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TRANSCRIPT - GR 03 11 22 "Emerging Issues in Liver Disease in Women" ***Carla Brady, MD, MHS*** **from Duke Health**

UVA IMR Chiefs

- Hi everyone and welcome to the Department of medicine grand rounds, today we have Dr Carla Brady from the University division of gastroenterology.
- 17:18doctor very easy to double duty, courtesy of her bachelor's and medical degrees after Medical School about grading we did our internal medicine residency and keep residency and.
- 17:28fellowship at drexel university program at MTV home and hospital prior to joining the Faculty ado, Dr Brady was a thought health service Research and Development Institute.
- 17:38Dr Brady now and associate professor of medicine division of GIs and intending on the patient hepatology and transplant but healthy conflict service and in their liver clinic.
- 17:48Dr grey is a multifaceted leader Duke serving as the Chair of the transplant intelligent fellowship program evaluation committee and I liked it a member of the academic Council and previously on the Executive Committee of the academic Council and additional.
- 18:01Responsibilities possibilities i'll try to do choose a crucial figure, the American Association for the study of liver disease.
- 18:07serving on the scientific program committee as Co chair and previously serving as the chairs of the program evaluation committee and the inclusion diversity committee for her.
- 18:15Contributions the larger hepatology me and patients they care for Dr Brody was designated as a fellow and then double as ld 2016.
- 18:24One of Dr brady's areas of particular interest in focuses on the care of women with liver disease and it's presented on topics such as compact lesions and pregnancy obstetric hepatology disparities in liberty is focused on.
- 18:40Giving her expertise, it should be a particularly eliminating grand rounds presentation today on emerging issues liberties and when I would that please join me in welcoming Dr Barry the virtual.

Carla Brady, MD

18:54You very much can everyone hear me.

- 18:57Yes, Lisa excellent well I like to take this opportunity to thank the Department of medicine for the opportunity to talk with you today.
- 19:07About emerging issues and liver disease in women, even though we are doing this virtually hopefully we can all meet again sometime soon I'd love to come back to my Alma mater someday in person and meet with all of you.
- 19:27They get my slides to advance there we go.
- 19:31So please take note of my disclosures.

- 19:36So I will first start with acknowledging that, when I was invited to speak and set out to prepare this presentation today I knew that I would prepare a talk on women's health and liver disease.
- 19:49But I had not really thought about the significance of the timing such a talk.
- 19:54As the data approached I remembered that not only is march women's history month but march 8 so earlier this week was International women's day so today's talk seems quite timely and so, as we have much ground to cover going to go ahead and get started.
- 20:11i'd like to begin with a general overview of the epidemiology of chronic liver disease.
- 20:16Chronic liver disease affects 1.5 billion people worldwide With 1.2 million deaths per year due to cirrhosis and close to 800,000 deaths per year from liver cancer.
- 20:30Within the United States, the burden of liver disease might not be as high as heart disease, but it does affect nearly 2% of the adult population, and it is responsible for loss of over 51,000 lives per year, representing the 11th leading cause of death overall.
- 20:50Interestingly, half of cirrhosis cases in North America are seen and those born between 1945 in 1965 much of this is related to hepatitis C infection.
- 21:03And a higher prevalence is seen among blacks Hispanics and those have lower levels of education, unfortunately, the prevalence of cirrhosis has increased to 1.5 fold over the past two decades.
- 21:19Regarding gender differences, whether due to chronic liver disease cirrhosis or hepatocytes carcinoma liver related mortality is actually more prevalent in men and women.
- 21:31However, increases and the rates of chronic liver disease related mortality are increasing in women and younger person's as well as non Hispanics whites and Native Americans.
- 21:45So today we will explore how rare disease is expressed and managed and women, focusing on liver disease throughout a woman's life across childbearing years into menopause.
- 21:57A key biologic issue that influences the risk for an expression of liver disease is estrogen estrogen has a number of beneficial roles and the body.
- 22:09Within the context of liver disease estrogen has been shown to inhibit fiber genesis protect mitochondrial structure and function and inhibits cell senescence.
- 22:21estrogen has also been shown to promote antioxidant effects, and it can increase innate immunity these functions have been shown to impact risk for severity of various liver diseases.
- 22:36So today we will look a manifestation of a management of liver disease in women with focus on three of the most common chronic liver diseases which are alcohol associated liver disease hepatitis C and non alcoholic fatty liver disease.
- 22:54So first let's take a look and alcohol associated liver disease.
- 23:00Alcohol associated liver disease is expressed in different forums, we can see it present as hepatic State of Texas, which is the presence of just fat in the liver.
- 23:10We can see that presents acute alcoholic hepatitis, which is fat with acute inflammation and injury to the liver and alcohol associate at cirrhosis and which now the ongoing entry in the liver, has led to widespread fibrosis or scar.
- 23:26Unfortunately, alcohol associated liver disease accounts for nearly half of liver related deaths in the US and the cost of alcohol associated cirrhosis represent over half of the total cost of services in the United States as well.

