

Hepatitis C: Update on Testing and Treatment

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Karla Thornton:

Thank you all for inviting me. I'm very excited to be here today. My name is Karla Thornton. I'm a professor in the Division of Infectious Diseases here at the University of New Mexico in Albuquerque. And I've been involved in the world of hepatitis C for a long time, for about 20 years. And I find that it's very exciting right now, so I have a lot of interesting things to share with you, with everyone, and I hope that I can provide some useful information.

I'm also one of the Associate Directors of Project ECHO, which I'm going to talk a little bit about at the end of my presentation, which is a project where we actually train other people how to take care of complex diseases in the primary care setting. And one of the ways this project started is with hepatitis C. So I'll talk a little bit more about that. But I really appreciate the invitation to talk to you today. And I have a lot of information to share, but I'm going to definitely try to leave at least 10 minutes at the end of the session so that you guys can ask questions as well.

So here are the other learning objectives. They all sort of, these in combination with what you saw earlier. So there's a lot of information I want to talk about. So as many of you probably know, hepatitis C is a really huge problem in the United States and globally. There are about 170 million persons with hepatitis C infection worldwide.

In the United States, you know, the epidemiology of hepatitis C is not great, but what we think is there are at least about 3.2 million people who are antibody positive in the United States. This epidemiology was -- the numbers came from the National Health and Nutrition Examination Survey, which is a CDC funded survey where people are contacted, they choose a sample of people to try to represent the U.S. population. They're contacted by telephone and someone comes to where they live and interviews them and draws their blood.

So this survey, unfortunately, leaves out people who are incarcerated, people who are homeless, people who are disenfranchised. So we think that the prevalence of hepatitis C is actually much higher than the 3.2 million.

We know that the prevalence of hepatitis C in certain populations is very high. This is an old slide but it's still very useful. I think if you look up at, like, incarcerated individuals, 16% to 40% of people who are incarcerated in the United States have hepatitis C; HIV-infected persons about 25%; injection drug users of course have extremely high prevalence of hepatitis C in that population, because this is the way the hepatitis C is transmitted through blood; alcoholics have a high prevalence of hepatitis C. One of the most interesting things is even people who live below the poverty level, independent of any other factor also have a prevalence of hepatitis C.

What we also know from the NHANES data is that people who were born between the years of 1945 and 1965 in the U.S. population have the highest prevalence of any age group of hepatitis C as well.

I just show this slide from the CDC about American Indian and Alaska Native. We really don't know much about the prevalence in this particular population. This is from the CDC. They do try to look at

acute infection with hepatitis C. As you can see, American Indians and Alaska Natives have a higher rate of acute infection with hepatitis C than other populations, which is really interesting, and I don't think anybody really knows exactly what this is about. What we don't know is really what the prevalence is in this particular population.

How is hepatitis C spread? Hepatitis C is spread blood to blood. That's why injection drug use is the most common way still that people obtain, people get hepatitis C in United States. It's the leading cause and the leading transmission risk factor in the United States still. Before 1992, before we were testing our blood supply for hepatitis C, a lot of people did get hepatitis C through blood transfusion. At that time, it was actually called, "Transfusion-Related Hepatitis."

You can also get hepatitis C through percutaneous injuries like in the workplace getting stuck by a needle, things like that. But again, that doesn't happen incredibly commonly. We also know that hepatitis C is spread through sexual contact, although it is not very common. It's very inefficiently spread sexually, however, it does occur. As you can see on this pie chart from the CDC, that they estimate about 15% of hepatitis C transmission is through sexual contact. And the reason that is, is because sex is a very common behavior, so there's definitely transmission that occurs.

There's more transmission in the men who have sex with men population of hepatitis C. And there have been many outbreaks now that have been documented of sexual transmission of hepatitis C in that population. There is also some mother to child transmission again very low rate, it's rare, about 1.7% up to 4%. It's more commonly transmitted from mother to child in persons who have HIV.

One thing about hepatitis C transmission is there are many patients who do not know that they were ever exposed. It's interesting because a lot -- I'll talk a little bit more about what's called the birth cohort of that population of people who were born between '45 and '65. But a lot of people got exposed-- of that age group got exposed, they may have injected drugs once and really not thought about it again and they got exposed to hepatitis C and never knew it.

There's certainly some transmission that we really don't understand. There are some low level transmissions from sharing razors, sharing other, toothbrushes, other household, what we call personal care items. There have been a couple of outbreaks certainly in patients in nursing homes where using lancets to check people's sugar for diabetes actually transmitted the virus as well. So there's transmission that goes on like that, that sometimes people have no idea that they ever got exposed. There are a lot of people, honestly, that the source of hep C infection cannot be determined.

