

MICHAEL A. DUNN: I'm here to talk to you about frailty, sarcopenia, and its impact on liver cirrhosis, especially within the context of abdominal transplantation. And this is a huge issue, and it's a highly prevalent issue. Our muscle loss and its lethal consequences are really highly prevalent in advanced liver disease, and many of you appreciate that it's the most accurate predictor of loss of patients from the transplant wait list with inevitable death within 30 days of delisting.

In addition, it is a huge cause of chronic disability after transplant where the expectation is that after a transplant, you're going to return to normal function and good quality of life. Post-transplant muscle wasting robs someone of that. And sarcopenic obesity is one of the key advanced complications after the transplant period.

I think at this point, I'd like to point out that this center, our UPMC Starzl Transplant Institute, is very likely at the top of the heap in terms of our liver transplant centers that have capabilities and have accomplishments in dealing with frailty and sarcopenia. Andres Duarte-Rojo and myself are fortunate to be sitting at the top of this pyramid, but we've got Pam Bloomer, who is the only full-time physical therapist assigned to any United States liver transplant center because we were able to show that she paid for herself 10 times over in avoiding morbidity and mortality. We have our total of five medicine residents in gastroenterology fellows whose major commitment to clinical research is frailty and sarcopenia.

So we have the critical mass. I noticed when Dr. Humar gave his talk that our number of living donor liver transplants was number one in the nation. Number two was University of California San Francisco. Similar situation-- University of California San Francisco, and I'll refer to some of their work in this talk, is very clearly number two, and it's going to be fun to maintain our position ahead of them.

I'm going to talk about pathophysiology of muscle loss in advanced liver disease. Pam Bloomer is going to cover some assessment of how you figure out what muscle loss, muscle wasting, functionally means. And Andreas is going to talk about management therapy and where we're going to be going in the future.

Bear in mind that cirrhosis does not just involve loss of liver cells. It also involves distortion of architecture. With a lot of fibrosis, that leads to blood flow disturbances, shunting, and a lot of the patients who die of advanced liver disease actually have sufficient liver cells to sustain life. But it's the mismatch of circulatory inputs and outputs added to that that becomes lethal.

And you've all seen patients with advanced sarcopenia in our clinic or are anywhere else that you've studied cirrhosis. The two panels on the right side of the screen show you cross-sectional images at the third lumbar vertebra level. They've been highlighted in red to show wall of the skeletal muscle. Here's the psoas, the abdominal musculature, of a normal person.

And compare that with the kind of muscle loss that you see in advanced muscle loss, sarcopenia. It doesn't take a lot of rocket science to tell the difference, and that's quite obvious. And if you look at that unfortunate patient on the left, you get the idea that muscle wasting is really a big deal, and it's quite prevalent.

So what's driving that? What's behind the problem? Let me introduce you to ammonia.

Looks like a kind of small, innocuous little molecule, OK? But there is some evil things that can occur when you've got advanced cirrhosis. You may have noticed looking at patients with advanced cirrhosis, looking at blood chemistry testing, that BUNs, Blood Urea Nitrogens, tend to be very, very low.

There is a reason for that. On the left panel, you see that in health, the liver is very much the predominant pathway for getting rid of ammonia. Two molecules of ammonia combine to urea, which then gets excreted in the urine. Only a minor amount of ammonia is handled by muscle.

So the reason why you have low blood ureas in patients with advanced cirrhosis is it's not being handled that way. Shunting, portosystemic shunting, is diverting the vast majority of ammonia away from the liver and into muscle, where it must be combined with glutamic acid in order to make glutamate. Muscle has no other choice than to handle that delivery of ammonia to it by combining it with glutamic acid. That's the premier excretion pathway for ammonia in advanced liver disease.

And if you know that, then you know this whole train wreck slide. I think the easiest way to understand the slide here is to recall the Allstate commercial with Mayhem. That's what's happening inside muscle cells when ammonia is presented.

