NAUDIA JONASSAINT: Today we're going to talk a little bit about the new paradigms in regards to the evaluation and management of hepatitis C. And I think that this is profoundly important. Because I think that the treatment of hepatitis C in the future is going to go from being in the subspecialty domain to being in the primary care domain. And many of you I think are going to be practicing general hepatologies in the upcoming years.

So I do have two disclosures. I do run a post-transplant hep-c treatment trial funded by Gilead and did previously serve on a medical advisory board for that same company.

So the objectives of this talk are really to advise in regards to the basic epidemiology and the scope of hepatitis C currently, both in the United States and around the world. Talk about the appropriate screening for hepatitis C, the basic treatment options. And obviously I'm not going to be able to cover how hepatitis C is treated for all genotypes within the course of this talk. But I will try to cover some of the basics.

In addition we're going to talk about the identification of some special populations. And when I say special populations, this really to me means those people who should be seeking subspecialty care no matter how nuanced the primary care provider is in regards to providing hepatitis C treatment. And then lastly, a little bit about the important information that's coming out in regards to post-SVR monitoring.

I would also like to say thank you to Richard Kalman, one of my colleagues at Einstein, for helping me with some of the graphic slides and allowing me to share his slides.

So just to convince you in regards to the importance of the talk, which I'm hoping I don't have to do too much of, Act 87 was passed by the PA General Assembly in July of 2006. And this really mandates that, throughout the state of Pennsylvania, patients that are Baby boomers born between 1945 and 1965, who are seeking inpatient care or primary outpatient care services, need to be offered hepatitis C screening. And the only exception to this rule is really three things. Individual is being treated for life-threatening emergency. The individual has already been screened or treated for hepatitis C before in the past. Or that individual is unable to consent for hepatitis C screening.

So it's clear that hepatitis C really imposes a significant worldwide burden with 130 to 150 million people infected worldwide with hepatitis C. In addition, there are three to four million additional infections every year. And approximately 3/4 of a million people will die from the complications of hepatitis C. But the impact of that is still fewer than that of hepatitis B, which 240 million, approximately a quarter million people in the world are infected with hepatitis B and will suffer from their complications.

In addition, there's a significant burden within the United States. And about 80% of what we see in the United States will be genotype 1, followed by genotype 2 and 3, which are also frequently seen. The drug choice, the efficacy, and the duration will depend on the genotype and the subtype that you identify. And when we talk about having hepatitis C, we're really talking about someone who screens antibody positive and has confirmed viremia. So actually has present virus in the blood.

Despite the fact that we're able to estimate that about 3.5 million people in the United States have hepatitis C, it's probably a gross underestimation. And a lot of people have said probably up to six million people in the United States are truly infected with hepatitis C. This is because, originally, those estimations came from the NHANES data. And as we know about the NHANES data, unfortunately it does not account for the high-risk populations which hepatitis C affect. And that includes the incarcerated population and the homeless population. So about 45% to 60% of people who are infected with hepatitis C in the United States are unaware. In addition, there are about 360 to 800,000 people who are homeless or incarcerated who also account for probably the gross underestimation of the number.

So who should we really be screening? So what I would like you to come away with are two or three things. One, again, hepatitis C antibody positivity is just the first screening modality. The diagnostic test really is to go and confirm viremia in the blood. The second issue is that, for primary care physicians, there are two cohorts that are very important to screen. The first one we already talked about which has been mandated by the state of Pennsylvania, which is the Baby boomer population, those born between 1945 and 1965. And then the risk factor-based population.

And that risk factor-based population are those people who are past or current drug users, those people who received a blood transfusion before we screened for hepatitis C in the blood population before 1992, patients who are on long-term dialysis, those people born to a HCV-infected mother, the incarcerated or previously incarcerated, those people who participate in intranasal drug use. And this was a huge issue because a lot of people didn't think that intranasal cocaine or the use of other intranasal drugs conferred a risk for hepatitis C. But that's been clearly borne out in the literature. Those people getting unregulated tattoos. You're 16. You're in the basement getting a tattoo by your cousin. Those people need to be screened. And then anybody who's had percutaneous exposures before in the past. So anyone who reports to you that they've had a needle stick in the past should actually be screened.