So the recommendations for people who live in households with somebody for hepatitis C is to not share razors, toothbrushes or needles of any kind, just because there can be very, very small microscopic amounts of blood in these personal care items that can transmit hepatitis C.

There still is no special precaution for sexual partners with discordant hepatitis C status; meaning, one patient has hepatitis C or one person has hepatitis C and one doesn't. There's not a recommendation to use barrier contraception in that setting in the monogamous couple, and no other precautions are necessary.

So who should be screened for hepatitis C? I know this is a really busy slide. This is what sort of the guidance that we had before very recently. So in 2009, the American Association for the Study of Liver Disease, which is what AASLD stands for, put out these guidelines. So, and it really reflects what we talked about with the routes of transmission. So anybody who had recent or past injection drug use, even if they used one time in their life. Anybody who had received a transfusion or transplant before July of 1992. And then this other sort of basket of people, groups with high hepatitis C prevalence. So persons who have HIV, people who are on dialysis, unexplained AST/ALT elevations, children born to women who are infected with hepatitis C, and healthcare personnel who would be potentially exposed

through needle injury and mucosal exposure with hepatitis C infected blood, and also current sexual partners of individuals infected with hepatitis C.

This slide I think is very informative. And we know, this is from the NHANES data as well, that with what we were sort of, how the way that we are testing in the past, which is called, “risk-based testing”, people weren’t getting tested. So we know that at least half of the people in United States who have hepatitis C are not aware of their infection. The CDC actually estimated that it’s more like 75%. So, we really, most people that have hep C in the United States have not been diagnosed.

Because of this, the CDC was really trying to figure out how can we get these people diagnosed, and what they focused on was this large population in the United States of people who were born between 1945 and 1965, which I’m going to refer to at this point as, it’s called the “birth cohort”. The rationale for trying to really get out this population was that they think that 45% to 85% of people who have hep C and are undiagnosed are in this age group. We know that, like I spoke of earlier, risk-based strategies to test are very inefficient, they didn’t work, and we learned that from HIV, actually. We stopped doing that with HIV quite some time ago, because people in the primary care setting where most patients that are getting tested really don’t have the time and they don’t ask all of these questions to try to assess somebody’s risk. Now, we believe that about 75% of chronic hepatitis C infections are in persons born between 1945 and 1965.

So the CDC came out with this recommendation a couple of years ago now, August 17th of 2012, that anyone born between the years of 1945 and 1965 should be tested for hepatitis C once. Unless they had ongoing risk factors and then they of course should be tested more often.

In June 24th of 2013, so almost a year after that, the USPSTF made this a Grade B recommendation, meaning that it will be supported by insurance companies and it’s co-pay support according to the ACA. Again, any adults born between 1945 and 65 should be tested at least once, and adults at high risk should continue to get tested as well.

In terms of IHS, hepatitis C screening – and I’ve been working with Brigg Reilley who can maybe comment on this at the end because this is not my area of expertise. But he did let me know that the IHS hep C screening has been a developmental GPR measure since 2011. Screening rates have tripled to approximately 30% of birth cohort screening in federal sites. And the leading service units have already completed screening greater than 50% of their population, their baby boomer or birth cohort population screened.

The leading sites do one or more of the following, either use a hepatitis C screening reminder in the EHR. I know that’s being used in multiple sites right now, or a standing protocol or order for hepatitis C screening. And they delegate screening away from providers. Which is a really useful way to do this, because again, in a setting where you’re talking to a patient about multiple things at one time, that often this will fall to the bottom of the list, and actually not get done. So if you delegate it away from the person who’s doing the primary care, then often it will get done more frequently. And I’ll let him speak to this again at the end of the presentation.

So, this is from the CDC as well, the recommended testing sequence for identifying current hepatitis C virus infection. And many of you may know this, but I think it’s important to go over because there are some changes certainly in the last decade about how hepatitis C screening has been done. When you have a patient, who you test first of course for the antibody to hepatitis C. If there’s no antibody to hepatitis C, then you stop. Basically, that person has never been exposed to the virus. If the antibody is positive or reactive, then you have to do a confirmatory test. And unfortunately, there has been a lot of data looking at what happens when people get tested for hepatitis C antibody and they never have a follow-up of RNA test or a viral load. So they really never know whether they have chronic hepatitis C infection.

In the past, and some of you may remember this, there was something called the “hepatitis C RIBA”. This was a test that was done after the initial antibody test, but it was also a serologic antibody test. So it was really just to make sure that the first one was positive. We don’t do anything like that anymore, but we do still have to do a confirmatory test which is called the HCV RNA or viral load. So what this test does is it tests for the actual virus in the bloodstream.

