you find that she has a BMI of 28, waist circumference is 38. She's got skin tags, suggesting some insulin resistance. She's got [INAUDIBLE] megaly, has mild right upper quadrant tenderness, but is otherwise normal. So what do you think is true about this physical exam? Her central obesity increases her risk of NAFLD? The skin tags suggest insulin resistance, I said, that's obviously true.

If her BMI was 25, then NASH would be very unlikely for this patient, who presented with pain and high liver enzymes and fatty liver. And if she had spiders, spider angiomas on her neck, then you would suspect liver cirrhosis. Now, of course, the answer to this is, yes to the first, yes to the second, and yes to the fourth.

Now, the 3rd may be surprising to you, that someone who has a normal BMI may have NASH. And this is a paper that's currently in press in one of our very good journals, which is a study from Italy, which is very sobering. Because what they're showing is that there is a significant percentage of patients who are lean, who may have NASH. We don't know very well what the clinical drivers are for these patients. But clearly, someone that has fatty liver, high liver enzymes, and you're absolutely sure do not have alcoholic liver disease, it doesn't mean, just because they are lean, or overweight and do not have obesity, that they may not have advanced fibrosis on a biopsy, or clinically, maybe at increased risk.

So for your patient, you get some more blood work, and you find that she had ANA titer of 1:80, and a borderline smooth muscle titer. Now the patients that are referred to me, I see that a lot of primary physicians are testing anti-nuclear antibodies, and are worried about that. The first thought clearly comes out, at this point, is whether this patient may have the autoimmune hepatitis. And the point that I want to make here is that the presence of antibodies is actually quite common in many diseases, including NASH and alcoholic liver disease, et cetera. And so it doesn't really have any clinical significance if you're sure that the patient doesn't have autoimmune hepatitis.

And in my mind, someone that has five times or higher upper limits of normal transaminases. You definitely have to keep that diagnosis in mind, which is autoimmune hepatitis. But someone that has mildly elevated liver enzymes, all the risk factors, perhaps obesity, diabetes, with mildly elevated serum transaminases with a positive ANA at borderline, or smooth muscle antibody, it's very unlikely that patient has autoimmune hepatitis. And really, has no clinical significance. So I don't tend to just ignore those auto antibodies. And it's not uncommon for me to not do a biopsy for those patients, if otherwise, I don't think that they have advanced disease.

So based on what we know so far about this patient, would you say that this patient has alcoholic liver disease, and ask her to stop alcohol and repeat labs? Would you say that she has NAFLD, and her to lose weight, and repeat an ultrasound and labs? Would you check other markers? Would you recommend a biopsy at this point, or would you start her on vitamin E?

So just for the sake of time, I'm just going to ask you one quick question. How many of you would start this patient on vitamin E at this point? Would anyone? Or would you do other work up? And that is the right answer. I'm glad no one is starting Vitamin E at this point. Because the current guidance that just came out says that you certainly have to rule out other etiologies, because there is no diagnostic test for NAFLD at this point. But Vitamin E is not recommended for a patient that does not have biopsy proven NASH, because many patients do not need any treatment for this condition, other than lifestyle changes.

It's also important to keep in mind that there are many other things, other than a classic obesity, diabetes, metabolic syndrome patient, and many of these are things that we see a lot in our clinics. You may not see them that commonly in the primary care setting. But the point I want to highlight here is that there are many drugs that you are prescribing in your clinic, such as Amio, Methotrexate, tamoxifen, and steroids, which profoundly effect hepatic steatosis, as well as the risk of fibrosis. So keep that in mind for a patient that has a history of fatty liver, or high liver enzymes, because they do change the clinical course of the disease.

So this is a very simple diagnostic workflow that I recommend, if you see patients in your clinic. Certainly if you see a patient that has high liver enzymes, which in my opinion, should be ALT of 30 for males and ALT of 19 for females. So ignore what's in your laboratory reference values because they were taken and tested at the time when NAFLD was unknown. So someone that comes in with a ALT of 54, and it's within your lab's normal reference range, is not normal. That's high ALT. So keep that in mind. It's always nice to repeat your labs, make sure you rule out other etiologies. If it's something else, than treat as necessary.