When we talk about burden, what are we really talking about? When you have to quantify the burden of hepatitis C in our population, it's fairly immense. Hepatitis C is the leading cause for transplantation in the United States. 1% to 5% of those people with hepatitis C will eventually die of one of the complications of hepatitis C. And the cost to the medical system is estimated at about $6.5 billion in 2012 dollars. And that is going to rise to approximately $9.1 billion in 2024.

When we also think about Hepatitis C, we should think of this as a significantly life shortening disease. Over 70% of those people who have Hepatitis C-related death, that will occur somewhere in between the age of 45 to 65, with the median age being about 57. So this is about 20 years taken off your life for the average person who's going to die or succumb to hepatitis C-related deaths.

So what is the natural history? A lot of people come to us and are very, very scared when they find out for the first time that they have hepatitis C. And the first thing that I can tell patients to try to encourage them is that the long-term side effects of Hepatitis C happens over decades. So if you know that you were using five years ago, and you may have been infected during that time period, the likelihood that you have a significant amount of fibrosis is fairly low. And probably only exception to that sometimes is genotype 3, which has been borne out in the literature to have an advanced fibrosis rate.

So when we talk about acute hepatitis C, we're talking about people that we may see in the hospital with jaundice. Remember, most of these people will not be identified. They will be asymptomatic when they acquire hepatitis C. It is a pearl to remember that those people who are symptomatic have more likelihood of clearing the virus spontaneously and by themselves, and typically don't need treatment. So acute hepatitis C, 80% of those patients will go on to develop chronic infection. Of that 80%, 20% of those will go on to develop cirrhosis. Even in the absence of cirrhosis, in chronic hepatitis approximately 1% per year of those patients-- again, in the absence of cirrhosis-- will go on to develop HCC.

In addition, in the cirrhotic population, 1% to 4% will develop HCC as a complication. And an additional 5% will develop decompensating symptoms, meaning a variceal bleed, the presence of ascites, or hepatic encephalopathy, per year within that population. So again, it's comforting to patients to know if they acquired hepatitis C within the last 20 years, the likelihood that they're going to have significant fibrosis may be fairly low. And that is what has really driven hepatitis C treatment thus far, the amount of fibrosis that people have.

So what we hope to do is we hope to actually halt disease progression. So when we talk about the presence of hepatitis C, we're talking about going from normal liver parenchyma through the stages of chronic hepatitis, cirrhosis, and then the presence of end-stage liver disease, which we talked about the decompensating symptoms in addition to the possibility of developing HCC. What we hope to be able to do is actually remove the end portion of this natural history, and take those patients who have chronic hepatitis and actually revert them to normal liver parenchyma over time, or at least halt them at the stage of fibrosis that they're currently in through the treatment of hepatitis C.

So that brings us back, again, to these two cohorts and making sure these people receive screening. And again, if you can concentrate on these things when people come to your office, you know who needs to be screened. As a quick tool to remember, if you're talking to people about colorectal cancer screening, you should also be talking to them about HCV screening. The youngest people in the birth cohort are about 51 or 52. So those people will need to be screened for hepatitis C. The reason why they're being screened is because this population has about five times as much hepatitis C as any other population. They also account for 80% of the people who have Hepatitis C in the country. So it's very, very important that these people be screened.

The reason why screening has been so important, and I think why the PA General Assembly passed the original Act 87 is that we know that diagnosis and awareness is key to bringing people all the way to achievement of SVR. And sustained viral response is something that we'll talk about later on in the talk. So 79% of the people with chronic hepatitis C in the United States are genotype 1. Approximately 50% of those patients know that they actually have the virus. 43% have been referred or linked to care. 16% prescribed medication. And only 9% of that population has achieved sustained viral response. So we have a long way to go. Again, this data is from 2003 to 2013, before the direct acting antivirals became available. But nonetheless, this is still a huge problem.