So if you get a positive antibody, you test for the virus, and if that’s negative, that means that they have no current hepatitis C infection. Again, these people have an antibody, so they have been exposed to the virus before, but they do not have current infection or what we call chronic hepatitis C virus. If RNA is detected and then the person has current hepatitis C infection, and needs to be linked to care. We’ll talk about this at the end if people have questions, but you do have to have a confirmatory test to confirm that patients have chronic hepatitis C.

In terms of patients who have a positive hepatitis C RNA and an undetectable-- a positive antibody and an undetectable hepatitis C RNA, if the patient previously was treated, this indicates a cure. So there’s no need to continue to repeat the hepatitis C RNA testing. And this is sometimes a difficult concept for patients because we’ll treat them and they’re cured and they have no virus but their antibody is positive for life. So people will tell them who don’t know their history, “Oh, you have hepatitis C.” But they actually, again, they’ve gotten rid of the virus but they just still have the antibody test. Unfortunately, having the antibody to hepatitis C does not imply immunity to hepatitis C, so you can get re-infected, even if you’ve been treated and cured.

If somebody continues to have abnormal liver function tests even if their RNA is negative, then you need to evaluate them for other causes of liver disease and you also -- if you have concerns that they may have been infected recently, then you would repeat their hepatitis C RNA within the next six months to make sure that you just didn’t miss, that it was too early on to detect.

So I’m going to talk a little bit about the natural history or the progression of hepatitis C. So somebody gets infected and they have, as you could see on this slide, a normal liver. And over time, people develop chronic hepatitis, and ultimately, most people, if they have hepatitis C long enough, live long enough, will develop scarring of the liver or cirrhosis. The consequences of that are people are at risk for hepatocellular carcinoma or HCC, liver cancer, end stage liver disease, and death. As you can see from this timeline, this can take a long time. So a lot of people who have hepatitis C for years have no idea that they have it and they have no symptoms that they can relate to their hepatitis C. There are some things that increase the progression of disease pretty quickly and I’ll talk about those a little bit as well.

So what are the long-term consequences of untreated hepatitis C? Like I said, most people will develop -- eventually, if they don’t die from something else, they’ll develop problems with their liver. So this was on a paper that was published now a couple of years ago at this point, but a very, very important paper, that was published by David Rein, looking at if we don’t increase the number of patients that we treat for hepatitis C, what’s going to happen in terms of the numbers of people who develop end stage liver disease, cancer, things like that, and need liver transplants. As you can see on the left of the slide, we’re at the very beginning. We haven’t even really hit the point where this graph is starting to go up. So if we were to do nothing differently than what we’re doing right now, by 2030 we would have this mass number of people who are very ill from their hepatitis C. And a lot of what this reflects is that there’s this whole group of people, most of them baby boomers, who are getting older and older and had hepatitis C for a long time and are going to develop complications from it in the near future.

So, in terms of the, like I’ve mentioned, the progression of liver disease can be very long. But for some people, it can be a lot shorter. And for people who have HIV, for people who drink a lot of alcohol, have other things that are really affecting their liver, their progression can be relatively quick. It’s really unpredictable. And what I put in this slide is that it’s non-linear. So we really can’t predict, at this

moment, you have no cirrhosis, and 10 years from now, you're going to have cirrhosis. It's a very difficult thing to estimate in any individual patient.

There are some modifiable risk factors and they are important in the primary care setting to discuss with patients. So we know that one thing that's becoming a huge issue in terms of liver disease is what's called "fatty liver". So if people are overweight, then that in addition to hepatitis C can really increase the progression of liver disease. We know that diabetes itself, which I know a lot of you are very interested in, can cause liver disease to be worse and they need to have, people with hep C need very good diabetic control.

Alcohol is probably the number one thing that causes severe liver disease in and of itself but also in combination with hepatitis C is really, really detrimental to the liver. We know that there have been a couple of studies published that show that daily marijuana use or heavy marijuana use can actually cause fibrosis of the liver as well. So in our practice, we counsel about all of these things; help people try to lose weight, control their diabetes, of course decrease or stop the alcohol use and decrease or stop marijuana use.

The other thing that I really want to just talk briefly about is the fact that hepatitis C is not just a liver disease. I think in the past when people thought about hepatitis C and thought about who should get treatment and things like that, they really don't think about the hepatitis C affecting anything but the liver.

We know that there are some very common symptoms of hepatitis C that we see in the absence of cirrhosis. So it has been well-documented that hepatitis C can cause fatigue in and of itself. It can cause what we call impaired cognitive function or brain fog. We've seen many people who got their hepatitis C treated and after they were cured from the hepatitis C, really had a very dramatic change in the way that their cognitive function and their ability to really remember things. It's very interesting. There was a study published in the last six months about this particular issue and they had neurocognitive testing on people prior to treatment and after cure, and there was a dramatic difference in their memory and their ability to concentrate and things like that. We know that it causes arthralgia and myalgia and it's been strongly associated with depression as well.

