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TRANSCRIPT - GR 10 07 22 ***"The NAFLD Epidemic: Diagnosis, Monitoring, and Treatment"*** – Zack Henry, MD from the University of Virginia

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UVA IMR

00:13:42Okay, welcome everyone

- 00:13:45uh welcome to medicine grand rounds. I'm. Excited to provide a slightly more formal introduction
- 00:13:50to a well known and well beloved physician, Dr. Zack Henry, from the Department of Gastroenterology and Hepatology. Dr. Henry is originally from Alabama, where he completed his medical school training at the University of South Alabama. He then moved to Charlottesville, and Hasn't looked back. Since, it seems, uh completing Residency fellowship,
- 00:14:09she included being a chief fellow, and then transplantology fellowship as well in hepatology. I think I combine those two words there.
- 00:14:16Uh here, all here at Uva, before joining faculty in two thousand and fifteen uh, And with all that free time, as you can imagine, he went on, to get a masters of science and clinical research Also here at Uva
- 00:14:29his research interests focus on the focuses on the prognosis and management of gastric connect topic Pharisees, as well as improving outcomes in patients with non alcoholic fatty liver disease and cirrhosis
- 00:14:41during his tenure here. With us, Dr. Henry has never failed to excel at the uh tripartite or three pronged aim of all great physicians
- 00:14:50being compassionate and highly sought after clinician, uh wildly productive researcher and award winning medical educator both at the Gme level and beyond, and his mentorship of faculty members new faculty members.
- 00:15:03Uh, I asked Dr. Henry to talk today about non alcoholic fatty liver disease, and i'm confident you'll leave here, not only with a better understanding of this, a heterogeneous group of diseases, but also armed with the knowledge to provide um
- 00:15:17better care for patients. Now, in the in your outpatient setting for those suffering from this condition. So please give a warm welcome to Dr. Zach. Henry.
- 00:15:31I can leave it to you here. Excellent! Can everybody hear me? Okay,
- 00:15:36all right. I'm gonna take my mask off because i'm beyond six feet of everybody. I won't. Come over there. Okay, Um. So thank you. That's probably the most prolific intro I've ever gotten um definitely. Send me a copy of that for all future talks so I can just give it to other people. Um we're gonna talk today about
- 00:15:56Naffold. Um Outside, It says the room is reserved from twelve to one forty-five so I'll try to get done by one hundred and forty-three um don't worry.
- 00:16:06It's only like eighty slides.

- 00:16:09Um! So this is what we're going to go over today. Um! But beyond all of these little specific points.
- 00:16:16My goal is to convince everybody to treat naffled like tomorrow, today, this afternoon a youa clinic, because it's a huge part of every patient you're seeing um, but a lot of times we don't necessarily realize it, and I want to make sure you understand the impact of the disease and what we can do about it, which is
- 00:16:35um something it used to be like, we kind of shrug and like, Yeah, you got this.
- 00:16:40We don't really know how to make it better. We do have some ideas now
- 00:16:44as a quick disclaimer. Um! And this is going to be important also for everybody in the room. Right now there is an ongoing Delphi Consensus Conference to change the name of Knaffold
- 00:16:56um from all different perspectives. Hepatology, primary care, patient advocates. Um. There are a lot of problematic issues with this name. Um, that I'm not even going to get into um.
- 00:17:08Okay, Um, Having been on uh
- 00:17:11some of these meetings in that consensus conference. But
- 00:17:15within the next twelve months there will be hopefully massive press releases and a lot of education on this name change. So you might see this change. Um, at the last meeting. I think this is actually just going to come generically, and you have hepatitis or Seattle Hepatitis secondary to. There's a laundry list of things that cost that alcohol drugs, metabolic disarray, et cetera. Okay. So just keep that in mind. But for the purposes of today's talk. Yes, I am exclusively using knaffold nash, et cetera.
- 00:17:43Is your Mike turn on? It is, huh? Okay, I can hear me right? Yeah, You guys can hear him. Right? Okay, I'll troubleshoot outside. He can keep talking. So. Um, this is the big the big problem right? So global prevalence of about twenty-five,
- 00:18:01one in four people in the world that's like eight billion of us. Now. So two billion people have fatty liver disease, and in the Us. We're kind of right at that. It's about twenty-four, and this statistic gets updated about every five to ten years and I can tell you going back about fifteen years.
- 00:18:19It's been one and four. So while it's not getting significantly worse in the Us, we're definitely not making it any better. Definitely. Other parts of the world um have higher rates than we do. They're different
- 00:18:31physiologic presentations of this. They're definite different physical presentations. Not everybody with Nash and Apple looks the same on the outside and in different parts of the world. That's more evident. So it's highly prevalent, and, like I said, you see it probably more than you think,
- 00:18:48and the United States estimated around two thousand and fifteen, that about eighty million people have naffled. Of those another six or not another. But within that sixteen million have Nash, which is kind of the more severe form that we actually worry about progression of disease, which I will talk about in a little bit,
- 00:19:07and of those we suspect about three million will develop cirrhosis, and on the right is kind of more recent data showing kind of incident.
- 00:19:16Um, cases of decompensated cirrhosis liver related deaths and hepato cellular carcinoma, specifically related to naffled between now and two thousand and thirty, and unfortunately you can see these lines are going up over time
- 00:19:30more explicitly. So two thousand and fifteen data is on the left. That's what I just showed you, but on the right, decimated by two thousand and thirty. We're up to one hundred million patients with fatty liver disease.
- 00:19:40And this actually breaks down Nash by fibrosis stages. Okay, So none stage one, two, three, F. Four is cirrhosis, right? So by two thousand and thirty, three to three and a half million people with Nash cirrhosis. That's a phenomenal amount in a massive increase, and to give you a little bit of a

- 00:19:59comparison, hepatitis, c. Okay. So ten years ago, when direct acting antivirals were coming up for Hep. See, we figured they were about somewhere between three and seven million people in the country, with Hepatitis, c.
- 00:20:12And we were willing to spend one hundred thousand dollars for twelve weeks of hepatitis, c. Therapy, because we would cure the disease, and it would prevent a protocellular carcinoma needs for liver transplants so long term you look at the financial implications of that. It made sense.
- 00:20:28What should have been included in those analyses, though, was at the same time hepatitis, c. Was going down. This was getting worse,
- 00:20:36and one of the big impacts in that factor right is preventing needs for liver transplant preventing about a cellular carcinoma. But as the Nash epidemic gets worse, we've just replaced all those hepatitis, c. Patients with a different problem. But we've still spent trillions of dollars on curing those people, and I'm not saying it's it wasn't worth it. Uh Dr. Dillingham, if you're watching, I'm very much
- 00:20:57on board with our Hepatitis c. Treatment protocols. But I just want to give you that a little bit for comparison.
- 00:21:03I also want to put this up there. This is a specific graph, obviously
- 00:21:08kind of separating males and females.
- 00:21:10I mean, you can put them together. What are more, I think, is more important. Here is age. So, yeah, males, females put them together in their fifties. Right? That's where, like the prevalence rates, fifties, and sixties are pretty much their highest, and then they start to plateau. After that
- 00:21:26a lot of that plateau is because in these patients in their sixties and seventies die
- 00:21:31not always from liver disease. There's a lot of competing risk competing illnesses in these patients with not about disarray. Right? That will kill them instead, but it's a pretty steady increase. But I'm also going to show you the left side, because, as internists,
- 00:21:45a lot of us, whether it's primary care or sub specialties and deal with that transition between pediatrics and adulthood, that's also getting worse, just like the obesity epidemic and type. Two diabetes is getting worse in our pediatric populations. So is Nash. I mean look almost fifteen for both males and females for children.
- 00:22:05That's its prevalence, and that's going off. And I can tell you we have, pointing to some of the other hepatitis. We all have cases of seeing twenty-two year olds who present to us with Nash Cirrhosis at twenty-two.
- 00:22:18So this is very much on the rise
- 00:22:23so hopefully I've convinced you it's everywhere, and scared all of you that we're all missing it, and it's in every patient We've seen. It's not one and four only one and four.
- 00:22:33Why should you care like? Why is it not just my problem?
- 00:22:37This is why so?
- 00:22:39I remember looking at this in a publication the very first time, and rolling my eyes and saying, Duh!
- 00:22:46What all of these things associated with, including knaffold
- 00:22:50obesity, metabolic syndrome, right like It's just all kind of a spectrum.
- 00:22:56So like,
- 00:22:57Yeah, okay, this makes total sense to me like, Why did anybody feel the need to publish it?
- 00:23:02It's actually because of the independent impact that fatty liver disease has on each one of these issues,
- 00:23:16however, in specific studies, looking at patients with fatty liver disease, it is an in dependent predictor while controlling for all of those other metabolic components
- 00:23:27for Ckd:

- 00:23:29Same with cardiovascular disease. Same with cerebral vascular disease. Same with malignant sees osa
- 00:23:36Why, I don't know
- 00:23:38that's still. There's a lot of work to be done.
- 00:23:41We have an excellent scientist here in the room doing some of that work hopefully. We can get some of these answers, it might be related to the inflammatory cascade that is unique to fatty, liver disease, Um, and some of these exogenous substances getting out into the bloodstream and affecting these other organs.
- 00:23:58It may be that fatty liver disease is simply another component of metabolic syndrome, Right? We know that more the more components of metabolic Syndrome we add up right the worse outcomes we have for, like cardiovascular Diseases, That's what we have an ascvd risk for right.
- 00:24:14Maybe Naffold is one that's just not in that table yet. That exact relationship we don't know, but it affects all of these. And very specifically, there are two big ones
- 00:24:25diabetes.
- 00:24:28So this is the global prevalence of Naffold. So the same kind of map. But in patients with type, two diabetes and look in the United States. So fifty-two percent of patients with type, two diabetes in the us are estimated to have a fatty liver
- 00:24:41and for reference in my small little corner down here that nobody can see. This is the first slide, right? Generally the prevalence is twenty four, just amongst everybody, significantly higher risk of this in patients with type, two diabetes, but it actually goes throughout the entire world. All of these rates are increased significantly,
- 00:25:00and so we know it's prevalent in patients with diabetes.
- 00:25:03But diabetes doesn't always come first. Diabetes does not cause fatty, liver disease, and I use that explicit sentence. Because I have patients come to me all the time saying, Oh, yeah, I got a fatty liver, but my doctor just said it was caused by my diabetes or my pre diabetes
- 00:25:20not true. This is actually a study of looking at patients who have naffled and what their incidence is to develop type two diabetes over time, and as you can expect, they segregated the groups into overweight. So anybody with the Bmi greater than twenty-five, and that that one all the way into like obesity as well
- 00:25:37versus non overweight, and then those with and without kn fold. And if you look at kind of the red and blue lines and the black and green lines. Those are kind of the I think the big demarcators right? So the black line overweight patients with Nap fold significantly increased risk
- 00:25:54of cumulative incidents of developing type, two diabetes over time and same with the non overweight. So normal Bmi patients with and without naffled, significantly increased risks of developing type, two diabetes.
- 00:26:07So these arrows go both ways. Right.
- 00:26:10Diabetes and naffled are highly associated. Neither one calls is the other one. Okay, but they are very much
- 00:26:17come together.
- 00:26:19Cbd Risk is the other big one,
- 00:26:21and I'm going to jump ahead and just go to the bottom right here.
- 00:26:26The number one calls of death in my fat deliver patients is cardiovascular disease, and if you look at the percentages on the right it's, not even close Right?
- 00:26:35Non-gi malignancy is number two.
- 00:26:38Okay, Then you get to have a cellular carcinoma. But again, look at the percentages, much less essentially. My patients die of cardiovascular disease
- 00:26:46and cancers that are not liver cancer. And then everything else is way down the list. Okay. And so I've actually gotten to the point. Now where, when I talk to my patients, you know. I say, hey, I'm a

hepatologist, admittedly. I get tunnel vision for the liver. Right? You're here because I want to prevent cirrhosis. I don't want you to die from cirrhosis, but I also tell them your number one risk of death.

- 00:27:10It's cardiovascular disease, and that's important because we have to control cardio metabolic risk factors. So i'm just going to say it because it's not anywhere in my talk. Now that I think about it, statins are safe in these patients. If they need a statin, they use stat and use it. Okay, treat their cardio metabolic risk factors
- 00:27:29on the bottom left. This was This was published ten years ago, eight ten years ago now,
- 00:27:36and this is a follow up like thirteen years. This is from one of these national databases and Scandinavia, which is why it's so great. But they actually looked at patients not just you had fat deliver on imaging, but who had a biopsy,
- 00:27:47and they segregated them into non nash fatty liver, and then patients that had fatty liver. But Nash right? So the more severe version of that,
- 00:27:56and what you see on the right of this bottom left box here. So even for non nash fatty liver. So it just kind of benigns theatosis, maybe some mild inflammation of the liver
- 00:28:05literally to death over thirteen years with zero. But Cb. Related to death is nine right?
- 00:28:11If you look at Nash. Significant increase in Cv really to desk and Nash, And compared to the general population, it's two times increased risk.
- 00:28:21Okay. And this is in a Scandinavian country that eats a lot of fish, and I'm sure has a lot of fish oil and a much healthier diet than most of us do in America.
- 00:28:29So this is very concerning to me, and this is why it's important for all of us.
- 00:28:35It's important to understand these differences, because I've already thrown these terms around a little bit right. So naffled, or whatever this name is going to become in the future is the overarching term for fatty liver disease that is generally associated with metabolic dysfunction, so metabolic syndrome, et cetera. Okay,
- 00:28:54all of these, all three of these pictures are naffled, but the one on the far left. It just shows some soap bubbles. Those are the fat droplets. And then you see all the little purple dots in between the fat droplets. Those are lump of sites, mild inflammation. That's non nash fatty liver,
- 00:29:11the one on the left here, or the one in the middle. Rather. This little arrow is pointing to what we call a balloon cell. It's a hepato site that has grown, and it's full of intracellular, Lipid. Okay? And actually, the cytoskeleton has collapsed.
- 00:29:27Did any of you remember, from medical school the Mallory dank body is associated with alcoholic Seattle hepatitis. Right? Okay. Same actual thing. In fact,
- 00:29:35we can't really tell the difference a lot of times between alcohol related, and non alcohol related to data hepatitis on a liver by apps you, because they both kind of look like this. We see a bunch of balloon cells fat drop with an inflammation, and then on the right is someone who's progressed to cirrhosis,
- 00:29:50and I know that because here this little band down here. That kind of makes a nice little nodule is fibrosis,
- 00:29:58and this is a regenerating module That's the nonchalary modular change of cirrhosis. We get these little circles of fibrosis,
- 00:30:07and these are important terms, especially because we're going to talk about how they impact progression and how I can use them, and how you can use them with your patients to understand severity of disease.
- 00:30:20So Knaffold versus Nash Doesn't matter? The short answer is, yes. So I just put that at the top. So on the left, or just some looking at kind of progression of disease of patients with uh Nash. But then also patients down at the bottom. I actually want to point this out here. It's just the atosis with mild inflammation This is the non-natch fatty liver patient that over time, forty-four percent progress to Nash