So again, hepatitis C care has rapidly evolved over the last 25 years. It was in 1989 that we realized non-A, non-B hepatitis was hepatitis C. And then in 1992 where we began to eliminate hepatitis C from the blood population. And this is why those people who were transfused before 1992 are in the high-risk factor cohort. And now in 2016, we're close to being able to cure just about any genotype across the board with one-pill, once-a-day therapy for hepatitis C. So as far as evolution in a disease process, this is pretty remarkable. Less than one generation. And we've essentially cured something that plagues a good part of our population.

So this is just to state that many of you may be aware that in the late 1980s, we were talking about interferon monotherapy for a year to a year and a half. And we were quoting the patients that really only one in 10 to one in four patients would be cured of their disease at that point. In 2014, we progressed to treating with interferon, Ribavirin, and protease inhibitors. And that provided somewhere between a 60% to 75% cure rate. And now we're at the point in 2016 where we're really talking about-- 100% percent cure is really the standard for any genotypic treatment at this point. So we've truly evolved, I think, over the last 25 years in regards to treating hepatitis C and what we've seen.

So let's talk about what cure really means in this population. When we talk about cure and hepatitis C, we are talking about something that we call in hepatology SVR12. And that means sustained virologic response 12 weeks after the completion of therapy. So we're talking about treating most people for 8 to 12 weeks with most of the medications that are on the market. And then three months after that, the absence of virus in the blood really is what we see as conferring cure to those patients. And this has, again, been looked at in the literature. And for years after looking at many of the therapies that are available now, only less than 1% of the population who achieves SVR12 goes on to viral relapse. So you can with a lot of confidence after you have actually treated someone for hepatitis C with 12 weeks of therapy, check them for virus 12 weeks later. You can pretty confidently say that you're at less than 1% risk of having viral relapse if you achieve that goal.

The secondary goals really are preventing progression to cirrhosis and the incidence of HCC, reducing the need for liver transplantation in the United States-- and as I mentioned in one of the previous slides, hepatitis C is the number one indication-- hepatitis C cirrhosis is the number one indication for liver transplantation in the United States. And then lastly, to improve and enhance survival within the population. And within the interferon domain, prior to us treating with the direct acting antivirals, when we look at all-cause mortality here, in the kind of right-lower quadrant here, we can see those people who have a sustained viral response have a much, much lower all-cause mortality than those who do not accomplish this goal.

What wasn't exactly clear to us was that SVR didn't only confer improvement in long-term outcomes in regards to liver disease, but also conferred some benefit in regards to other diseases. So when you look at these lines, the blue line is those people who did not achieve SVR. The red line is those people who were HCV positive and achieved SVR. And the green line are those people who were hepatitis C negative to begin with. And what you can see from each of these graphs in regards to hepatic disease, extrahepatic disease, liver cancer, and chronic liver disease and cirrhosis, is that those people who achieve SVR essentially travel along the line of those people who are hepatitis C negative.

And that's pretty remarkable. And when we say extrahepatic disease, we're talking about things such as renal failure, lymphoma, etc. Things that have been obviously linked hepatitis C before in the past. But you're talking about conferring long term improve outcomes in many organ systems when you talk about curing hepatitis C. If you cure someone of hepatitis C, you should really pat yourself on the back in regards to improving long-term outcomes and really having affected that person's long-term outcome.

So then we get into kind of the treatment options. And this is a very, very complex ever-changing system. But there are three major classes of medications that we use currently to treat hepatitis C. Those three classes of medications are the protease inhibitors-- and you all probably remember the telaprevir, boceprevir, time period. And not so long ago, we were also treating with simeprevir. The NS5A inhibitors, which typically end in asvir, which include declatasvir, ledipasvir, ombitasvir, many of the medications that we use today. And then lastly, the polymerase inhibitors that normally end in buvir, which include sofosbuvir, which is essentially the backbone of most of the medication, the combinations that we use today. And then the non-nucleoside nucleotide inhibitors, which include desabuvir.