We think that about 40% of patients who have hepatitis C will develop what we call extra hepatic manifestations, meaning a manifestation outside of the liver. They're often not clinically recognized and it's partly just because people aren't aware of these issues. And I think it's important to know that there are things to look for in hepatitis C patients that aren't just, that don't just have to do with their liver. And a lot of these patients who have extra hepatic manifestations don't have any evidence of actual liver disease.

The main extra hepatic manifestations, and I don't really have the time, this could be a whole lecture in itself. Hepatitis C can affect the kidneys. It can cause mainly a peripheral neuropathy, so pain in the hands and feet. There are some very particular dermatologic manifestations, I'll show you one of those, but there are actually many. It has been highly associated with diabetes, and people who have hepatitis C are at much higher risk for diabetes. We're learning more and more about this but there's a very close relationship with B-cell lymphoma and hepatitis C. So we're getting a lot of patients referred to us now from the Cancer Center who have B-cell lymphoma and hepatitis C. They're asking us to treat their hepatitis C prior to them being treated for lymphoma.

So this is just one, maybe some of you have seen this, it's called Porphyria Cutanea Tarda. It's a skin disease that causes these blistering, particularly on sun exposed areas. It's highly associated with hepatitis C. And when you treat the hepatitis C, this skin disease will go away.

I want to talk a little bit more in depth about diabetes because I know a lot of you are very interested in this. The risk of diabetes is increased by 70% compared to non-infected controls, with an odds ratio of

1.7, meaning again, people who have hep C are much more likely to have diabetes. And we know that successful hepatitis C treatment is associated with decrease in insulin resistance and reduction in incidence of diabetes as well.

Why does this happen? We don't know exactly, but there have been some interesting studies, and this one that I'm showing here, the brown on the right side of the slide, the brown staining of the islet cells itself is the actual hepatitis C virus. So we think that the virus itself can cause dysfunction of the cells where insulin is produced and released. We know that diabetes itself exacerbates the progression of liver disease, and it reduces the efficacy of hepatitis C treatment. And it also increases the risk of hepatocellular carcinoma or liver cancer, which is very interesting, again, not really that well understood but we do know that it increases the risk of cancer.

Patients with extra hepatic manifestations like this should actually be prioritized for treatment, and I'll talk about that when I'm talking about treatment. We know that successful treatment of hepatitis C reduces the risk of diabetes and of lymphoma, and we know that it also has an effect on vasculitis and kidney disease.

I'm going to switch over and talk a little bit about treatment because this is all the news as many of you have seen in the paper about the new hepatitis C treatments. This just shows, in 1991 is when they really started treating hepatitis C. Hepatitis C was discovered in 1989. So a couple of years after that, people started using Interferon alone to treat hepatitis C. And as you can see from the very low response rate or SVR which stands for Sustained Virologic Response, or cure, it didn't work basically. So, they started adding Ribavirin, a nucleoside analog which we still use in hepatitis C treatment, in 1998, and that increase the cure rate a little bit but not much. And we really didn't start getting high cure rates for hepatitis C until 2011 when the first -- we call the DAAs, or Direct Acting Antiviral, was introduced. At that point, the cure rate went up to about 70% in genotype one patients.

I'll talk about the far right in just a minute. I'll talk a lot more about these new drugs. So the first really exciting new drug to come out for hepatitis C came out a little over a year ago now. It has been out for about a little over a year, it's called, Sofosbuvir or Sovaldi. This is again a directly acting antiviral, meaning that it goes into, when the virus is replicating it will go in and terminate the chain of the virus replication. So it's called a polymerase inhibitor. It goes in and basically stops replication of the virus. It's a very, very potent drug and it works against all genotypes one through six. It's one pill, once a day itself, it has to be combined with other stuff, which I'll talk about in a second. It's very safe and well-tolerated, and it's extremely expensive. It was actually the most expensive drug to be released on the market, ever. So, one pill, once a day. It's about a 12-week course, so it's about a thousand dollars a pill.

This is the studies that got the FDA to approve this drug. They were very, very impressive. As you can see, over all of the genotypes, really above a 90% cure rate which has never been seen before in hepatitis C. And when you're looking on the left at the neutrino trial, at this point, Sofosbuvir or Sovaldi was being used in combination with Interferon still. So we weren't completely free of linterferon over the last year, but had very, very high cure rates for hepatitis C in the last year using this particular drug.