- 00:30:45and thirty-seven actually progress to fibrosis. Okay, One of the biggest predictors of this was actually the presence of type. Two diabetes. Alright, So understanding if our diabetes ha patients have fatty liver, and honestly, vice versa is very important. Okay,
- 00:31:01the way we think of this, and I borrowed this from from Dr. Argo at the very bottom. Because I do like this. The way I think of a non nash fatty liver patient is that they're on deck to have Nash. This is not a dichotomous disease. It's not one or the other people can actually move back and forth. People can resolve nash, which I will show you later.
- 00:31:20But just people with non-nash fatty liver can progress to Nash and then progress through stages of fibrosis. So again, the arrows are going both ways. And just because somebody has fatty liver disease doesn't mean they're fine that's still somebody we have to monitor just how we monitor them may be different.
- 00:31:38Fibrosis is a big deal. Okay. So if you have Nash on the top left graph, the little dotted line is Nash and the other one. It's the controls, and over many years eighteen is about where these lines segregate on the top left there. Patients, with Nash
- 00:31:54do have worse long-term survival. That's what this is showing you. But if you break it down on the top right
- 00:32:01patients with nash that have either stage three or four fibrosis. And that's that really terrible line that just ends at twenty-eight years, and no one's left that's that group
- 00:32:10so fibrosis matters too. It is a significant predictor of progression of disease and long-term mortality for these folks
- 00:32:18kind of another slide, showing the same thing. But by each fibrosis stage, and the important thing here is, if you look at the very top of the graph, whether you're stage zero. So no fibrosis or one or two so kind of
- 00:32:31yeah minimal to moderate fibrosis. Your long-term survival is about the same. But once you cross into stage three and then stage four fibrosis, your survival is significantly changed. And I'm pointing this out because these are the patients we really need to capture right. If eighty million people in this country have fatty liver disease, what I really need to get at right now are these folks who stage three who stage four right, who's already got cirrhosis and is on deck for hcc decompensated cirrhosis,
- 00:33:00who's not yet cirrhosis that I could maybe prevent from getting cirrhosis This is what we want to know
- 00:33:06so naturally, then, how to identify these high-risk patients
- 00:33:12all right. The reference on the bottom left is probably the most important reference that I have put in the talk today. It is from uh, obviously a year ago, two thousand and twenty-one, but literally like one year ago, October of twenty twenty one.
- 00:33:24This was a kind of multidisciplinary consensus um paper from hepatologist, endocrinologists, primary care doctors, I can't where there might have been some other people in there. Um! Essentially saying what is the most
- 00:33:39efficient way to screen not just for naffled, but to screen for nappled patients that are at higher risk for fibrosis. Because if you Haven't noticed that's really what I kind of care about right. I kind of care about fibrosis. It's my best predictor for who's going to? Who's going to have worse survival? Who's going to progress to cirrhosis.
- 00:33:59That's the patient I need to know. And so they broke it down into this nice little graphic on the right here
- 00:34:06and basically said, Well, we think there's three high risk groups. Group number one, all type, two diabetes patients period. No caveat. Just type, two diabetes
- 00:34:15group number two. I can actually swallow type two diabetes, by the way, just based on the data. I've already showed you

- 00:34:21Group two, though any patient with two or more metabolic issues we're going to get into this. That's a big group, right?
- 00:34:30I mean. So obesity is one.
- 00:34:32Forty percent of the United States qualifies as obese. So now add a second one
- 00:34:38hypertension boom diabetes. They'll need one more right. Hydroglycerides low. Hdl:
- 00:34:44They only need one. That's a huge group of patients potentially,
- 00:34:49and then the one on the far right group. Three. That's the easiest one, I think, for any of us. If you incidentally find steatosis on imaging they got fatty liver right.
- 00:34:58If you have elevated liver enzymes. Part of our work up for elevated liver enzymes always right, includes the possibility for fatty liver. So we're going to talk about the group on the right, but it's the first two that I think are the most interesting. This is why diabetes is interesting. There's like thirty-four or thirty-five million people in this country that have diabetes, and of those thirty to thirty-two million um
- 00:35:18are probably type. Two.
- 00:35:20That's a lot just right there, right if we're screening thirty million people for fatty liver disease tomorrow.
- 00:35:26Um! And one of the ways they came to. This was: they did a study where they took type two diabetes patients from our primary care, and they did these Mr. Studies to look for fat, and then to look for um signs of advanced fibrosis. So f three or f four disease Of all of the diabetes patients in this study sixty, five
- 00:35:46had fatty liver by definitional criteria, so they had a fat fraction greater than five percent of their liver.
- 00:35:51Interestingly, of those only twenty-six had a lovely deliver in time. So we were just using blood work in our diabetes patients who probably wouldn't have suspected that they had anything going on in their liver. But they did.
- 00:36:03Seven already had advanced fibrosis. So this is F three or F four, not just any fibrosis advanced fibrosis, and many of them had normal liver enzymes in that group.
- 00:36:14So I saw that, and I was a little scared, right? Because i'm scared. Now, okay, I'm missing people. So in my type two diabetes populations. Maybe this is worth it.
- 00:36:25And this is kind of a different graphic. So just breaking down those kind of thirty, some odd million people, and the one in the blue is kind of the majority you're going to have naffled just plain, old naffled Non nash fatty liver. It's a much smaller portion down here that are going to have like advanced fibrosis, and this is the number that could potentially be missed without any kind of screening.
- 00:36:47And so this is what they were basing kind of their recommendations on.
- 00:36:51But is it worth it? So another study? So I’m going to go back, and two thousand and fifteen? There was a study looking at this exact question
- 00:36:59and diabetes patients is the prevalence of fatty liver high enough for me to screen everybody. Is that A cost-effective strategy, And again I think back to the old hepatitis, c. Studies from two thousand and twelve and two hundred and thirteen, where we're Looking at this, knowing that these new drugs were going to be super expensive
- 00:37:15and again in two thousand and fifteen. They just kind of looked at general costs, cross-sectionally, and said, This isn't cost to, for like we can't afford to do this right? It's too much
- 00:37:24in this study. The authors explicitly said, Well wait a minute.
- 00:37:29Are We really taking into account fully the long-term effect, right Development of Hcc. Development of decompensated cirrhosis and the impact and cost that that puts on hospital systems. And then the impacting cost of liver transplant

- 00:37:41and the old study hadn't done that and the Us. Pstf. Said. We don't think this is worth it, and actually made a statement that said, You shouldn't screen, all type, two diabetes patients for fatty liver, which is why this study was done, and this is modeling. So this is like Markov models and all that kind of stuff,
- 00:37:57but they actually found two strategies screening strategy, three and strategy six, which were cost effective. Okay,
- 00:38:06this is based on the premise that has been around for a very long time, that anything that's less than fifty thousand dollars per quality just of life here is a cost-effective
- 00:38:14uh
- 00:38:16intervention.
- 00:38:17The only difference between screening strategy. Three and six is one. Use the alt, and one used to Asd, otherwise they're the same. It says, if you have type, two diabetes, and I do an ultrasound, and I look for fatty liver, just simple theatosis on an ultrasound. If I see it,
- 00:38:30I follow that up with transcending mystography. So most of you probably know that is our fibro scan that we do on a lot of these folks,
- 00:38:37and then based on the fibro scan. If the fibro scan says that you have at least stage two fibrosis or higher,
- 00:38:44this is also dependent cost, effectiveness on implementing high intensity, lifestyle, intervention.
- 00:38:52And that's an interesting tweak, right? Because that's not just screening that's not cost-effectiveness of screening. It's cost effect in this of a screening program and it leads to a treatment that I'm. Not trying to be cynical. Most patients Don't have access to right
- 00:39:03high intensity. Lifestyle intervention is a very explicit intervention That's paid for by Cms and patients with diabetes, in which they basically see a provider every Other Week for twenty, six weeks, fourteen total visits, just talking about diet and exercise and working on weight loss, and it is highly effective.
- 00:39:20But again, think about our resources medically. It's not always accessible, so
- 00:39:26it seems like it's probably cost effective to screen these patients. If we can treat them, I will say the author is substituted using Piageta zone,
- 00:39:35which is actually one of the best drugs to date that we've seen for reversing Nash
- 00:39:39in the place of high intensity, Lifestyle intervention, just to say, Hey, people don't have access to this, but most of them have access to Pi. I go to zone, and it was just as cost effective.
- 00:39:49So the metabolic risk factors. As I said, this one's a little tricky. So on the far right of the slide, right? These are the risk factors they included,
- 00:39:58and these are risk factors. If you look right. This is like the eighty-three criteria for metabolic syndrome. Right? You get three or more of these you have metabolic syndrome.
- 00:40:05I will point out, because I. I kind of unfortunately just use the word obesity previously,
- 00:40:12both for metabolic syndrome. And in this study it is explicitly central obesity, right? It's actually was circumference, not Bmi, that we should be worried about in folks right? It's where the fat is. Visceral. Fat is worse than subcontaneous fat. That actually does matter, which is why that's part of this criteria,
- 00:40:30And I show you this really complicated table on the left, just to show you the bottom, where what they found is the more of these complications, you add, than the risk of developing either Cirrhosis or Hcc. But honestly, either one individually goes up significantly, especially for hepato cellular carcinoma.
- 00:40:50And so they came up with this graphic,
- 00:40:53which they found that if you have two or more