The classes of antiviral medications and why they work so well are based on the combination of their antiviral effect and their resistance barrier. What you want, the optimal drug, is one that obviously has a very, very high antiviral effect and has a high resistance barrier. And the best class of drug for that is really the NS5Bs. And this is why you see sofosbuvir as the backbone in many of the medication combinations that we use today. In addition to that, the NS3 protease inhibitors have a very high antiviral effect and a moderate resistance barrier. And the other medications, the NS5Bs and the NS5A inhibitors, also have a pretty potent antiviral effect, but a very, very low barrier to resistance. And sometimes that makes them less than optimal in regards to treatment.

So there's no way for me to go over all of the AASLD, our national liver disease guidelines, in regards to the treatment in genotype 1 through 6 for treatment naive patients. I just put this up here so that you know there are multiple combinations. Many of those combinations involve 12 weeks of therapy. Which is remarkable, because we came from 72 weeks of monotherapy to 12 weeks of therapy. And we came from a point where we were at 10% to 25% cure to a place now where we're at a 95% chance of cure, particularly in those that are treatment naive and do not have cirrhosis.

These are really the guidelines for those who are genotype 2 through 6. Also treatment naive with and without cirrhosis. And again, these slides are just to say that we are able to provide cure in most of these patients despite the presence of cirrhosis.

So this is something that's very important to me, and I think is critical to say here and at this point, which is it's very, very important that we are all able to identify special populations. And there's one special population that's not listed here that I'll talk about at the end, that I'm fairly concerned about as hepatitis C treatment moves from subspecialty care into the primary care domain. So the special populations that we typically talk about are decompensated cirrhosis. Again, those patients who have some sign of decompensation, whether it be variceal bleeding, encephalopathy, or ascites. The post-transplant patient. So remember, 100% of people who have hepatitis C going into transplantation with active virus will have recurrent virus in their graft. And those patients should be seeing, obviously, a transplant hepatologist, particularly because of some of the interactions between tacrolimus and sirolimus and the current medications.

Another special population is HIV and hepatitis C co-infected population. And again, to be aware of the DTI interactions with many of the medications that we use. Again, in our domain many of these people are taken care of by our infectious disease colleagues. And in the case of post-transplant patients, the transplant hepatologist. But many times the HIV medications sometimes need to be switched around, particularly for the population of patients who have had HIV for a prolonged period of time and are on some of the older medications.

Another special population is the chronic kidney disease population. So up until probably the last six months there were no great medications for those patients who are currently on dialysis. Recently, there has been introduction of medications that can be used on dialysis. But again, because it's such a sensitive area and things need to be watched so closely, I really do suggest that, if you see patients with chronic kidney disease-- particularly those on dialysis or those with a creatine clearance less than 30-- that you send those patients to a hepatologist.

And then lastly, the treatment experienced population. And treatment experienced previously meant those people who were previously exposed to interferon in the past. But now that we are currently 18 months to two years into the direct acting antiviral therapies, this really means those people who have failed those therapies before in the past. And those people, I think, also should be referred.

The last group of people that I don't put here, because we typically don't talk about them as a special population, are those patients who are compensated cirrhotics. And the reason why I say that is because I feel like there is a chance that those patients can be missed in the future when I think care for hepatitis C will shift from the subspecialty care backwards to primary care. Again, these patients don't have ascites. They don't have a history of variceal bleed. They don't have any hepatic encephalopathy. So it's very, very important to kind of understand some of the nuances that you may see in these population. Effective, very low normal platelets. An albumin that may be just slightly low. Some of the things that-- some of the small nuances. And if you're at all concerned or you don't know, it's OK to biopsy these patients, even during this time period where noninvasive measures are coming to be a little bit more popular. And we'll talk about some of those noninvasive measures later on in the talk.