It's always a good idea to start with an ultrasound. And if the liver looks bright, as in this patient, was an echogenic liver, chances are the patient has NAFLD. Now the next important step is to figure out a noninvasive way of determining how much scarring the patient has. And the one that I like to use in my clinic is something called NAFLD fibrosis score. If you have these smartphone apps MDCalc, or some of these-- all of them have NFS NAFLD Fibrosis Score built in. It's based on platelet count, ALT/ASD, presence or absence of diabetes, BMI an age. And it gives you a number that has to be less than minus 1.455, which means there's a very high negative predictive value that the patient does not have advanced fibrosis. Or if the value is plus .676 or higher, which is a very high positive predictive value that the patient has advanced fibrosis.

The second step is to do a noninvasive test called fiber scan, and I'll talk to you about that in just a minute. Now patients who have a very high risk, noninvasive profile probably need referral for treatment, et cetera. Those who have a very low profile, I think it's quite safe for you to follow those patients and give them lifestyle advice. Those who are in this yellow group and are indeterminate, it's not quite clear what to do with them, my practice right now is to just wait for six months or a year, give them a chance to change their lifestyle, or perhaps lose some weight, and then repeat these steps in 6 months to 12 months.

So the patient tells you she doesn't want a liver biopsy, and would rather avoid a biopsy or a referral to a gastroenterologist. So what can you offer her? Well so I told you about the NAFLD Fibrosis Score. You could certainly try this. There's also a bunch of other noninvasive markers, based on common laboratory parameters, such as ASD/ALT. And these are all complicated logarithmic formulas, but if you have these smartphone apps, most of these are built into them. So you can easily use any of these. And I've put this here, it should be in your course packet, you can use these various cutoffs for the low value, and high value, based on low fibrosis risk and a high fibrosis risk.

So you could certainly start with that as your first approach. The second approach is to use an imaging based noninvasive assessment. And there, you could use a fibre scan, which is an ultrasound based technology. We have that in our clinic, and unfortunately is not covered by the major health plans right now, so we're certainly hoping that can change, because this is a remarkable piece of technology that gives you the answer within 30 seconds. It takes less time for me to do a fiber scan then it takes the MA to do a blood pressure for a patient.

But it's not covered by our insurance, as most of them, so that's a real problem for us. And it tells you two numbers. In blue here, it tells you semi quantitatively how much steatosis, or fat, there is. And the orange number here tells you the liver stiffness, which is an approximate indication of the degree of fibrosis. And there are some cutoffs that have been established, based on large clinical samples. And so if you do this, you have an answer in a few minutes, and the patient can be reassured if they are low on these scores, or they can be referred if they are high on the scores. So this is a very, very helpful technology.

A very similar technology is shear-wave ultrasonography, which is incorporated into regular ultrasounds that radiologists do. It's just starting to spread. These are all FDA approved technologies. And the third one, which we have in Presbyterian now, in two of our MRI scanners, is a similar technology called MR elastography. But you certainly can't use a test that calls costs $3,000 for screening, so we only use this for special purposes, only when you have a very high pretest probability that the patient has advanced fibrosis. But these are all ways to avoid a liver biopsy for a patient that doesn't want a needle, for example. This is just a close up view of the fiber scan. The machine is really small, and we kind of wheel it from one room to the other in our clinic. It works pretty well.

So the patient then comes back with a score. This is a vibration controlled transient elastography, or we call it FibroScan for short, of 10 kilopascals. And she comes back to discuss the results. So what does that mean? If you do a fiber scan and the patient has a score that's, perhaps seven to nine, that would be considered moderate scarring. Anyone that has 9 or higher is at higher risk for having advanced scarring, and someone that has a score of greater than 12 probably has cirrhosis.

So for a patient like this, I would definitely recommend a liver biopsy. So the patient gets a biopsy and has a result that shows 70% steatosis. There is some inflammation. And the pathologist says that there is F-3 fibrosis. Or, if a specialist sends you a letter saying that the patient has F-3 fibrosis, what exactly does that mean, and should you be worried for this patient?