There is ammonia right here, and it's being are combined with glutamic acid to make glutamine, that excretion product that I told you. That's pretty much the whole ballgame. Glutamic acid could have been used over on this ribosome array here to do muscle protein synthesis. It's being diverted by having to be combined with ammonia.

If you're a real devotee of the Krebs citric acid cycle, you know somewhere back there in your occipital cortex, you may have this vague notion about alpha-ketoglutarate OK, glutamic acid, yada, yada, yada. Well, alpha-ketoglutarate does go to glutamic acid. In addition to robbing protein synthesis, you're robbing the citric acid cycle, which is where all your energy and ATP comes from.

So that's three hits. In addition to that, as if that wasn't bad enough, ammonia stimulates the formation and release of this little sucker called myostatin. It is a messenger molecule that shuts down protein synthesis. Ammonia also stimulates this little funny licensing in there it triggers autophagy so you're digesting yourself from within.

And ammonia also directly inhibits contractility of skeletal muscle. So you have a five-fold damage pathway. Ammonia simply is not a good thing for muscle health. That's the key thing to remember.

A couple of definitions because we talk about these things in slightly different contexts-- frailty is a performance-based construct. Frailty simply means decreased reserve, decreased physical capacity to deal with stress. And here's the classic definition of that-- diminished reserve. And it's measured by measuring physical performance.

Sarcopenia is an anatomic definition-- less actual muscle mass as measured anatomically. Malnutrition, which is intimately related to muscle loss, is clearly a broad concept that includes deficiencies, all kinds of precursors-- fat, calories, protein, carbohydrates, and so forth. And that underlies muscle loss and cirrhosis. Cachexia, which is a pretty end stage term, means you've lost greater than 5% of your body weight.

And as you can see and as you've all seen cirrhotic patients, that's getting near the end of the line. If you have a patient who's got trouble making it out of the wheelchair and making it up to the exam table, that individual's likelihood of being able to withstand the physical stress of a 12 hour operation and recovery in an ICU and getting out of there after a transplant is not very good. So again, the number one cause of waitlist death, the number one cause of delisting.

This may be the most significant slide in the deck here. I think the majority of the audience here does have an IQ higher than your MELD score, OK? The top solid line, the black line on the top is the, Kaplan Meier survival curve of patients with advanced cirrhosis who are not frail, who are robust, who are physically performing OK and getting around at a MELD score of 14.

Notice, though, that the solid green line you can see there in the middle-- I'm trying to point at it with the arrow-- represents the survival of a patient who is frail, who has that same MELD score relatively low of 14. And if you compare it with that superimposed line of MELD 23, you'll see that you're paying a survival penalty with frailty that is just as bad as nearly doubling your MELD score. So the effect of frailty and sarcopenia on survival if one has advanced cirrhosis is independent of and just as significant as an increase in one's MELD score. And of course, if you've got the double hit-- high MELD and advanced frailty-- you're in a world of hurt.

Does everyone who understands a MELD score have a pretty good shot at passing the gastroenterology boards or the liver transplant fellowship boards or the surgical boards? I would think so. Is there a single question yet about frailty or sarcopenia on any of those board exams? Dream on.

It's not there. This is new stuff. It's only been around for about the last four years, and we're just beginning to really understand its implications.

Here are some Stone Age metrics to look at both frailty and sarcopenia. As I showed you earlier, this is a cross-sectional CT. Shaded in red are the major muscle groups of the third lumbar vertebra level.

We've also shaded subcutaneous and visceral fat, but that's a good way of assessing anatomic sarcopenia. We can assess function. Here is a hand grip measure. And this little gizmo here is a Fitbit, which will give you steps per day, amount of aerobic activity, amount of cardiovascular performance. All of those are the ways that we were able to assess frailty and sarcopenia up until yesterday.

As of yesterday-- well, to be honest with you, not until Tuesday-- we're going to be investigating looking at stable isotope deuterium-labeled creatine. If you've ever gone into GNC and bought 50 kilograms of creatinine in order to bulk up, you get the idea that creatine if you take it orally, goes exclusively into skeletal muscle. That's the only place it goes.