So just recently in the last two months or so, the AASLD guidelines actually changed and started to say that we need to test people for hepatitis B prior to initiating treatment for hepatitis C. And the reason for this is that there have actually been case reports of fulminant hepatitis B in the setting of treatment with the DDA therapies. Hepatitis B DNA should be ordered when you see someone who's hepatitis B surface antigen positive to suggest that patient might have active disease. Patients meeting the criteria for hepatitis B therapy, which is fairly nuanced-- and again, I would say people who are coinfected with B and C probably should be referred to a subspecialty center. But if you meet criteria for hepatitis B therapy, you should be initiated on that therapy prior to starting the new DAA medications.

In addition, those people who do not meet criteria for hepatitis B treatment but have low level viremia in regards to hepatitis B should also be closely monitored. And I would suggest that these patients probably need to have labs drawn, both AST, ALT, and the level of HBV DNA, at least every three months. In the absence of hepatitis C, we would normally check those enzymes every three to six months in this population.

In addition, there is one caveat, which is those people who have an isolated hepatitis B core antibody positivity-- meaning, typically, that the patient has been exposed but has spontaneously cured hepatitis B on their own-- are not at zero risk for reactivation. And in these patients it's also probably the better part of valor to go on and monitor for reactivation during the course of therapy. Remember, the course of therapy is relatively short, with just 12 weeks of therapy. So to bring the patient in either monthly or every six weeks in order to monitor both their hepatitis B viral levels in addition to their AST and ALT is probably very reasonable.

This is something that's obviously near and dear to my heart. We had a patient call our practice last week saying, I'm going to commit suicide. My hepatitis C antibody is positive. And I supposedly cleared the virus. So after SVR, there's really no routine indication for rechecking the hepatitis C RNA level. But there's certainly zero indication under any circumstance to check somebody's HCV antibody. The anti-body is always going to be positive. So to recheck that and have that rechecked can be very disturbing to patients. Because they don't realize that the antibody will be forever present, despite the fact that the patient has accomplished cure.

The European guidelines suggest that confirming SVR 24 and 48 weeks probably is not unreasonable. We did just say that the marker of cure is SVR 12. So the absence of viremia at 12 weeks really confers a 99% chance that you'll be virus negative for the rest of your life unless you're reinfected. But given that many of these medications are new and just on the market for the last six to 12 months, I still check SVR one year after the completion of therapy, just to make sure patients have not relapsed.

It's also reasonable to continue to check liver enzymes on patients. And if they become abnormal, to recheck for virus in the blood. Just remember that if you treat someone for hepatitis C, and they clear, they accomplish SVR 12, concomitant liver disease with either nonalcoholic fatty liver disease or alcoholic liver disease is fairly common in this population. So you shouldn't let that go. And if you find those concomitant diseases, I think it's also reasonable to make sure that those patients see hepatology the future.

And again, as I emphasized before, there's no reason whatsoever to recheck the hepatitis C antibody under any circumstances. And it's important, I think, to advise patients that if this is checked, it will be positive, essentially for the rest of their life. There are some circumstances under which hepatitis C antibody can disappear, but more so tends to happen in the immunosuppressed population in the post-transplant population.

So I do want to talk a little bit about fibrosis and post-treatment considerations. So we can cure hepatitis C in this day and age. You can have someone come into your office, no matter the genotype, and you can say, there are options for you for cure. The issues really are that in this day and age we can't provide everyone with cure because the medications tend to be so expensive. So if you see my name, and you sent a patient to me with hepatitis C, and I send them back to you with no treatment, it's not because I'm negligent. But because many insurance companies will not pay for the level of fibrosis that we see in a great majority of our patients, which is typically F0 to F2. And we're going to talk a little bit about fibrosis. And then talk a little bit about, when we do treat patients, what are those post-treatment considerations that we need to make sure we keep in mind.

So what's seen underneath the microscope is really, really important. Because many of you probably get across your desk things from our pathologist. And the question is, what are they really seeing? And how does this affect the patient and their options for treatment?

So as you can see here, this is kind of a cartoon of the liver. These represent the lobule or the hepatocytes. And in between the lobule and the hepatocytes, we see the portal triad, which really typically contains the biliary tree, the hepatic artery, and the portal vein.