So important take home message here is that the most important prognostic factor in NAFLD and NASH is the degree of fibrosis. So here is a patient that has some degree of fibrosis here, based on this chicken wiring. And they are now very large, long term, high quality studies, suggesting that the most important feature on a biopsy, or if you don't do a biopsy and use noninvasive assessment, is the degree of fibrosis. So all the other details-- the degree of fat, inflammation-- doesn't seem to matter. It is the degree of fibrosis that's most important for us prognostically. And the higher your fibrosis stage, which goes from 0 to 4, where four is cirrhosis, the higher your liver related mortality. The important point though here is that even though your liver related mortality depends on fibrosis, the presence of fat in the liver is never normal, and the risk of cardiovascular death, and the development of diabetes in the future, does not depend on the degree of fibrosis, although that also increases with fibrosis. So it's an important thing to keep in mind for these patients.

So here's your patient. Now she's got fibrosis. She's got diabetes. She's got a BMI of 28. You tell this patient to lose weight. She doesn't want to start any new medications at this time. So would you tell her to lose 5% of the weight? Would you ask her to exercise? Would you recommend weight loss surgery? Or would you say, well 5% is not going to cut it, you need 10% to 15% weight loss.

So the recommendation that I usually use in my clinic is to first determine where the patient is on the spectrum? Are they early stage, intermediate, or late stage, based on a combination of noninvasive markers, or biopsy, or one of the other imaging modalities, based on the situation. And for patients that are an early stage NAFLD, I think it's quite safe to have these patients just focus on lifestyle. So diet, exercise, if you want to send them to a nutritionist. For those patients who are very late stage NASH, I strongly recommend referral to a gastroenterologist, or a liver clinic, because these are the patients who develop liver cancer, hepatic decompensation, vericeal bleeding, and so you clearly want these patients to be evaluated before these complications take place.

And for those patients who are in the intermediate stage, you can go either way. You could wait, give the patients a chance to change their lifestyle, or refer at that point. But lifestyle is helpful. Intervention is helpful in every stage. And bariatric surgery is helpful in the early stages, but there is an increased risk of mortality in the later stages. And like I said before, you have to screen for liver cancer and various varices in late stage of these disease.

It's quite clear that weight loss does improve fat, inflammation, and even scarring, but the degree of weight loss that's necessary is at least 7% to 10%, which is quite hard for most of our patients to achieve. In terms of the optimal dietary advice, it's not quite clear. Some people believe that a high protein diet may help, although it's a little bit controversial. We clearly know that 5% weight loss improves just the fat, but not necessarily inflammation or scarring, for which we need a higher degree, perhaps as high as 10%.

It's quite clear, and certainly anecdotally in my clinic, you have to have these patients stop sugar sweetened beverages. To me, it's sugar sweetened beverages driving non alcoholic liver disease, like alcohol is driving alcoholic liver disease. So if patients from using refined sugars, refined carbohydrates and sugar sweetened beverages, that's a huge step forward for many of them. And many of them lose weight without much effort once they make these minor changes in their diet. There is some data emerging on a Mediterranean diet, with the use of a vegetable based diet, with healthy fat, seems to be helpful, which is independent perhaps of weight loss. There are some other studies ongoing, so they should have some answers soon. And then certainly it's OK to have these patients continue coffee, which may have some beneficial effect.

In terms of exercise, the best study that has come out so far suggests 250 minutes per week, which is a lot. And since I don't exercise 250 minutes a week, it's kind of hard to recommend that to our patients, many of whom have obesity, osteoarthritis, heart disease, et cetera. But certainly, if you can get patients to that level, then that's been found to be beneficial. It's interesting here, though, that all the patients who did achieve the 250 minutes per week, and this is a study from Japan, also lost weight. So it's not quite clear whether weight loss is necessary for that or not, although some people believe that exercise by itself may be helpful.

It's quite clear that bariatric surgery will, and can help NASH. There is an improvement in inflammation, in fat, in fibrosis, and now we have many patients who have very advanced fibrosis who have a regression of their fibrosis after weight loss surgery. This is a study from France, which demonstrates that really nicely. So certainly, if you have a patient that is interested and qualifies, this is a great option. In my clinic less than 1% of patients are either interested or have insurance coverage for bariatric surgery, so it's not an easy thing to convince patients to consider that. In case of cirrhosis and portal hypertension, I usually recommend against it, because their risk of more post-operative mortality rises to about 5%, so that is a non-trivial number for this very, very high risk population.