- 00:40:57comorbid metabolic risk factors, you have a significantly higher chance of developing cirrhosis or Hcc. And if you look at Hcc. Specifically it really breaks out at three or more.
- 00:41:08That's where that risk goes up, and their suggestion is actually, if somebody has this, you don't do an ultrasound. You just jump to the next step and evaluate for fibrosis. This is where I depart a little bit,
- 00:41:20I actually think there's not a cost. Effectiveness analysis for this kind of a model. I do think this is a lot of patience, and I think if we want to be cost effective right now, what I would do is add one little step to this, and actually say, Well, this is a patient. If they've never had it, they just need an ultrasound to look for steatosis.
- 00:41:37Then you can go down the rest of the pathway just like the type two diabetes patients I wouldn't necessarily just say, Oh, I see this patient because I don't know I'm being maybe cynical again. And please correct me. If I'm wrong. At least fifty of youma patients probably fall into this.
- 00:41:53It's a lot of patients to start putting down that fibrosis pathway that can potentially lead to a liver by. I've seen all kinds of other things, so
- 00:41:59I think. But ultrasound don't just go straight to fibrosis,
- 00:42:04and then this one's pretty easy, I think. If you find sea Atosis somebody has fatty liver.
- 00:42:09We still got to figure out why they could be drinking a six pack a day, and that could be why they have a fatty liver. They could be taking Tamox a finger at the trek sate, or depth of coat. That could be. Why, they have a fatty liver, but
- 00:42:20fatty liver on imaging when found, it's pretty specific.
- 00:42:24When you add elevated liver enzymes, that actually makes things worse, which seems obvious. But just to show you this is a study where they took looking at a Lt. And steatosis,
- 00:42:36and you'll look at proportion with cirrhosis. So if you have steatosis and an elevated iot, your risk of cirrhosis is significantly higher versus a normal alt with or without see atosis, but with liver cancer. It's a more significant gap,
- 00:42:52right? So presence of any steatosis and the liver significantly increases your risk of liver cancer, even with normal liver.
- 00:42:59So I think I'm gonna get right through this, because I think this group's a little more easy for all of us. If you see a patient at you, and A with all the delivery enzymes. Just do your normal workup, which generally will include evaluating them for fatty liver disease.
- 00:43:13So you got your high risk groups. What do you do next? Rule out other stuff,
- 00:43:18right? This is what's an up to date Dynamite, whatever your preferred source of information is gonna be um rule it out. Alcohol is number one, right,
- 00:43:29hepatitis, c. Everybody over the age of eighteen, according to cms. And the Us. Pstf should have a one-time lifetime screening for hepatitis, C. Patients with high risk behavior should have regular screenings.
- 00:43:40Hepatitis. B.
- 00:43:43You could try to be uh a little pointed here and ask people really explicitly about risk factors. That being said, if you have any question, I would actually screen them for hepatitis. B. Most of these viral hepatitis. Infections are asymptomatic people. Don't know they have them. That's why they show up with cirrhosis forty years into their in section. And so it maybe we're screening for that
- 00:44:03now at the very bottom. Right? Those are tests for autoimmune hepatitis, hem, chromatosis, and alpha one, and I tripsin. I'm going to be honest I don't send Alpha one levels on hardly anybody, unless they have a really good family history, or I just have no idea what's going on. I would do that last. Not in necessarily. In this,
- 00:44:21I will say a ferretin level and a patient with fatty liver is dangerous because most of them have elevated ferritin levels. It has nothing to do with humor from itosis. So if you are going to send

Ferritans, send your iron. If you're transferring and calculate your percent sat as well. Don't, just send a ferrett, and for autoimmune hepatitis

- 00:44:39autoimmune diseases are overwhelmingly sexist, so I will say, in women with elevated liver and signs. It is worth screening them, because autoimmune hepatitis can present just about any way. Men
- 00:44:50maybe maybe not. Kind of depends on their history.
- 00:44:54Um. From there. If you find one of these concomitant diseases, just go ahead and send them to us, because even if they do have underlying fatty liver, which they probably do, because that's the bane of my existence. Now, even when I see a hep, see he be your autoimmune, patient, and diagnose those things
- 00:45:09low, and behold half of them also have a fatty liver that even if I treat that disease, I'm also now managing a second one. But go ahead and send them to us if you ruled everything else out. Now we want to go to step three. We want to look for fibrosis.
- 00:45:24So non-invasive tests
- 00:45:27in that diagram they use something called the fib four, which i'll talk about in a second. My personal preference uh is this: an appled fibrosis score? Um! They're actually both. If you look at kind of the testing of these models and their C statistics, their diagnostic accuracies are both somewhere in the eighties.
- 00:45:45Um. The naffled fibrosis score was created like fifteen years ago, specific to fatty liver disease. One of the reasons I like it. This is it on the right, just from Md. Cal. This is kind of the breakdown that you get from the scoring system. It's basically three tiered for all of these, either. They have a very low risk of having any advanced fibrosis. They're in a gray area,
- 00:46:07or they have a high risk of having advanced fibrosis, which is this bottom column. Super easy to use
- 00:46:13if you Google knappled fibrosis score. There is a very, very old website
- 00:46:19that was originally made for the original score fifteen years ago. But if you plug in the numbers there they are wrong. You're going to get an incorrect answer. Just so, you know. So don't it's actually I think, called an apple fibrosis, scorecom, or something don't use that one.
- 00:46:36The fib four slightly different also has, as T and Lt. Has age and platelets does not have anything about Bmi insulin or album in like the last one does. It was originally created for Hep, c. And then have B. So it's got stronger validation for viral hepatitis, but it has been used in fatty liver disease,
- 00:46:56one caveat to this, and again a reason i'm doing these. These are all things you can do in your office right? Because most of our patients already have all of these labs. They've already had probably a comprehensive. They've had a Cbc. These are things that we can calculate freely. That's why they're so nice, and they don't cost the patient any money. It just costs us about thirty seconds to actually go in and do it
- 00:47:17with fib four. There are explicit cut off changes based on age. So it's important to remember right. There are slightly different cut offs depending on that. Otherwise also very simple to use, has similar diagnostic act accuracy to the naffled fibrosis score.
- 00:47:35Once you do that,
- 00:47:37generally we do that first. I've done this a lot. Now it's kind of part of my normal routine when I see these patients in clinic, if that's very low, I'm probably going to send them back to their primary care Provider. Give them some general recommendations on lifestyle management metabolic syndrome in general and leave it there. Okay,
- 00:47:55it's when they're intermediate or high. That I say, Well, your diagnostic accuracy is somewhere, probably in the eighties kind of the low eighties.

- 00:48:04Can I do another? Test. It's going to increase that. And that's elastography. Okay, Us: photography has a better diagnostic accuracy than these composite blood tests Do This is transcending osteography that we use as the fiber scan machine,
- 00:48:18and where it's really good is ruling out advanced fibrosis so this meta-analysis that's up here. Actually, I'll draw your attention to the second point. This is where it's really good, and we get this cut off value of eight. If someone has a fiber scan and trans me in my started to value less than eight. They have
- 00:48:35a really low risk of having advanced fibrosis. I could probably repeat that in two or three years, and then, unless it starts going up, they're okay, and we can just kind of manage what we can manage right when it's greater than eight.
- 00:48:48That's when you should consider sending them to us
- 00:48:51because we may talk to them about doing liver biopsy. Other things will come into play. Family history of cirrhosis, family history of Hcc. Sometimes, even if it's greater than eight, I still just monitor it every two or three years
- 00:49:03when it's greater than twelve. That's highly significant for almost cirrhosis definitely F three. That's a patient that definitely needs to come and see us. But this is what this is trained in us. If you are fiber, scan.
- 00:49:17So then we get down here, and this is what I was just saying these three groups, so the low risk is relatively easy. If I have an apple fibrosis score that's low I'm going to send them back. But if I send them back to like Youma to you guys, I'm going to send them back with the express recommendation to repeat that every two or three years.
- 00:49:34So every couple of years they come in, and you happen to be checking in their lipids and sending a comprehensive Send a Cbc. As well get a plate with count, because with that you can calculate either apple fibrosis or fib four and get another answer. And if it stays in the low range, just keep doing that and hopefully at some point, right,
- 00:49:54we will make an impact in this patient's life, they will lose weight. Their metabolic complications will get better, and maybe you don't even have to worry about it anymore, because they'll resolve their disease
- 00:50:03if they're in this yellow area kind of the gray area in the middle of the fiber scan, you can send them to us,
- 00:50:08and I would probably say, do that right now, because the way resources are, if you just try to order a fiber of scan, I have no idea. If for when that will happen so you can send those people to us. That's fine. We may send them back
- 00:50:19once we've evaluated them with again a recommendation to just re testing every two to three years, and instead of doing non-invasive testing and maybe do the fiber skin instead. The easy patients, the patient on the right.
- 00:50:31So the patient has high liver stiffness. They're coming to us. We're going to talk to them about biopsy. We're going to talk to them about, monitoring them more closely for progression to cirrhosis and fibrosis. We may talk about clinical trials,
- 00:50:43because even with lifestyle interventions, we that's the patient that i'm a little more urgent about treating and trying to reverse their disease,
- 00:50:53and that comes to management. So I'm not going to go through this
- 00:50:56in detail. Um, I can definitely share this general article with the chiefs, so that everybody has access to it, because I do think it's a pretty good algorithm
- 00:51:06what I'll show you the top two lifestyle intervention and weight loss recommended for everybody. Um, I think that goes without saying. We recommend it for all of our patients. With all these various complications of metabolic syndrome, Cbd. Risk reduction recommended for everybody. So again, if they need their Stat and put them on their statins, follow the same thing right?