When we start to see fibrous expansion within the portal tract-- and you'll see something called periportal fibrosis that may be mild-- that is really considered F1 fibrosis. And it's a fairly mild fibrosis. An F0 and F1 is typically what we see in probably more than 50% of the patients that we see in our practice. When you start to get bridging fibrosis, which is something that you all probably remember from training, is when the fibrosis actually extends from the portal tract into the lobule. And you start to see these long bands of fibrous tracks across the hepatocyte. And that's really typically called F2 fibrosis.

Beyond this point is really where most people become eligible for therapy. And most patients may come into your office saying, I was told that I have stage 3 or early cirrhosis, some people call this. And this is really when you start to see bridging across many lobules. And this is fairly severe, and people who probably need to stay in therapy despite treatment. And then lastly, when you see severe bridging, you start to begin to form nodules. And this is really what we see when we see cirrhosis. And this can even start to be appreciated-- the nodular surface of the liver-- even on radiographic films when we see patients really late into the course of therapy.

It's important to realize, though, that, though we still consider liver biopsy the gold standard of fibrosis scoring, there are many noninvasive measures of fibrosis out there. I know that if any of you work for the VA, VA likes to use FIB-4. There are also FibroTests, something called FibroTest. There's also something called FibroSure. And these are noninvasive measures. The most important thing I can say about these noninvasive measures are, garbage in, garbage out. These tests should be used, and can be used, in the regular healthy population that's typically coming into your clinic on a daily basis.

But when you start to use these in kind of people who have acute inflammation-- for example, I can give you one example. I was asked to see a heart transplant candidate. And the man had an LVAD. And he also had hepatitis C. And we were asked to grade his fibrosis. Tell us whether or not he has cirrhosis, and he's appropriate for heart transplantation. One of my colleagues had suggested-- not a liver doctor-- but had suggested, well, maybe we can use one of the noninvasive tests. And one of the noninvasive tests was sent. That noninvasive test said that he had F4 fibrosis.

Unfortunately, the noninvasive test that he got sent had haptoglobin-- which is the FibroTest-- had haptoglobin as one of his measures. You could imagine in someone with an LVAD who's constantly up against the shearing forces, against their red blood cells, that the haptoglobin is going to be excessively high. So unfortunately, in this patient, we ended up having to do a liver biopsy while the man was on an LVAD, stop his anti-coagulation, and tried to prove to the heart transplant team that he was a candidate.

This was not at this institution. Another institution. That man went on to have hemobilia and ended up dying as a result of hemobilia. But again, it's just the idea that you can only use these when they make sense. And in somebody who's acutely inflamed for some reason, these may not be the best measures. There are some other things that you can use that may be better measures of fibrosis in those particular cases that may tell you a little bit more.

The most common one that we use in the United States-- and you may see this come across from UPMC, because we have one of these-- is transient elastography. And what happens is we typically tell our patients, this is similar to ultrasound. You get jelly placed over the liver. There's a probe placed along the liver edge. Sound waves are sent out and then sent back to the probe. And that gives us some idea of how stiff the liver is. And for us, stiffness is equivalent to scar or fibrosis. And then we get a number consistent in kilopascals of stiffness. And we can translate that into the typical fibrosis scores that we're used to seeing of F0 to F4.

The most critical marker for these patients, if you tend to see a FibroScan that comes back to your desk, is 9.5. Because that's really the cutoff in between F2 and F3. So if you see a FibroScan that you look and scan documents on Epic, and you see a FibroScan, and the kilopascals are greater than 9.5, you can typically-- you should typically realize that your patient has an advanced level of fibrosis. And those are going to be the people that are most likely to be eligible for therapy in the United States currently.

So you have a patient. You get a hep C antibody that's positive. You confirm viremia in that patient. They have active disease. You go on to treat that patient with 12 weeks of therapy. You confirm the absence of viremia 12 weeks after the completion of therapy. They've achieved SVR. You can tell that patient now you have less than 1% chance of ever relapsing at this point.