So the patient comes back to you after three months and she has elevated LDL. She's got high triglycerides, she's got low HDL. And you want to start the patient on a statin. So how many of you would start the patient on a statin, and how many of you would not? Is there anyone who would not start this patient on a statin because of her liver disease? So this is an important take home point, because I get about one referral per week, precisely to answer this question. And this is an important take home message, very important take home message.

The most common cause of death in NAFLD is not liver disease. It's cardiovascular disease. So if you think the patient needs a statin, please go ahead and prescribe a statin. Because you really want to decrease the cardiovascular risk profile. Except, in patients who have decompensated cirrhosis. So if they have the ascites, vericeal bleed, hepatic encephalopathy, then you can perhaps, at that point, stop it, or not start it, at least. For every other patient with NAFLD, it's perfectly fine to start a statin or continue a statin. And now there are a large number of studies with hundreds of thousands of patients showing that statins are extraordinarily safe in the setting of fatty liver disease. So that's an important take home message.

Now the patient comes back in six months and she's lost only about 3% of her body weight. What options do you have? Well, are a few things that you could consider, and a few things you should no longer consider. Ursodiol, Omega 3 fatty acids, metformin, and obeticholic acid, which is a new drug we've been using in clinical trials, not recommended, at least in 2017. You could consider Vitamin E at a dose of 800 international units daily. You could consider Pioglitazone, although an average patient will gain four kilograms on Pioglitazone, and then there are some other risks associated with it. Or you could consider referring a patient for a clinical study.

So the good news is that there are about 200 clinical trials going on around the world right now. There's many different pathways that are being targeted. The ones in red here are the ones that we have ongoing studies in our clinic, so certainly, if you have patients that have NASH, or you think may have advanced fibrosis, please consider referring these patients. Even patients who have compensated cirrhosis, because they are some phase 3 studies now, targeting these pathways. And what's really exciting is that they may actually target the fibrosis pathway, which is the most important prognostic factor that we discussed before.

Now the patient comes back a year later and her sister wants to establish care with you. Her sister has a BMI of 34, diabetes, and had a CT scan which shows four kidney stones. But that showed fatty liver and splenomegaly. Her liver enzymes were normal, but she had a platelet kind of 145,000-- which, 150,000 it's typically normal-- so it's just slightly below that. What would you recommend for this patient? Now this is a referral I get perhaps about half a dozen times a month. And the point I want to make here is that the clinical signs of early stage NAFLD cirrhosis are extraordinarily subtle.

In this case the only two things you have to watch out for are the splenomegaly, and borderline low platelet count. To me, this patient has NASH related cirrhosis. So this is a very, very subtle finding. But you've got to watch out for that platelet count, and the presence of portal hypertension or splenomegaly in these cases.

So just look for these two clinical pearls. This is just a small thing that can sometimes make a very big difference in your management plan. Just to make the point that patients who have NASH may have portal hypertension. Many other complications without cirrhosis. So that's something to think about. And then there is an increased risk of liver cancer in these patients, sometimes without having cirrhosis. But typically these patients will have advanced fibrosis, short of cirrhosis.

And the other important message, besides the statins, that I want to make, is that if you have a patient that has diabetes that you're treating with metformin and has cirrhosis, there's now quite a lot of observational data suggesting that there's decreased risk of mortality for those patients who are on metformin. So unless there is a strong reason to, do not stop the metformin, except in patients who have decompensated cirrhosis, because there are some very important effects, such as antineoplastic effects, as well as decreased risk of hepatic decompensation, or development of complications for these patients. So remember statins and metformin, both good for patients with NAFLD.

If you have a patient that has decompensated cirrhosis, certainly think about referral, they do great after transplant. And these are just the take home points. To make the point to make sure you rule out alcohol. That's really important, because you can't tell them apart otherwise, by any other diagnostic test. Think about noninvasive assessment, and I've given you a few ways to do that. Think about a liver biopsy.

But before you start treatment, it's always a good idea, before you subject this patient to lifelong therapy. Lifestyle modification does work, so please think about that at every stage. Think about clinical trials, or certainly vitamin E, I think is a great option for some patients. And think about referral for those patients who have cirrhosis. Thank you very much.