Now creatinine gets converted non-enzymatically to creatinine. And creatinine goes into the urine. So if you use a tracer dose of isotope-stable deuterium creatinine, it'll go into muscle. It'll stay there.

It'll get converted into isotope creatinine and if you can measure the dilution of that isotope creatinine in the creatinine that is excreted in the urine and if you know what the creatine content of muscle is, it's. Simple math to know what the total body muscle mass is. And in about 2,000 elderly adults, the normal total body muscle mass runs around 30 kilograms for a man and 20, 25 kilograms for a woman. Never been measured in anyone with advanced liver disease to date.

So starting Tuesday at a medical center very near you, we're going to be looking at this kind of our flow of creatine into creatinine in patients with advanced fluid overload and cirrhosis. We've got to be able to prove that creatine is handled in the same way in advanced liver disease-- not going into acidic fluid, for example, not going into edema fluid-- so that we can really know what we're looking at. The advantage of a method like this is that if you have a patient who's got acute on chronic liver failure, multiple organ dysfunction, it's been shown that they can lose up to 20% of their muscle mass in one day.

So thinking that you can know what muscle mass is by checking the contrast CT scan, that's not a thing you can do on a daily or even a weekly or a two week basis. You've got to have a clinical reason to want to use contrast dye and want to use radiation exposure. So this is a really good, valid way, at least in non-cirrhotic individuals, to actually know what muscle mass is all about. And if we play our cards right and if our four of those ambitious residents and fellows that I talked to you about remain ambitious enough through this project, we will actually be able to validate this methodology and have the best game in town for looking at total body muscle mass.

Here is just a plot showing our impedance versus muscle mass in healthy, elderly individuals, showing a nice linear relationship of the creatine method versus an imaging method for showing appendicular skeletal muscle mass. So it's a good method. We just have to prove that it works in liver cirrhosis, and we'll be off to the races and having a lot more fun being able to follow patients.

So I'm going to turn this over next to Pam Bloomer, our physical therapist, and she's going to tell you about this liver frailty index that was put together by my friend Jennifer Lai at UCSF, the number two center in the nation on frailty and sarcopenia. And that is a good way of determining who is at risk for serious problems both with advanced cirrhosis and on a wait list. And with that, I'll ask Pam to come up here and wrestle with this computer and get her presentation going. Thank you.

**PAMELA
BLOOMER:**

OK, as Dr. Dunn said, I am Pam Bloomer, the transplant physical therapist, and I'm going to go over what I do as part of the frailty assessment. So there are several components to the frailty assessment itself. The first is the usual gait speed.

So what I do for that is I ask the patient could they please walk their normal speed for me. Basically, it is a one meter acceleration phase. And then I time them for four meters.

And then there's a one meter deceleration phase. I have them do that three times, take the average, and then calculate it out. We typically like them to be 0.8 meters per second or faster.

The next component is the balance test. So there's three positions that I ask them to assume. The first one is feet together, which is typically the easiest for them, see if they can hold it 10 seconds.

The second position is called semi-tandem, which is the ball of the one foot next to the heel of the other and pretty close together, see if they can hold that 10 seconds. If they can hold that 10 seconds, we progress to the next one, which is the tandem stance-- so basically like you're standing on a tightrope. The third component is the grip strength of the dominant hand only, and that's using that tool that Dr. Dunn had on one of his slides. It's the handheld [INAUDIBLE].

That will give me-- I tell them to squeeze as hard as you can. It gives me a measurement in kilograms. And then I take the average of that as well after three trials.

The fourth component is a five time repeated sit to stand from a chair. I ask them to please stand up and down as quickly as they can. They cannot use their arms.

So for that, basically, we would like them to be 12 seconds or less. And then the last component is the six minute walk test. For that, I actually have a core setup in a hallway where it's a 12 meter span one way.

And I ask them to make laps around the cones, time them. I tell them, OK, I need you to walk for, if you can, six minutes. I can't stop the timer. And if you have to stop, you do.

I want him to be safe. However, they know that if they do stop, that's going to obviously take away from their distance that they cover. For that particular test, we like them to be 250 meters or more.