So like I said, in the last year, we've still been using Interferon for genotype one patients, and we were all waiting for this moment when we would not have to use Interferon anymore. And it's pretty much here at this point. This drug was released very recently, October 10th of 2014 called Ledipasvir/Sofosbuvir or Harvoni is the trade name for this drug. Again, this was released, it's a one pill once a day regimen for genotype one patients, who are the most common patients and had been historically the most difficult to treat. This drug can be used without Interferon, so we're really not using Interferon for any patients at this point since the release of this drug called Harvoni. Again, one tablet once a day with or without food, very well tolerated, has not been associated with a lot of side effects. Again, extremely expensive medication. This one is -- because it's a combination of two different drugs, it's over \$1,000 per pill, and the duration of treatment with this particular drug can be eight,

twelve, or twenty-four weeks. Of course, people who have very early liver disease and are healthy, have a low amount of virus in their blood stream can receive eight weeks, but other people have to receive at least 12 weeks of treatment.

Again, I know these slides are sort of, they're really just for almost the shock value, because if you look at the cure rates for these particular drugs, with or without Ribavirin, you can see that it's almost 100%. And this is again something that nobody has ever seen in this disease and it's extremely exciting for everybody who's been involved in hepatitis C for a long time. So this is a medication that you can give without Interferon, very easy to tolerate, and can actually get rid of the virus in most patients.

So the indications for use here, this just shows, as I've mentioned, the duration of treatment. In the past, when we used Interferon for genotype one patients, we would use it for up to generally a year, would be the minimum amount of time that a patient would have to be on treatment. And now we've gotten that down to 12 weeks for most patients. Patients who have more severe liver disease or have been previously treated often have to have more, but the majority of patients can be treated with 12 weeks of therapy.

So who should be treated for hepatitis C? This is the big question in lots of people's minds, including insurance companies and the people who are actually having to pay for this drug. This is my own personal opinion, but I believe that anyone who has chronic hepatitis C infection should really be considered for therapy. Because of the things that I mentioned earlier, particularly the extrahepatic manifestations, the decreased quality of life that a lot of people with hepatitis C have even if they don't have severe liver disease, I think it warrants that most people, if we can get the medication for them, should actually be treated.

So, because of the cost of this medication, there's been a lot of discussion about who, you know, should we prioritize people who have severe liver disease. And that honestly is what's happening with most insurance companies, is that you have to meet a certain criteria of liver disease before you can actually get treated.

So this is from the hepatitis C guidelines put out by the Infectious Disease Society and the American Association for the Study of Liver Disease. So people who should be considered highest priority for treatment are people with advanced fibrosis or cirrhosis; meaning, scarring of the liver -- and the Metavir score, I will talk about in a minute, but that has to do with liver biopsy. People who have organ transplant. And then the other last two are actually some of the extrahepatic manifestations that I talked to. So if somebody has renal disease that's related to their hepatitis C, they should be prioritized for treatment.

People who are considered high priority or at high risk for complications are those who have some scarring, have co-infection with HIV or hepatitis B, have other co-existent liver disease, like I mentioned earlier, like fatty liver, NASH is non-alcoholic steatohepatitis or fatty liver disease, people who have debilitating fatigue. And actually, type 2 diabetics are in this high priority risk list for treatment as well, and people who have porphyria cutanea tarda, which I showed you a picture of that particularly dermatologic disease associated with hepatitis C.

So I'm just going to mention this because I think that as primary care clinicians, it's important even if you're not going to be involved in treating hepatitis C to try to get some idea of the liver disease that your patients have. In the past, liver biopsy was considered really the gold standard, but honestly, we, at least in our practice, very rarely do liver biopsy anymore because there are ways to assess people's level of scarring. They're not perfect and neither is liver biopsy, but we think the risk of liver biopsy most often outweighs the benefit at this point. In addition to that, as I mentioned earlier, at some point when we can actually -- if we could get this drug for anybody who had hepatitis C, we would prefer that. We really don't want to have to stage them based on their liver disease.

There are some other ways to look at fibrosis. One is called the Fibroscan, which is like an ultrasound, but it actually measures the stiffness of the liver. We don't have access to that even at UNM, so it's not something that I don't know that a lot of you would have access to. There are other laboratory markers, one is called the APRI score, one is called the FIB-4, which you can calculate easily using labs that you would have on the patient anyway. The calculators are easily accessed on the internet. This is a program, a curriculum that the University of Washington puts up called "Hepatitis C Online" which is a really, really excellent curriculum that I would have anybody do if they were interested in learning more about hepatitis C. One of its tabs where you can see it says clinical calculators. So you can go into this website and put in the AST, the platelet count and then get an APRI score and it tells you how to interpret it, and you can also do that with the FIB-4 calculator which is on this website as well.

So why should we treat hepatitis C now? We know that when people, that the cost for people who have hepatitis C are significantly higher for those with more severe disease. So the more severe liver disease you get, the higher you're going to cost the medical care system. So we know that people that have hepatitis C, even if they don't have liver disease, actually have a higher healthcare cost than people who don't. But as your liver disease progresses, then you definitely become much more expensive.