- 00:51:24They're going to have a baseline of sixty or seventy, with fatty liver, maybe.
- 00:51:28Put them on their stat unless it goes up to like two hundred or three hundred. It's probably not the drug effect, right? They'll still fluctuate. Just do what you would normally do, Starter Stat. And a few months later we check the liver. Enzymes look for a significant change. Different statins have different effects. If you put somebody on eighty of lipitor right off the bat highly likely that patient's going to have
- 00:51:47some alterations in the liver enzymes. If you start with lower doses, or use a drug like Chris Crest or uh Suvistan or pravastatin right? The ones that are um, I think, more hydrophilic. They tend to have less issue with that.
- 00:52:02And then Diabetes care. I'm going to point out, because if I didn't point this out, Jen Kirby would kill me, and I really do believe in this
- 00:52:09patients who have co-work with diabetes. Number one for me, Piageta Zone.
- 00:52:14I'm going to present the data. I think you can ignore that Um, Most patients are going to gain weight. They don't like pye glitz zone, and I think now there's some better strategies, but glp one or sept, or agonists right or ag with tight some magnetide at some point there's up a tide right?
- 00:52:29Much better weight, loss, good diabetes, drugs rarely cause if it all low blood sugars right, the weight loss is what we need, and these drugs will help the patients get it. So two for one. Actually, it's like a three or four for one. Come to think of it all right. So glp one receptor. Agonists always consider those.
- 00:52:49So you learn how to risk stratify diabetes, patients, metabolic patients incident. We'll see atosis elvis deliver and design patients. We've done all this we've risked, stratified them. So now let's move on to a very rigorously tested proven therapy for fatty liver
- 00:53:05weight, loss. Super easy, Right?
- 00:53:08Yeah, I mean, I just blew your minds right. You've never told a patient about this right? You've never tried to get anybody to lose weight. So, but I want you to start today. Okay.
- 00:53:19So this was one of the early studies. Um, just looking at the amount of weight, right? So they just very small, right? Thirty patients total. They have a lifestyle intervention. They have a control group,
- 00:53:30and what they found is actually just amongst patients undergoing lifestyle intervention compared to the control group. Significantly more of these patients. Um! Reduce the fat in their liver.
- 00:53:40Okay, other things didn't change so much. But fatty content did.
- 00:53:44And then they said, Well, okay, but not everybody in the lifestyle group lost weight.
- 00:53:49So is there a cut off? And they found yes, greater than seven percent total body weight loss
- 00:53:57was significant, right? So you can see here on the right. Not only did those patients significantly lose more liver fat, they also decrease globular inflammation and ballooning injury. So so ballooning injury, right? That's my definitional criteria for nash. That means that patients just with weight loss seven percent total body weight loss. Okay,
- 00:54:16reverse Nash:
- 00:54:18Not all the time, but they can.
- 00:54:21So that's it. That's hugely impactful, right?
- 00:54:24And if you think, let's do simple math so seven percent.
- 00:54:28So for the two hundred pound patient that's fourteen pounds
- 00:54:31can you work with the patient to get them from two hundred to one hundred and eighty-six.
- 00:54:35Okay, And I’m talking over like six months, Not like four weeks, right?
- 00:54:41Sometimes even a year. That can be hugely significant for that patient and what they're going to think. And I know this because I've told them this all the time. They think it's a very marginal amount of weight loss. They will tell me. Oh, my goals, one hundred and thirty, my goals one hundred and forty, and I’m like, Okay, cool.

- 00:54:56My goal is like ten or fifteen pounds. That's all we need right to make a huge impact and not just on fatty liver. I won't even go into the obesity medicine data on all the other improvements in metabolic diseases, right? But for us it works
- 00:55:08So this study, So that was thirty patients. So this study thankfully, much more almost three hundred patients a year
- 00:55:15of lifestyle intervention. That's actually the first six months was just in person classes. The last six months was like once a month like a group meeting, and occasionally a phone call. So not that intensive. And, in fact, if you compare it to like wait watchers, it's actually pretty similar.
- 00:55:30And you can see,
- 00:55:32when people down here at the very bottom resolution of Seattle hepatitis, if people lost greater than or equal to ten percent of their total body weight,
- 00:55:41ninety of them completely resolved, Nash,
- 00:55:46and it goes down as you go to the left, but seven to ten, sixty, four completely resolved Nash, even five to seven of one and four, resolved Nash. That's huge right like that, because this is now means people who aren't on that pathway to cirrhosis, and about a cellular carcinoma.
- 00:56:03Now, one of the downsides to this study, and I think, is what many of us experience in clinic right? Is this right here the actual percentage of patients achieving that amount of weight loss. So for ten percent or more and seven to ten it was only about ten percent of the total population, right?
- 00:56:21So what we really need to work on are access issues which we can always do directly in clinic, one on the patient to get patients to resources. They need to do this stuff.
- 00:56:30This is just an interesting slide that I really like for hepatitosis, another small study. But basically they did a study where they made people lose weight. They said, We're going to do lifestyle intervention. We're going to do diet. You're going to lose weight, and then we're just going to get out of your life. So six months of weight loss, and then eighteen months of all right. You're never going to hear from us again, and then they called them,
- 00:56:49and after eighteen months the people lost weight. After eighteen months, right they gain some back. The subcue fat went back up visceral fat went back up eighteen months later of inter hepatic lipids did not.
- 00:57:03So Maybe there's some memory to this as well. So that's the other thing I use as an this is a small study. I haven't proven this on any large scale. Okay, nobody has. But I use this as motivation for patients, right? Because everybody worries. We're going to lose weight, and we're going to yo go back and they do need to work on weight maintenance. But there's some evidence that even if they don't,
- 00:57:23they're still going to do. Okay, at least from a liver perspective.
- 00:57:26So if it's so easy, what do you do?
- 00:57:29What diets the best?
- 00:57:31Well, this study, said Fructose, was bad, but that's really misleading, because these servings of fructose were. So does so in reality. What this study proves is that high fructose, corn syrup, and a liquid form seems to be bad for the liver, and actually increases the risk of fibrosis pretty significantly down here,
- 00:57:52greater than or equal to seven servings in a week.
- 00:57:56Yeah, right? Not a day, because I have patients who yes, kill twelve pack of coke or pepsi in a day, right in a week
- 00:58:07significantly increases the risk of fibrosis and fatty liver disease, right?
- 00:58:12So that doesn't mean fructose is bad fructose, isn't fruit right? I mean apples have fructose. I like tickets, can eat apples,
- 00:58:20soda. So one thing universal, I think, in all fatty over disease patients. If there's one dietary intervention, I can. One hundred percent say to them, do not drink liquid sugar,