So we also-- we do try to get that same data on our inpatients as well. They have also been trained by me to do that. We typically try to get it, if we can, within three days of discharge if possible.

And then so what happens to all this data, both outpatient and inpatient, it gets entered into this website from UCSF. And it calculates the liver frailty index. So what will happen is typically, what we're using right now is 4.2.

So if they score 4.2 or higher, if they're discharging from inpatient, what we like to see is that they will schedule an appointment with me in the clinic for follow-up. As outpatient, that's typically the patients I tend to follow within the clinic as well and give them some type of intervention to try to correct what's going on.

So the next slide actually shows you. This is where the data goes in. Pretty simple-- you put in their gender.

You put in the grip strengths that we obtained during the testing. You put in the chair stands, and then you put in the balance times-- so whether they held for 10 seconds or not. And then this calculator will come up with the LFI, which you see on the right hand side there.

This just shows typically where our patients fall. So 3.2 or lower, they are considered robust. Typically, these patients I don't get involved with.

And then the next category is considered pre-frail. So that's 3.2 to 4.5. A lot of our patients fall within this category. So like I said before, we're using a cutoff right now of interventions of 4.2 or higher.

Not to say that I don't get involved with some of the lower ones because I've had patients ask me even if they're considered robust, they want an exercise program for home, they want to stay strong, or if during the testing they come up with impairments that didn't really know they had until we actually went through the testing and they want exercises to address those impairments. So that's what happens with that. And then I definitely will follow, if they are 4.5 or higher, that's considered you're frail category, and they definitely get interventions.

So some of the interventions or the recommendations, what we like to see happen is in a five day span, we're asking them to complete some type of activity for 30 minutes a day-- so whether it be aerobic, walking, riding an exercise bike, whatever it may be, something that they're going to enjoy something they're going to do-- in combination with a resistive program-- so whatever would work for them for 30 minutes on top of their normal daily routine. Examples of what I do within the clinic-- I give them a home exercise program if I think they're going to be compliant. And you can kind of get that feel whenever you're assessing them.

So what happens is I will print off an exercise program for them using one of the programs we have right now, go through every exercise with them in the clinic to make sure they understand and can perform properly at home, see if there's any questions. And I do have bands that I can give them to take home. So it's not very-- so they don't assume extra cost.

They can also do them with dumbbells if they wish. Typically recommending between one to three pounds for the most part and trying to keep, again, costs down as well for that. So what will happen-- we're eventually going to also incorporate L-FIT, which Dr. Duarte-Rojo is going to talk about in a little bit later. So that will be an option down the road as well.

Another intervention that we sometimes recommend is if people go into a gym, a local Y, that kind of thing, they want to be more independent. They want something a little bit more aggressive. They can do weight machines.

Somebody that has severe arthritis, a lot of pain, joint pain, that kind of thing, doing water aerobics classes is excellent for them as well. What we found out too is anybody that's typically 65 or older, sometimes their insurance plans will cover the gym memberships. So that helps them out as well. They usually call it like a SilverSneakers program. So that helps with compliance.

Another intervention that we try to use the least amount is the home health physical therapy because in that case, you're looking at some of the most frail patients. And typically, they have to be considered homebound. So basically, if they are getting extremely fatigued just getting out of their home, this might be an appropriate intervention for them-- somebody that needs a little bit more guidance than just handing them exercise program and saying, here, you need to do this. So that is another option for them.

And then the final intervention that sometimes I can recommend-- and I would have to work together with the hepatologist on this because we would need a referral for them-- is actually having them go to an outpatient physical therapy clinic where they're going to be seen in the clinic two to three times a week for a more aggressive, more vigorous strengthening program than what a home program could accomplish and also, for somebody that you're kind of questioning as far as compliance goes, that they would need that extra guidance. So one of the nice things is too, if these patients choose to go to one of our outside clinics, which is our centers rehab services, I educate those therapists at those facilities. I'm in close contact with them. I can kind of give them a heads up and try to help schedule these patients and tell them what we're looking at right now, what we're trying to improve, what the goals are so that they kind of have a guide as well, so what they need to target.