Chronic hepatitis C infection increases mortality. It increases mortality related to the liver, but it also increases overall mortality, which is a very interesting thing that I don't think anybody quite understands, but the overall mortality is increased unrelated to liver disease for people who have hep C. We also know that if you treat somebody with hepatitis C when their liver disease is mild, they're actually much easier to treat and they get higher cure rates than people with advanced disease.

So, this kind of tells you what do we get with hepatitis C treatment, and this was again very interesting information that came out in the last couple of years. So when patients are cured of their hepatitis C, they have a 70% reduction of liver cancer, 50% reduction in all cause mortality, and a 90% reduction in liver failure, and this was over a 10-year period.

We also, this is something that is not well-known as well, is that when we do treat patients for hepatitis C who already have cirrhosis, their cirrhosis can actually be reversed, not in all patients but in some patients. What the slide shows is that F4, which means cirrhosis, basically, the dark blue color, these are pre-treatment liver biopsies of patients, and 61% of those patients who were treated and were cured of their hepatitis C had some reversal of their cirrhosis, as you can see on the right. So some even went to F2, F1 which is very -- the scarring went down dramatically in their liver. The liver does have the ability to regenerate. So, that's why we can see reversal of some scarring.

Lastly, I'm going to talk a little bit about access to care. So this is called the "Hepatitis C Cascade", which came out of, again, the data from the National Health and Nutrition Examination Survey. As you can see on the left, if we think that this is estimating that about five million people have hepatitis C in the United States, which I think a lot of us think is a more realistic number than 3.2 million. The majority of them, a lot of them don't know they have it. As you can see, as you go down this, how many have been tested, how many have been referred to care, how many have been treated, and how many have achieved the cure. It's a very, very small number. Even though we have good testing, we have great therapies now, very few people have actually accessed treatment.

I just want to talk a little bit about the role of primary care in hepatitis C. So I think it's extremely important and this is where most people are going to be screened for their hepatitis C, is in the primary care setting. Now that it's a grade B recommendation, it can actually be paid for by insurance. At that point, if somebody does have hepatitis C, you would confirm it with RNA and counsel them on modifiable risk factors, which we've talked about, things like weight control, and alcohol use, and things like that. I think you can do some staging of the liver disease without liver biopsy. So it's probably important to calculate one of those markers of fibrosis just to see where you think the patient's at. Again, very important to think about these extrahepatic manifestations that I discussed because a lot of

them go unnoticed. If somebody has severe extrahepatic manifestations, they should really be linked to treatment very quickly.

Then certainly, the way things are going with treatment, it's something for people to consider in the primary care setting. At this point, I would still say it needs to be with mentoring, and I'll talk a little bit about that. If you're not doing that in your own setting, then you-- certainly linking them to care with somebody who treats hepatitis C is very important. Now that the treatments are very well tolerated and have a high cure rate.

So, some of you, I see actually some of the people and the participants that I recognize that were involved in Project ECHO, and if any of them want to say anything at the end, that would be great. The Project ECHO is a project where we have a multidisciplinary team of people. As you can see on this slide, we have a hepatologist or myself; we have a pharmacist, a psychiatrist, a bunch of people sitting around the table. And we do tele, we do these things called clinics where providers who are around the edges of this slide, as you can see, present their patients to us, their hepatitis C patients, and we give them guidance about how to treat them. We mentor them and help them treat them over time. So this has been going on for almost eight years now, this Project ECHO Hepatitis C Clinic. It's changing dramatically because of these new drugs, but it is still a very useful way to learn how to treat patients in the primary care setting.

In March of 2013, we actually started an IHS Hepatitis C Clinic, some of you may be on this call that are in this picture, but this is a picture from our IHS Hepatitis C Clinic, that's run out of the University of New Mexico. Same concept, but we do it specifically with IHS clinicians, and these are the places on this map where we have sites, where people have been presenting patients from all of these different IHS participating sites.

In terms of opportunities for getting involved in something like this for mentoring through telehealth, we do have the University of New Mexico ECHO. There are several other ECHOs that are very active that would be really happy to hear about your patients. The University of Washington in Seattle, Arizona in Phoenix at St. Joseph's Hospital has an ECHO, the University of Utah has a hepatitis C ECHO, Baylor in Houston and then Alaska has -- they don't do ECHO specifically, but they also have a telementoring model for hepatitis C treatment.

Through ECHO, we provide CMEs for attendance, even if you're not treating patients. So even if you just want to come on and listen and learn more about hepatitis C, you can get CME for that. We also have continuing pharmacy education credits available at the Albuquerque site. So we do provide CPE for pharmacists as well.