- 00:58:30soda, sweet tea. A lot of patients drink sports drinks because they think they're good for them, and don't realize how much sugars and a lot of those things, And when they're not really working out, do they really need it? Probably not now. Getting them off is a whole different thing. I'm not going to talk about the implementation of this, because that would be another hour long thing.
- 00:58:47So what Di? It's the best. Okay, What about low car versus low fat? This low calorie diet on the left is actually a low, fat diet compared to a low carbon diet.
- 00:58:56That's what this was looking at, and then you can see from a weight, loss, perspective. And This is change in Bmi, but you can look at the kilos, either one. It's about the same right in each group, so low carbon, low, fat diet patients are going to lose about the same amount of weight.
- 00:59:10But look at the change in hepatitis, theatosis the low-carb diet. They lost dropped herpadoxes by fifty five percent
- 00:59:19versus twenty-eight percent and a low fat diet. So maybe there is something to this high fructose corn or a carbohydrate ingestion where the liver is not processing this stuff, and we're just packaging a bunch of triglyceride from all this excess sugar we're eating, and then it just sits in our liver and we don't like it.
- 00:59:35That's the hypothesis. But look at the number of patients.
- 00:59:39This is a study of eighteen people, and I just told you fatty liver disease affects eighty million people in the Us. So let's not extrapolate eighteen people to eighty million just yet.
- 00:59:50Not, I mean, it might be true, but i'm not ready to do that.
- 00:59:54This was looking at the Mediterranean diet on the right, just a randomized control trial, but very small, only thirty pounds total, showing that intra hepatic liquid content for those on the Mediterranean diet versus a low fat diet, as well as like insulin sensitivity. All better.
- 01:00:10Okay, Mediterranean, that's good
- 01:00:13the one on the left a little harder. So they just looked at patients on a Mediterranean diet, and they said, Well, who has, like low grades and high grades of steatosis in patients that were more adherent to the Mediterranean diet, were more likely to have the absence of saddle hepatitis.
- 01:00:33And this is really crazy right? Because i'm saying more likely to have the absence of something. It's very confusing. They were also more likely to have the absence of fibrosis, and so their assumption was like, Well, then, Mediterranean diets the right diet for everybody. This was about eighty patients total,
- 01:00:48so all that to say I don't know.
- 01:00:51I think so. It is bad. I think liquid sugars bad. I do try to get patients to stop that. Beyond that. The only thing that I know for sure from this previous slides is that weight? Loss helps, but I have nothing to prove what the right way to lose weight is for these folks,
- 01:01:06so does exercise help. Sure
- 01:01:09you can see here, right? So on the left hepatic, triglyceride content goes down. Visceral autopsy goes down. The beauty of exercise is that these things get better. Why, I say beauty and weight doesn't change.
- 01:01:22I think it's awesome.
- 01:01:31I'm down like one pound. I'm not doing this anymore. And i'm like, Whoa! Whoa! But you probably just dropped your a one, c. By like one entire point just from exercising, and all of this got better like
- 01:01:44keep doing it, but it's very hard, because they can't see the results Right? They can't see what's happening internally with exercise, but it's beneficial, and it's dose responsive. So we know the dose response in bariatric surgery patients, at least any medicine patients. But even in liver patients we have found that hepatitis and even inflammation
- 01:02:02are better, the more you do so. Less than two hundred and fifty minutes, more than two hundred and fifty minutes, and you have significantly better changes in hepatitis from the beginning of

the study to the end of the study. And that's what this little that's. That's the significance between the two separate groups.

- 01:02:18So more exercise is good. We know greater than two hundred and fifty minutes of exercise a week, with no change in weight,
- 01:02:24will actually decrease the
- 01:02:28what kind of exercise.
- 01:02:30Almost every patient I see comes in expecting me to tell them to go. Do aerobic exercise, and I know this because even before I've said anything like I got my knees hurt. I can't get on a treadmill.
- 01:02:41Oh, no, my hips heard. If I sit on an exercise bike, I can't do that. I'm like great. That's awesome
- 01:02:47good. With some ways
- 01:02:49Lightweights go to do a weight machine right something. But you don't need to do aerobic exercise,
- 01:02:54and that's because both in obesity, medicine, but also in fatty liver. What we have found is whether it's aerobic or resistance training people tend to lose the same amount of hepatic fat content. They have the same improvements in inflammation, regardless. And if you look at like the American College of Sports medicine, and I think the American College of Electr Physiology.
- 01:03:14Their guidelines say the same thing. Exercise should be a mix right. We should be doing aerobic exercise. We should be doing resistance training, we should be doing yoga and stretching, which nobody does. I just had a conversation this morning with a seventy year old about that, because he was like ready to just go to the gym tomorrow after doing nothing for decades,
- 01:03:33maybe stretch a little bit, maybe like work into this a little bit of everything to keep from hurting ourselves is what's really important.
- 01:03:41Okay,
- 01:03:43diet exercise. Those are good ways to lose weight. Diet really helps people lose weight. Exercise really helps people maintain it, and exercise makes everything better internally, even if they don't awesome.
- 01:03:54Not everybody can do it. We know this, but we also know bariatric surgery is very good at helping people lose weight.
- 01:04:00These studies. These are just pulled cohorts right? So these are not randomized control trials. It's just a bunch of different people who published and said, I did this many ruin. Why, gastric bypasses, I did this many sleeve gastrectomies, and this is what happened to the patients who had Nash.
- 01:04:16This is phenomenal.
- 01:04:18So the pooled effect down here at the bottom of these little boxes, improvement or resolution of nash, eighty one percent
- 01:04:26improvement or resolution of fibrosis, which is my biggest concern. Sixty five of these folks. Okay, And with all these studies combined, this is like thousands of patients
- 01:04:38complete resolution of Nash so definitively on a biopsy no balloon cell to generation. Nash is gone
- 01:04:44almost seventy percent with bariatric surgery. This may actually be our best therapy for fatty liver disease. Is it an indication that insurance recognizes?
- 01:04:56Of course not. That would be too easy.
- 01:04:59They might in the future, but not right. Now
- 01:05:03that, being said, many of these patients have morbid obesity, which is an indication by itself, where they have class to obesity with diabetes or hypertension. They have other indications for biatric surgery. You don't necessarily need to push them into it immediately, but it should always be in the back of your head for these folks when you're working with them.

- 01:05:19And I want you to remember seventy percent chance for complete resolution of Nash periodic surgery, or keep that number in your head,
- 01:05:27Because now this is what I hear a lot from my colleagues. I'm going to call out Steve called. Well on this. That's Okay, him and I love to go back and forth. He really wants to find a drug to treat Fatty liver. I do, too.
- 01:05:37But my concern is that once we have a drug, people are not going to be that interested in weight, loss, right? And that's what's going to improve everything.
- 01:05:44So give me a drug to use. Well, vitamin e was a big player for a long time.
- 01:05:49I'm just gonna ruin your day and say, don't use vitamin. E: Okay, the pivots trial. This New England journal trial from two thousand and ten. This huge trial that said we should all be using vitamin e for nash was wrong.
- 01:06:00They based it on a research score called the Nas. The Knaffold Activity Score. See in the in the italics over here primary outcome reduction of Nass by two.
- 01:06:12Who cares? Nas does not have anything to do with disease progression? I can't use nas to predict who's going to get cirrhosis in Hcc. Right?
- 01:06:21But if they resolve Nash, that's a benefit for me. If they improve fibrosis that's a benefit for me, and if you look at their approval in fibrosis, provide a Mini versus placebo. It was zero point zero five for the record. They set their p-value at zero point zero two, five, so, Even though that seems borderline. It actually
- 01:06:40was less significant than what they set just for the record, but really regardless, It did not definitively resolve Nash,
- 01:06:49but this did. Their other group was pilgrims,
- 01:06:54and although they said it didn't work because it didn't have as much of an improvement in this mass score. If you actually look here at definitive resolution of Nash. It was close to fifty in the pi of Good Zone Group, and was definitely, statistically significant.
- 01:07:12One study, the result of this. The conclusion of these authors at the end of this study was that vitamin you should be used for Nash period. Don't use Piagletism.
- 01:07:22Mine was obviously the exact opposite.
- 01:07:26This is what Piaget Zone does right So on the left. It's great. You get treated for ninety-six weeks. Your answer and resistance looks good or yeah.
- 01:07:34And then, when you stop taking it, it goes back to baseline or gets a little bit worse, Why would it get worse
- 01:07:40Because of the graph on the right, despite all those things been, if changing internally, people gain weight, and then you stop it. Their weight doesn't magically go away when you stop it. In fact, it keeps going up. In most cases
- 01:07:52this is the problem with Piaget Zone. This is why most patients don't want to take it, because i'm telling them they need to do things to lose weight and then giving them a drug that's just going to act against it. Okay, I've maybe used this drug two or three times in the last eight years.
- 01:08:06However, beyond the doing with journal trial, it's one of the only studies that has a confirmatory study. This was done by an endocrinologist in Florida, who did the exact same thing basically as pivots, but without vitamin E, and fascinatingly found the same result. Look, resolution of Nash. I gl to zone right at fifty, and again statistically significant.
- 01:08:26So it does seem to be a good drug. That's why it was used also in that cost, effectiveness, analysis that I showed you before with diabetes and Nash.
- 01:08:35So by going to zone right now to be chair is probably the best drug we have to treat fatty liver disease specifically. Nash patients. Not all Fatty Liverpool.