And then finally, from a physical therapy perspective, there are kind of things that we have to look at with these particular patients as you well know. So we always look at the upper GI studies, the EGDs, whatever to see if there are presence of varices. And then based on that, we try to look and see what type of treatments are being provided and kind of gauge the aggressiveness of our treatments off of that because if they have a grade three varices and not really being treated, just kind of being observed, then we're probably going to do more of like anti-gravity range of motion exercises for these particular patients or focus more on the aerobic type activity whereas if they only have like a grade one, then we can pretty much do whatever we need to do from a therapy perspective.

But again, most of these patients we're recommending to stay one two three pounds, five pounds at the max. We do educate them too about no heavy lifting as well if they do have the varices. You know, try to do no greater than the 5 to 10 pounds, you know, don't move heavy furniture, that kind of stuff. So it's an education process as well.

As a physical therapist, if we ever have a question as far as safety goes with an exercise program that we want to give that we really feel that the patient would benefit from, we will definitely check with one of the hepatologists to make sure that they are actually safe with what we're actually thinking. So communication is the big thing there. And like I said before, I have actually trained the inpatient physical therapists as well so that they know about the contraindications.

They know about the exercise programs. There's actually protocols set up for the exercises for them on a program they can access so that there is a continuity of care when these patients are discharged from the hospital and then whenever I see them in the clinic so that they're already familiar with the exercises that they're going to be possibly given. So with that, I am actually going to turn it over to Dr. Duarte-Rojo.

ANDRES DUARTE-ROJO: So I'm going to try to continue with the frailty, sarcopenia, cirrhosis talk that Mike started and Pam gave us some more insight about it. So we're going to talk a little bit about what are the strategies how we can reverse this frailty and sarcopenia, what are the difficulties in delivering this intervention, and then going to a proposal for a home-based program that we actually hopefully will start soon in our transplant center. So these are the 13 clinical trials that have been done evaluating exercise in patients with cirrhosis.

And we're not going to review all of them. Don't worry. But I just want you to realize that it's very few patients that have been included.

You know, the largest has been this study with 60 patients where actually only 50 eventually completed the intervention. There are studies with as few patients as only like six patients with cirrhosis here or 13 patients there. So it's really very few patients. The majority of the inpatients have been supervised. So home-based interventions have been actually not very frequent.

The other thing is that in the models, we have the supervise where the patient is actually exercising in front of somebody that is a trainer, that is an exercise physiologist or a physical therapist. Whereas there is one where the patient just goes and does the best they can do as an outpatient-- pretty much similar to what [INAUDIBLE] was telling us. We just tell the patient, do the best you can.

This is your goal. You have to walk or you have to do this number of minutes of exercise. And they just do them ad libitum.

And of course, we have some other model [INAUDIBLE] structure where we give them specific things to do as outpatients, and we have also some hybrid programs. And the reason for emphasizing this is that we have big issues in trying to get these patients to exercise, both because we don't have a third payer that will pay for this physical therapy or for these patients to exercise. Many patients don't have the means for transplantation, joining a gym, buying a Fitbit, et cetera. So we have to be creative in serving our patients better with all the difficulties that we have in our medical system.

So just summarizing the 13 studies that I showed to you, these are the effects that we have been able to see. So muscle mass increases and strength improves, weight decreases, adiposity decreases.

Insulin level improves, inflammation as well, even if there is no decrease in weight. So just exercising per se without having any changes in weight is actually beneficial to our patient population. Fatigue, mood, and quality of life, although not shown in all of the clinical trials, have shown some benefits.

Hepatic venous pressure, which was a big concern in the past-- initial studies done in Barcelona showed that actually, while the patient was exercising, there was an increase in the portal venous pressure. And that made us think that patients were going to bleed more from esophageal variceal rupture during exercise. And we have actually been able to show with two studies that is not the case.