But what do you do with that patient? Is that patient done? Are they never to see a doctor again in regards to their hepatitis C? And this is really critical. Because this is new information that we're starting to understand from this population of patients.

Some of these patients are not to be discharged from therapy just because they don't have cirrhosis. So when you see these patients in the post-treatment phase, it's really important to go back to their pre-fibrosis score. So what did they have on the FibroSure, or the FibroTest, the FibroScan, or the liver biopsy? When you look at that level of fibrosis, F0, F1, F3, it's important to divide that population into the F0, F2, meaning early fibrosis group, and late fibrosis group, F3 to F4. Because those patients are treated differently.

Those patients that have early fibrosis, those patients in this group, F0 to F2, those patients can typically be discharged from care. And you can fairly confidently say, you will not have any long term manifestations of liver disease or HCV affecting other systems in your body. But those patients with advanced fibrosis, clearly F4, cirrhotics, need to be followed up every six months. And those with F3, which we typically think of not being cirrhotic but having severe fibrosis, we now understand need to have long-term follow up. So those people should not be discharged from therapy.

So if you've cured people in your practice, and you realize now, OK, they had F3 fibrosis, those people should be brought back in or at least referred to a hepatologist for long-term follow up. Because we are starting to realize that even those patients with early fibrosis will, again, manifest with some of the decompensating symptoms down the line.

So post-SVR with early fibrosis. What should we do in those patients? Again, these are patients with F0 to F2. You should consider annual liver tests and CBC in these patients. And the reason for that is that, again, concomitant disease with fatty liver disease and alcoholic liver disease is very high in this population.

There is no indication for HCC surveillance. The guidelines of the National Liver Society say that HCC surveillance is typically ultrasound every six months to make sure there's no HCC, in addition to alpha-fetoprotein. And there's no reason to do that in this early fibrosis population. There is no indication for variceal screening. The likelihood that you're going to have early fibrosis and then go on to develop portal hypertension and variceal hemorrhage is very, very low in this population. But mentioned before, it's imperative to stay vigilant about the possible concomitant disease processes that happen in these patients, including fatty liver disease, alcohol mediated disease, and hepatitis B, which also falls along the same lines.

So what do you do in that advanced fibrosis population, those people who on one of the either noninvasive tests or a liver biopsy have F3 or F4 fibrosis? Those people with F4 should have a hepatologist. One of the big things for people with cirrhosis that actually decreases mortality is every six month follow up with a subspecialist. And we know that from the literature. In addition, even in those people with F3, or what we typically call early cirrhosis, those people should be monitored for decompensating symptoms, the presence of ascites on clinical exam, variceal hemorrhage, and even sometimes subclinical encephalopathy.

In addition, you should perform screening for varices with an upper endoscopy, and for HCC. Because what we know now is that the HCC risk after sustained virologic response lasts for at least eight years. In addition, I would suggest that those people with F3 and F4 fibrosis on every visit to you have a MELD score calculated. And that's the model of end-stage liver disease, which includes the bilirubin, creatine, and INR. And recently added on to that was the serum sodium. And that will give you some idea of how severe the liver disease is.

Just as kind of a checkpoint, your MELD-- you have one, obviously-- is typically six if you don't have liver disease. The upper end of normal-- we don't calculate MELD beyond 40. So if somebody starts to creep up to a MELD of greater than 15, those people should really be referred to a liver transplant center. Because those patients should probably be listed based on our guidelines for transplantation, just in case they get acutely ill are in need of a liver at some point.

You should advocate for strict alcohol sobriety. This is probably one of the toughest things I do in clinic. Sometimes I feel like I'm counseling more than anything else. Tell people that just because they're cured of their hepatitis C, overconsumption of alcohol can still be an issue, particularly for those people who already have fibrosis. This is just kind of adding fuel to a fire and will probably enhance the rate at which they develop fibrosis in the future.