So a couple of other issues, which are probably burning in your mind. There are a lot of issues about this drug because it is so expensive. If this drug were \$100 or \$50 or, you know, expensive, but just much less expensive than it is, I think that there will be no question about everybody who has hepatitis C being treated. But it is very expensive. There's a lot of the state, Medicaid and insurance companies are limiting access by, again, having a lot of criteria about who gets treated and treating really the people who have the most advanced liver disease. So, that's a huge issue. There are patient assistance programs through the drug companies, and they're a lot of work because of the paperwork, but if you get involved in this business and you learn how to do it, then it won't be too cumbersome. And our partners who work with us in the IHS have had a lot of success with the patient assistance program so far. There is going to be a webinar that's devoted to patient assistance programs, including templates for forms and things like that. Again, I'll let somebody from IHS speak about this at the end of my slides.

Final thoughts, the hep C epidemic is upon us, there are a lot of people who are chronically infected who have not, first not been diagnosed, and certainly not been treated. There's a rapidly rising liver-related mortality that I showed you in the slides. I call it the "tsunami slide" because again, if we don't

do something, we're going to have a ton of patients who have end stage liver disease because of hepatitis C. Testing and linkage to care are needed. We still think that only 25% to 50% of people who have hep C are diagnosed. So there are a large, large number of people who we don't even know about.

There are a limited number of providers familiar with hep C treatment. And even though the drugs are getting a lot easier, the decision-making is still very complex to treat what genotype, with what duration of therapy, with what drugs, things like that. I still think there's a role for mentoring, but I do think there's a role for primary care clinicians to learn how to do this in that setting.

We know that hepatitis C treatments are improving rapidly. Unfortunately, costs may be prohibitive to allow equitable access, and this is a huge issue, which is again, a whole another very thing that we could talk about a lot, but there are issues about who's getting treated for hepatitis C. Particularly, the Medicaid programs are really limiting access in a lot of states to Medicaid patients for access to hepatitis C treatment.

This is a very complex medical and societal issue. It's really never happened before where there's been a drug that is this effective and that's this expensive, that we need, that five million people in the United States need to be treated. So it's a huge, huge issue for us as a society to address.

So those are some final thoughts. I wanted to acknowledge some people who I have used some of their slides, and I also have a link to the hepatitis C online curriculum from the University of Washington which is a really, really excellent curriculum that I hope some of you will visit. They also give CME from that as well, if you complete the modules in the hepatitis C online curriculum.

That is the end of my presentation and I would love to take questions. I know there has been a lot flowing down there. So if someone wants to guide me on how to answer these, that would be great. And I also wanted to ask Brigg Reilley to just say anything, add anything that he would like to about my presentation. Thank you.

Brigg Reilley:

Hi, Karla. Thank you so much. This is Brigg. I'll just say, Jessica Lessons typed in the chat window a few solid ways that health workers can support any site they want to on either implementing hep C screening for the boomers, or getting more information and training on follow-up with your hepatitis C positives and getting them linked to treatment. Finally, we have a walkthrough webinar coming up on costs and how to get those drugs for free for our patients. That's all. I'll step out and let you answer the questions.

Karla Thornton:

Okay, great. Should I just read the questions?

Jan Frederick:

That would be great. Thank you, Dr. Thornton.

Karla Thornton:

Okay, so the first question was, you stated that hepatitis C causes diabetes to be worse. Have there been any associations with diabetes making it harder to treat hepatitis C? Yeah, absolutely. So we don't know with these new drugs that hasn't really been looked at, but when we were using Interferon, people who had uncontrolled diabetes were actually much harder to treat. So, we think that there was definitely a decreased cure rate when we used Interferon-based therapy. Like I said, I don't think we

know with the directly acting antiviral, but historically, it has been more difficult to treat patients who have diabetes or to treat patients for their hepatitis C who have diabetes.

Next question was, how does the drug company justify such price of new drugs? Well, that's a really difficult question that unfortunately I can't answer. Like I said, it's never happened in this country where, you know there are drugs that are this expensive, but they're mostly in oncology where there are rare cancers or things where there just aren't going to be very many patients who have to take the drug. This is the first time that this expensive a drug has been created that millions of people need. So it's a little mind boggling that it could be so expensive, but we have no price control of drugs in this country. So, they can basically ask whatever they want for the medication.

Next question was, modifiable risk factors are important in disease progression and should be addressed. And it says, how so? I would just say that, I mean, in terms of weight loss, certainly, we just counsel people about the effect of fat on the liver. So I think a lot of people don't really understand what fat does in the liver, and fat honestly, it's toxic to the liver. So when you have deposition of fat in the liver, it acts almost like a virus. So people get fibrosis. Fatty liver is becoming a very, it will probably overtake hepatitis C for the reasons for liver transplant. If we can cure the hepatitis C, then fatty liver would be absolutely the most common reason for liver transplant. So one of the ways that we do talk to our patients a lot about the effects of fat on the liver because I think sometimes people don't really, really understand that. How to get people to lose weight, that's another very difficult question that I probably can't answer.