And actually, as you keep your patient exercising over and over before a period of many weeks, 12 to 14 weeks, you can actually see decreases in the hepatic venous pressure gradient, which is a surrogate of the portal vein. Liver chemistry, ALT, AST, DGT, all of those guys improve.

Ammonia also. The increase in hyper [INAUDIBLE] the patients might have after a meal or do an exercise actually will decrease in this population. And their fitness is better. In other words, how the body from heart, lungs, vessels, muscle, how the body manages all the oxygenation, consumption of oxygen, production of CO₂, is improved. And this is what we refer with aerobic fitness or cardiopulmonary fitness.

So this is one of the studies. This is a supervised study that I'm showing you here to your left. And you can see how this VO₂, which is your consumption of oxygen-- it's a measure of your aerobic fitness that we get from a cardiopulmonary exercise testing-- actually improved in the patients that exercise. But it did not and even perhaps got worse in patients that did not.

The same can be seen in this study. Now here, we're not using the VO₂ from cardiopulmonary exercise testing. We're actually using or this author used a six minute walk test, what Pam just mentioned to you.

And you can see how patients walk more after two weeks of exercise. Whereas they pretty much do almost the same if they are in the control group. This is a home-based and very well-structured study done in Canada, in Edmonton, where they actually paid a company to go and set up a cycle ergometer to these patients' houses.

So they had specific goals. And a physical therapist, physical trainer, will go and tell them exactly what to do and tell them exactly what were the goals, how to use the equipment. And you can see again on the VO₂ from cardiopulmonary exercise testing, there is an improvement in exercise, and there is no improvement in control. And you can see the same when you take a look at this six minute walk test just like it was done in the previous study.

This is perhaps the most recent study, and the reason why I like showing this, even though it's a very small cohort-- it's only 18 patients-- is because for the first time-- all of the previous studies that I showed to you, I'm telling you that the markers of fitness are improved. But I didn't tell you whether they were able to improve frailty. So in this study, for the first time, they actually show that frailty measured by this scale went from 50% to 10% after two weeks of exercise and some other-- the distance that they walk and the measurements or whatever they were able to accomplish physically improved in all patients before and after.

Now the problem with this trial where when we review it is that these are the exercises that patients were asked to do. They were asked to do lunges, rock press, frog squat, and bear crawl. And they were supposed to be doing that during the period of 12 months at least three times per week.

I cannot see any of my patients or any of the patients here in the United States to actually do these exercises. This was done in the UK where the [INAUDIBLE] for patients who actually get transplanted is way lower and where the time on the waiting list is also way shorter than whatever it is in the United States. So even though this sounds fantastic, a great resistance training program, it doesn't seem to be applicable to the United States.

This is a study that I directed when I was in Arkansas. I just moved from Arkansas a few months ago. And here, we were using Fitbits, just the Fitbits that Mike mentioned. And we asked patients just to exercise with their Fitbit best they could.

And we have controls, and they also have to wear the Fitbit. And we just didn't intervene. We just let them do whatever their doctors will tell them to do, which is pretty much what Jay said.

The doctor will see the patient and say, hey, guess what? You need to eat less and you need to move more. So that's exactly what happened.

Nobody provides a specific exercise prescription, whereas the exercise group, they get a very precise exercise prescription. And you can see that the exercise group, there is an increase of about 1,000 steps per day. And in the control group, you can see a horrible decline from almost 4,500 to less than 3,000.

You have to understand that for a human being to do less than 3,000 steps, you actually have to put some effort into not moving at all. It's not easy. I mean, if you were one of these-- those were wear things actually can realize that it's not so-- like, those days that you hit something between 2,000 and 3,000, boy, you were really lazy. And we have patients that were doing less than 1,000 steps per day.

And when we actually saw that in the six minute walk test-- and you can see how their aerobic fitness again improved in the people exercising and it did not and actually got worse in the patients in the controls. And you can see these patients that actually did terrible and eventually die while on the transplant wait list being denied for transplant for being too frail to transplant. And that's exactly what we want to prevent with this population.