And then lastly, in regards to nonalcoholic fatty liver disease, if it is present trying to get those people to lower their BMI. And just as a caveat, the only thing that's been shown to decrease the inflammation in the liver in the presence of nonalcoholic fatty liver disease, really is loss of at least 10% of your body weight. That's when we start to see the AST, ALT actually change. And histologically, when you look at the liver underneath the microscope, you actually see improvement in the amount of inflammation in the liver in those patients.

So what has driven this idea of splitting the cohort of patients who have hepatitis C into an early fibrosis cohort and a late fibrosis cohort really is the idea that, in post-SVR monitoring, patients still had a significant recurrence of hepatocellular carcinoma despite SVR. Our typical thinking as hepatologists was like, when we cure virus, we actually decrease the rate at which HCC both occurs and recurs. But it's coming out from a lot of the European literature that people despite SVR-- and sometimes maybe even because of SVR-- are actually having an increased rate of recurrence of their HCC. So in most of the literature it is now theorized that SVR, sustained viral response, leads to possibly decreased immune activity in the liver, and perhaps is actually conferring an oncogenic potential that's actually increased in these patients, because the immune system is not drawn to the liver as heavily as it is in the presence of HCV.

So the question is, after all I've said, are you still hopeful about the future? I am. And the reason is because my colleagues here at the University of Pittsburgh actually looked at modeling HCV. And the truth is that under optimal and ideal circumstances, if we screened properly, if we were able to provide people with greater than 90% cure rates-- and they actually use an ideal 80-- I think they use 80% cure rate in these patients-- we could make hepatitis C a rare disease by 2036. And that's fairly phenomenal. We're talking about 6 million people with hepatitis C. And we're talking about having less than one in 1500 people infected with hepatitis C by 2036.

We have completely revolutionized hepatitis C treatment in the last 25 years. By going from the point where we were calling hepatitis C non-A, non-b, to being at a point were greater than 95% of people with hepatitis C can be cured of their disease. And in the next 25 years, we have the chance of basically making this a rare disease. And that's, I think, pretty phenomenal.

But this always kind of comes up. Cost may be prohibitive to that progress. And when you look at how much these regimens cost, it's pretty phenomenal. We're talking about spending between $50,000 and $150,000 on full regimens for the treatment of hepatitis C. And that's pretty remarkable, and is the reason why you may send patients to a hepatologist and get them back and they haven't been treated. Because really what is driving the absence of treatment in these populations is really insurance. Hopefully there's nobody in the insurance domain here. But really it does prevent us from treating patients.

And currently we're at the point where F2 and above are pretty-- F3 and F4 are pretty easy to treat. If you're Medicare, F2 is pretty easy to treat. And in some states it's easy to treat Medicare and Medicaid patients regardless of fibrosis. But really what's going to change this is making these medications easy, accessible, affordable. And what's going to move hepatitis C treatment in the primary care domain is that eventually there will be one-pill, once-a-day, pan-genotypic therapy for all of these patients.

So the truth is the only thing that we'll be doing in the future is like walking through the village. We'll just be saying, hepatitis C antibody positive. Great. Confirmed viremia. Great. We can treat with this medication. We don't care about viral load. We don't care about genotype. We don't care about subtype. The only thing we care about is the presence of viremia. And eventually we'll be able to just pick that medication off the shelf and treat, hopefully, for 8 to 12 weeks-- in some cases, people are even talking about four weeks of therapy-- and essentially curing hepatitis C in the future.

So in conclusion, I hope that you've taken away from the talk that the cure of hepatitis C is certainly going to change and already has changed the face of medicine, hepatology, and transplant surgery. In addition, the most important part of the treatment paradigm and continuum is screening and identification. People can't get treated for something that they don't know that they have. So catching those Baby boomers and catching those people at high risk for disease are critical.

The wave of the future, as I just said, is pan-genotypic treatment with one pill, once a day, or less. There are even people who are looking at injectables in Europe, where you get injected once per week, or even less frequently. And still cure rates seem to be fairly high. And then lastly, those patients who have hepatitis C and advanced fibrosis belong to a special group of patients who, despite how easy it is to treat hepatitis C in the future, should probably be referred to a subspecialty care.