- 01:08:48What about these? I just harped on this right? I love these drugs. I've been using these in my own practice for probably the last five years, because an endocrinologist was very nice to me and taught me about them, and taught me how to prescribe them and use them for patients. Um,
- 01:09:03this is a phase Two study with laraga tide. Again. I'm using the endpoint resolution of Nash forty compared to nine, statistically significant, This is actually a pretty low placebo response rate. Surprisingly in our studies. The placebo response is usually about twenty, so you know, if it had been that it might not have been statistically significant. But still this is the next highest resolution compared to pi a gooda zone.
- 01:09:27Aside from what
- 01:09:29bariatric surgery. Okay. So the rag with tide helped, but it didn't get moved on after that,

Unknown Speaker

01:09:36because the same company makes this drug, and they already knew, based on their diabetes, studies,

UVA IMR

01:09:43and their obesity studies, that this drug causes people to lose way more weight than lorag with tide right,

- 01:09:49and it's just a wonderful drag. Oh, man, those don't line up! That's a bummer. Okay, anyway. So some hag with tide.
- 01:09:58If you look at this with increasing dose resolution of Nash sixty with the higher dose, with no worsening of fibrosis. The fibrosis changes may not really work that well, um but for resolution of Nash, one of the best drugs.
- 01:10:13Oh, those line up there we go, and then it's clearly probably related to this right. The higher dose you go, the more weight people lose, the more weight people lose. I've already shown you that graphic right. The more likely they are to reverse their disease.
- 01:10:25So right Now this is in a phase three study in the United States. Looking at this exact thing, i'm going to tell you physiologically, this is not a direct effect in the liver. What's going to happen is this drug is going to make people whose weight, and secondarily, by losing late, they're going to improve Nash,
- 01:10:40and so I suspect this drive will be approved within the next two to five years. For the third indication. So right diabetes, obesity, Nash.
- 01:10:49So look out for that,
- 01:10:51and I do believe in it. I do think it helps people lose weight.

UVA IMR

01:10:58I had to put this in here because it would be disingenuous and biased to me not to include this drug.

- 01:11:04This is probably going to be the first drug approved for fatty liver disease. In fact, I got a message a week or two ago that said that their face three results they were happy with, and that they were going to the Fda. I think, if not now, sometime in two thousand and twenty-three
- 01:11:20o beta colic acid.

- 01:11:22It's a bio acid synthetic bio acid does something to the farsenoid x receptor and the nucleus. I'm not going to go into all that, because, to be honest, I don't fully understand this mechanism of action, either.
- 01:11:32But they've looked at this phase Two study non serotic, Nash: Okay. So Nash, Some of them do have fibrosis, but not definitely not cirrhosis. And they looked at this and they found that the resolution of Nash was not significant. I mean only twenty two percent compared to what I've just shown you.
- 01:11:50But somewhat unexpectedly they did find it improves fibrosis
- 01:11:55significantly. And that was interesting, Right? Because this may be one of the first drugs that can actually reverse fibrosis irrespective of weight loss or any other change.
- 01:12:06The downside to a beta callic acid is that Ldl goes up. Hdl goes down homa ir worsen insulin levels go up
- 01:12:15weight goes down.
- 01:12:16But that's not good right. We just worsened like every kind of bog factor of metabolic syndrome. Aside from their weight per se
- 01:12:24with one drug. And What's the thing that kills my patients more than liver disease,
- 01:12:31cardiovascular disease? I don't particularly want a drug that increases their Ldl. Lowers the Hdl. And makes them more influen resistant. Okay,
- 01:12:39on top of that, I don't even think I included this. Oh, yeah, I did Paritis.
- 01:12:45It's a bio acid. It makes them itch like stink. We've seen this. Okay, they do not like it
- 01:12:53very, very itchy, and I'm going to be honest. Pritas from bio acids like think Pbc: and Psc. Patients very difficult to manage right. Ssris. Add or acts out to cream all that stuff, and they're still itching like crazy until they bleed. So It's not really a side effect that I want my patients to get.
- 01:13:11But
- 01:13:14it worked. So they went to phase three face three results, almost the exact same.
- 01:13:20It still doesn't show really any improvement significantly.
- 01:13:24And Nash I mean a little bit. But the fibrosis is what they were uh sorry fibrosis improves nash doesn't. But this is pretty interesting. I mean, we are looking for drugs that can reverse national liver disease in general. So I am excited about that. However, in this much larger phase. Three trial.
- 01:13:44Oh, wait! I guess I didn't include the slide. My bad, exact same results with Ldl. Hdl. Home, Ir. Et cetera. They even did a significant breakdown of the lipid profile to look at the particles.
- 01:13:57It's. All the bad ones go up, all the good ones go down, and it increases risk of cardio metabolic disease
- 01:14:05so long term, because this is also not a curative treatment. Right Now, this is not going to be something where you put them on the drug.
- 01:14:12They resolve Nash, because they don't right, They might lose some fibrosis, and then you stop it. The presumption is that if you start this drug they are on it.
- 01:14:20So it's counteracting a lot of what we're doing. They are doing studies looking at their drug plus a Torb of statin to see if they can mitigate some of that. But still long term biggest concern is cvd risk. So when you see this drug,
- 01:14:35and the next I don't know. Twelve to twenty, four months
- 01:14:38it'll be the next one on Tv. I don't know what they're gonna name it saying it's the first and only drug for Nash. Pause. Be ready for patients to talk about it. But everybody doesn't need to get this drug. In fact, I think very few will.
- 01:14:52So now I'm gonna come back to this. We're almost done. I promise
- 01:14:57that talks about general management, and we're going to go back through these three phases, because right, we identified our patient as low risk, intermediate or high,

- 01:15:06our fatty liver patient. And then we want to treat them so. Lifestyle intervention. Right? So we know diet and exercise work. We want to work for weight, loss on everybody.
- 01:15:16Um, you can see bariatric surgery is in all of these columns, and a lot of these patients like, I said, We'll have indications for that that. Go way beyond the liver disease pharmac with therapy for nash. So in this group not so much right,
- 01:15:31and I will tell you one of the reasons this is in here. All these clinical trials with some aggregate or beta-collic acid are explicitly in patients who have Nash and Firosis advanced fibrosis, either stage two or beyond so, even if the drug gets approved for a lot of patients. It will at least require a fibro scan, if not a liver biopsy to prove they have fibratic disease before we could even prescribe it. Anyway.
- 01:15:53Cbd risk reduction everybody all the time. Diabetes my main goal. Use a Gop one for subdirect.
- 01:16:01So remember, first off to look for it.
- 01:16:04This is more prevalent than we think.
- 01:16:07Secondly, you have to counsel patients on Cbd Risk. At least I think so. That's what kills them. And this is additive. Remember that, too. It's not just. Oh, you got all the other things. Well, now we found fatty liver, and that's actually going to increase your risk for Cvd right cardiovascular disease.
- 01:16:23So look for it. Counsel them, counsel them on the cancer risk. Okay, you'll need to freak them out, but they need to understand that while we're trying to prevent cirrhosis. We're also trying to prevent more common diseases and death.
- 01:16:34Um, And this is true when I tell patients you asymptomatic by the way nobody feels this, that Oh, yeah, you might get cirrhosis in twenty or thirty years. They just gloss over. If I tell them that they're at a significantly increased risk to have a massive heart attack in the fiftys and sixtys. They seem to listen So that's the other benefit of telling them about the increased risk.
- 01:16:54And then, lastly, remember to assess for and monitor fibrosis, because that's what matters right. Fibrosis is what's going to make people progress
- 01:17:03This on the left is what I would follow. That's the reference at the bottom left. We're all here. Sorry to Carolyn, because I don't have a picture, and I didn't want to just find one on the Internet because people hate it when you do that, because they may not like that picture. But Caroline's picture will be added to this list shortly, and I think that's it.
- 01:17:22And for the first time in my life I'm only three minutes over time.
- 01:17:38Got one in the chat. I can read um. Sorry that's just about sharing slides. Just kidding. I'll ask one instead. Um. Aside from the Gop. One receptor agonists any other drugs you're excited about. You know about in the pipeline that maybe aren't in the trial level yet.
- 01:17:55Um! Well, there's some drugs in the pipeline that there's one Lana Fibrinore and another one Ella fibrinore that are specifically, we think, anti fibratic. In fact,
- 01:18:06I I get them mixed up because they both end in fibrinore, and I can't remember which one, and they're both being looked at in fatty liver as well as Pvc. Um. They seem to have like significant anti fibratic properties, but don't seem to have all that elevated Cvd risk, and I do think those that pathway of Drugs in the future may be something that we see
- 01:18:26current drugs that are available for everyday use. I mean the magic trifecta, and any of my patients that have at least pre diabetes would be map, format, and glp, one receptor agonist and an Sgl. T to inhibit
- 01:18:39right like, I think, if they could make that into a Combo pill, assuming patients don't have, like a contradication to one of those primarily like the Sl. T. Two inhibitors that to me, from like a cardio metabolic perspective, seems to be the best try factor right now,
- 01:18:54and I think leads to weight loss, right? The sqlt. Two inhibitors help prevent cardiovascular disease, which is what I'm also worried about
- 01:19:02the weight loss will help their chatty liver, so that would be my go to