So having said that, we have three different ways how we can prescribe some type of exercise to our patients that are proven in the literature. We have a few caveats in there. So overall, one big thing is that we are a sedentary society. Just like we like to drink, we also like not to move and like to eat a lot.

And we don't have enough expertise, for example, on the hepatology side. So when the patient comes to the hematologist, the hematologist can say or the PCP can say, these are your goals. These are the exercise.

This is what you need to do. There is not such expertise within the group in hepatology. And would you send the patient to a physical therapist, you know, we have Pam.

Pam has been working with Mike Dunn for a while. So she is now very used to seeing patients with liver disease. But very few centers in the world have somebody like Pam that understands what are really the limitations these patients have and that can tailor a proper exercise prescription to whatever their needs are.

Of course, there is a lot of pressure for all the time seeing more patients in less time. And there is fear of complications, as I mentioned to you how many providers actually fear in the past that these patients were going to bleed if we will ask them to exercise. And there was actually a more traditional recommendation and even telling the patients not to exercise in order to decrease the risk of bleeding. So we kind of did this to ourselves. And now we're suffering the complications.

Unsupervised, I just mentioned what the problems are. And in the home base, now we have equipment. We have the motivation.

We have better compliance. We can use telehealth. And there are a lot of things that we can use for try to get these going for our patients.

OK, so on the components of the exercise prescription, we have to consider that there has to be a minimum of 30 minutes per day, a minimum of five days per week. The patients need to combine aerobic and resistance training, and they have to target some degree of intensity. And they have to consider that there is a need for warm up condition, cooldown, et cetera.

So none of those things are actually provided to the patients whenever we tell them to exercise. I'm just going to move faster through these. So this was just put published by the American Society of Transplantation where we actually identified that about half of our patients are pre-frail, are within this group that Pam just described.

And this is the group that we want to target right now in a home-based exercise prehabilitation program. We have developed some tools. This is an app that we've developed and that we are ready to start using in our program where it's called L-FIT Exercise and Liver Fitness.

Can show it to you later on if we have some more time later. But the things that it does is that it provides all of the expertise that a hepatologist doesn't have into an app and has already adopted a lot of exercise so that these exercises are safe for our patients. It goes into an Android and Mac platform.

This is how it looks. You have to join the study, do a lot of things, including putting your MELD, labs, and some other characteristics. And then eventually, with all of this information, the app will actually determine whether the patient is eligible for mild, mild intensity, moderate, or-- moderate, low-- sorry-- mild, low, or moderate intensity training.

And we'll unlock the videos that actually correspond to the type of exercise that they can do. It links with a Fitbit. So you can actually see what the patient is doing every day.

You can see the intensity of the exercise that the patient is doing. So you can actually check if your patient is indeed reaching moderate intensity or not. And you can ask them to be more intense about whatever they're supposed to be doing.

There is a leader board. You can actually compare what patients can compare to each other, even seeing their MELDs, since their MELDs seem to be so important for our patients.

I'm going to skip these videos. And the other thing that this program has is that it can actually-- it has a dashboard that is linked to the app so that the physical therapist can send messages to the patient, can change [INAUDIBLE] to the patients, and can remotely monitor the patient.

So bottom line-- what we're trying to do is that through a physical-- by identifying patients that have defects in physical function, we can see who is frail, who is sarcopenic. We can put him into a rehabilitation program. We can check their endpoints.

And hopefully, this is going to improve and make some more patients reaching transplantation with better outcomes. And the patients that are more frail and [INAUDIBLE] sarcopenic, we'll just continue monitoring them until they reach either a transplantation, frailty, or sarcopenia. Whenever they reach frailty or sarcopenia, we're going to include them into these studies.

And of course, along with this, this is both a clinical program and clinical research that we want to combine and see if it is actually leading into less revenue, less expense, and if we have actually-- the enterprise can recover its investment just by doing these type of programs. To finalize, these are the exercise recommendations by some of the professional associations. We don't have one in transplant, only hematology. So the idea is that we produce the science so we can eventually come up with those recommendations and provide an accurate exercise prescription to our patients. Thank you very much.

[APPLAUSE]