Do you know if the HCD treatment is covered my Medi-Cal? I do not know the answer to that. I know about some states. I know Texas Medicaid is not covering hepatitis C medications, but I'm not sure about Medi-Cal.

Will the manufacturing process ever progress to the point where it will become generic? Unfortunately, in this country, a drug becoming generic takes so long that by the time that will happen -- I mean, it would take many, many years for this drug to become generic. One of the hopes that we have in the world of hepatitis C is that there is some drug competition, and I didn't even mention this, but another drug came out about three weeks ago called Viekira Pak, which is a drug that came from AbbVie which is a combination of directly acting antiviral. It's highly effective, but they basically priced it the same as Harvoni. We were hoping, everyone was hoping that they would price their drug a lot cheaper so they would create some competition in the market on price, but that didn't happen. So it's very difficult to predict what's going to happen with the price of these drugs over time. But I don't think we really can count on them becoming generic anytime in the next decade.

How costly is doing just the screening? I'm not sure if that question is how much does the test cost, or how costly sort of is it to screen the population. If it's the second question, then the CDC did their cost effectiveness analysis of screening the birth cohort and it was a cost-effective measure. It's not an extremely expensive test. Like I said, it is covered by insurance because it's a USPSTF recommendation.

The next question is, does everyone with hepatitis C need to be treated? If there are people with hepatitis C who live a healthy life and liver counts stay in the healthy range, will they eventually get cirrhosis of the liver if they do not receive treatment? That's a great question. I mean, this is sort of the million-dollar question because unfortunately, from a personal point of view and as a clinician, when somebody comes to me who has hepatitis C, I cannot predict if they will get cirrhosis and liver cancer. It's impossible. There's no test to do that says, okay, well, you're fine, you really don't need treatment, but the next person isn't fine. They do need treatment." So personally, I think if somebody has a chronic viral infection that is treatable, that you should treat it.

I did talk about extrahepatic manifestations, so again, it's not all about the liver, and I do think that we also don't really understand ultimately what it means to have 10 million copies of hepatitis C virus per

milliliter of blood in your body for 50 years. I'm also an HIV practitioner and we know now that having, we really recommend anybody who has HIV to get treated, because we know that independent of immune suppression, HIV does a lot of other things. So when people have chronic, what we call "chronic viremia", they can have more coronary artery disease. They have a lot of other things that are caused by having inflammation in the bloodstream all the time, and that's what we think is also related to lymphoma. So having this sort of chronic stimulation of the immune system can cause things like lymphoma. So in my opinion, there are many, many reasons to treat hepatitis C, not just the liver. So I would again say that I can't predict that somebody is going to have a healthy life without any complications from their hepatitis C. So I would be an advocate just for treating everybody if possible.

Have you had any luck in getting insurance companies to pay for extended treatments for genotype two. That's a great question. We just started in our own practice extending to 16 weeks for genotype two, and we have had no luck so far getting anybody 16 weeks of treatment. So we're going to continue to try, but we haven't had luck.

Would you treat someone who is still actively injecting drugs? That's another great question. There have been a lot of discussions now that we have treatments that's relatively straightforward without Interferon about treating active injection drug users. It's something that is being done in other countries. Scotland, in particular, has a very active process where they're trying to treat their active injection drug users to try to decrease transmissions. Basically, country-wide, and it's a really interesting concept. In the guidelines in the United States, they actually put active injection drug users as a possibly priority for treatment to try to decrease the amount of virus in the population. So you know, we're not treating, I'm not personally treating anybody who's actively injecting right now, but we are definitely treating people who have injected very recently who are now in some sort of -- we want them to be engaged in some sort of drug treatment program to try to decrease their risk of getting re-infected, certainly. It's something that we're considering a lot more. We're seriously considering more than we have in the past.

The next question was, what are some side effects associated with hep C treatment? So honestly, with these new drugs, there are very few side effects with the Sofosbuvir Sovaldi treatment. Headache has been the main complaint that people have had, in about 5% of patients that have a headache. The other thing, we're still using the drug, Ribavirin in combination with a lot of these medications. So Ribavirin can cause a rash, it can cause anemia, headaches, and things like that. But we aren't seeing a ton of side effects from these medications, which is very exciting. People are sort of sailing through treatment now.

Jan Frederick:

It looks like that you have addressed all of the questions, Dr. Thornton, and we want to thank you so much for your presentation and also for taking time to respond to all of the questions.