- 01:19:06I'm. Heavily influenced by two hundred chronologists at Uva, Jen, Kirby and Meg Stomp. So that's where I get a lot of this.

Unknown Speaker

01:19:14Thanks.

UVA IMR

01:19:16Any other questions,

- 01:19:18Thoughts. Yes, Dr. Lobo,
- 01:19:24is it? Recur and transplant livers absolutely, and at alarming rates like thirty-five percent or more
- 01:19:32um and
- 01:19:34patients who get transplanted for nash compared to other indications have increased risk for cardiovascular disease. Within the first three years of transplant
- 01:19:45after transplant um. Some of that depends on how well we manage those risk factors, because their highest risk of death is still cardiovascular disease, not like recurrent cirrhosis and liver disease,
- 01:19:57and so I mean some of them within three to five years. But I think if we manage them Well, they can have the same long term outcomes as our other liver patients, but part of that's recognition on our part after transplant of their dyslipidemia right their hypertension,
- 01:20:15their blood sugar, their insulin resistance, right? Because right, our call center and inhibitors all most of our drugs right, affect all of those things in a negative way. So in the transplant world, if someone gets transplanted for Nash, we have to be a little more aggressive about capturing those things, working with them on weight, because, like our cirrhosis patients, are these malnourish people right? Going to transplant? They have like no muscle mass. They have no appetite.
- 01:20:38Then they get transplanted one month, three months later. They're starting to feel better, and those are the folks that we see gained forty or fifty pounds in the first year.
- 01:20:47Some of them need to gain that much way. You believe it or not, but they need to gain it healthy, right. They need muscle mass going on that they need to be eating a healthy diet and exercising. So I think those are things we could probably do better with in the post transplant patients.
- 01:21:12Yeah. So the question is,
- 01:21:15Is there a difference from like genetic Naffold so genetic? Naffold right now? Pretty much comes down to P. And Pla, three polymorphisms which are more prevalent in the Hispanic population. Um, that very first slide I showed you about the world. Distribution actually goes into some more details about that, but
- 01:21:33even more specifically in Mexico as compared to even like the Dominican Republic and Puerto Rico, significantly higher rates of P. And a three polymorphisms
- 01:21:43response to some of the therapies that I spoke to. I am not aware of any of those studies specifically looking at that, However, a lot of those studies do include genomics, and that's going to be, I think, part of the
- 01:21:56sub analysis or secondary analysis for a lot of these drug trials is looking at.
- 01:22:05I apologize. Whoever is asked in the chat. I just can't tell exactly who it is, but they just also want to hear um some more commentary about the other side effects of vehicle to zoom. Oh, that's Dr. Caldwell. Okay, Great fair point, Steve: I didn't go into the side effects.
- 01:22:21So lower extremity. Edema Osteopenia. There's been some risk of water cancer, however,

- 01:22:28in that second study of Piaglitzone from Kin, Qc. In Florida I did not include the adverse effects slide, because I knew I was already going to go over, and I had to get through this
- 01:22:38um specifically, for, like bladder, cancer and osteopenia or prosperity, and not porosis. They didn't notice a significant difference in that Qc. Trial between Piaget Zone and controls,
- 01:22:50I think symptomatically. Weight, grain, and edema are the biggest ones. The other Tcds significant right heart Risk with it, Rosie Gl to Zone, I think right with the one that has significant cardiac risk related to it. Pi good is, though not as much,
- 01:23:08and he's talking about p part agonist looking promising, and I think
- 01:23:12so. That's this class of drugs. But I think Lana fibrinore, and I will Fibon or fall into that category.
- 01:23:19Yeah, great.
- 01:23:20He agrees. Okay,
- 01:23:22alright, Thank you. Oh, yeah, no, yeah. I'm: I'm:
- 01:23:26Um. So what is my car

Unknown Speaker

01:23:29out. Let's see.

Unknown Speaker

01:23:31Um.

Unknown Speaker

01:23:34It's kind of our diabetes

Unknown Speaker

01:23:36full part of it.

Unknown Speaker

01:23:40It's reasonable for that for

UVA IMR

01:23:43the same question. Um! So if you might go to the whole algorithm. And you have a low um

Unknown Speaker

01:23:52as an initial.

UVA IMR

01:23:59Yeah, that's a good question. Um,

- 01:24:03I don't know the answer to that, like just a screen in general, right like. So they're completely negative that diabetes patient, and they roll right back up into the top.
- 01:24:12So
- 01:24:13you know one of the reasons it says, like with the non-invasive like blood composite test and fiber scan every two to three years, is because
- 01:24:20things in the liver generally take decades to change, including like fibrosis. Um, we've seen it go faster right? I mean. There's always exceptions to the rule.
- 01:24:30I think it would be reasonable in a diabetic patient to maybe say every three to five years you could repeat an all for sound. But there are also studies I didn't include, because their association studies
- 01:24:41so metabolic Co. Factors also kind of help us predict what's happening in the liver right.
- 01:24:49So if metabolic co-factors are getting worse if they're everyone sees getting worse over time. If they're lipids, they're getting worse over time. If they're weight and waist circumference are getting worse over time. That might be a patient that I'm a little more prone to say. Well, maybe I'll repeat that all, son, in two or three years right?
- 01:25:05But if you do it, and there's nothing there that's not a hundred percent, either, right? Because, like it's not a hundred percent sensitive like you can miss.
- 01:25:12I think there was a study that said, If they have less than like twelve percent total liver fat, like an ultrasound, has a higher chance of missing it.
- 01:25:19But three to five years would seem reasonable that if you do it again you could pick it up.
- 01:25:24And if you're significantly worried like because their metabolic risk factors are like getting way out of control, and their ultrasound still doesn't show it.
- 01:25:32That's kind of what the authors of that study we're getting at. Those people still have a high enough risk for fibrosis,
- 01:25:40and you may have just missed it on ultrasound um, and there's no study that says if I add a second over sound, or even a third one, Am I more likely to pick it up? So if you were really worried just from a metal log perspective, you can actually just do the non invasive test. See if you think like. They have fibrosis and kind of treat them as if they did.
- 01:25:58Now for medical treatment.
- 01:26:01Now as a biopsy diagnosis,
- 01:26:04Right? Because I have to see those balloon cells.
- 01:26:06Medical treatment is going to be based on fibrosis.
- 01:26:09Thankfully, we're not have to buy up to everybody that's for that fiber scan will help, because fiber scans are part of all these clinical trials as well. Um, But to get somebody on medical therapy specifically for Nash. Not just kind of like my drug trifecta that treats all kinds of different metabolic things.
- 01:26:25Um, you're going to need some assessment of fibrosis.
- 01:26:31Awesome!
- 01:26:32Thank you.