- 23:44It is an increasing indication for liver transplantation and what we know about this disorder is that continued alcohol use is the strongest predictor of mortality, particularly for those with alcoholic hepatitis.
- 24:00It has been shown that women are more susceptible to the negative effects of alcohol and liver that women with alcohol associated liver disease have a more rapid progression to fibrosis and that women are disproportionately affected by alcohol use disorder.
- 24:19However, women more susceptible to the negative effects of alcohol on the liver, it has been shown that women have decreased body water content compared to.
- 24:29invest have a smaller volume of distribution, as well as having reduce gastric alcohol dehydrogenase that leads to impaired first pass metabolism.
- 24:40Additionally, there are sex related differences and how hepatic inflammation develops an alcohol associated liver disease, noting that higher into toxin levels and women, along with estrogen driven activation to ourselves, contribute to a greater likelihood of inflammation and deliver.
- 25:01gender disparities are also seen within alcohol use disorder behavior modification and various FDA approved pharmacologic therapies have been shown to have modest benefit and alcohol use disorder.
- 25:16Interestingly, utilization of these therapies and the general US population is alone at 7.7% within a year and 19.8% across one's lifetime and those who seek such therapies tend to be older male and with longer substance abuse history, as well as with mood disorders.
- 25:40Women are more likely to have histories, that would influence risk or alcohol use disorder, such as a family or spouse history of this disorder.
- 25:50A history of being raised in a vulnerable environment and a family history of depression, women are less likely to seek any type of treatment or alcohol use disorder.
- 26:01And many treatment barriers that they report includes social stigma attitudinal barriers financial concerns and competing family and or childcare responsibilities.
- 26:15What about gender disparity and alcohol use disorder among patients with alcohol associated liver disease.
- 26:22A more recent study looked at this issue specifically among over 60 s uninsured patients with alcohol associated cirrhosis.
- 26:32Within this cohort 32% are women, and the majority of patients had insurance coverage that would have allowed for behavioral modification and our pharmacologic therapies alcohol use disorder.
- 26:47Interestingly, only 1.2% used an FDA approved a hall relapse drug and only 14.5% attended mental health and substance abuse visits, two years after a diagnosis of cirrhosis.
- 27:03As you can see from the bar graph women as represented by the library bar were significantly less likely than men represented in the dark Gray bar to attend clinic visit and use alcohol relapse medications.
- 27:20Regarding alcohol associated liver disease and pregnancy it's important to note that increased rates of alcohol use disorder happens seen and reproductive age women with heavy episodic used to report it and up to 36%.
- 27:37there's a strong association of alcohol use and pregnancy with preterm birth small for relational age presentation and the fetal alcohol spectrum disorder.

- 27:49The most important focus and preconception management is abstinence from alcohol and there should be consideration of a delay in conception until abstinence from alcohol is achieved.
- 28:03In the setting of pregnancy and there should definitely be screening for alcohol use.
- 28:10Regarding pharmacologic therapies for alcohol use disorder and pregnancy risks and benefits of these therapies, need to be weighed very carefully.
- 28:19With a note of data, suggesting positive possible negative effects of a campus eight and isolated from us and pregnancy and no data is showing negative outcomes of naltrexone based on data from its use in opioid use disorder in pregnancy.
- 28:38As a result of the earlier data on sex and gender differences and this disorder guidance from the American Association for the study of liver diseases.
- 28:49On alcoholics associated liver disease has stayed at that safe levels of alcohol use for men, without liver disease would be no more than two standard drinks for 24 hours.
- 29:00Whereas in women there should be no more than one standard for 24 hours and for patients with liver disease, there is no safe level of drinking unless he should abstain from drinking alcohol all together.
- 29:16So now let's turn our attention to hepatitis C.
- 29:20About 2.4 million people in the US have hepatitis C infection, an increase in the number of new hepatitis C cases was seeing between 2009 and 2014.
- 29:32Which to start to be related to injection drug use, noting that women of reproductive age at that time accounted for about half of young persons who injected drugs.
- 29:45In particular, the number of acute hepatitis C cases and be significantly across 2006 to 2014 and over half of these cases occurred in non Hispanic white women.
- 29:59This slide depicts the observed upward trend and acute hepatitis C cases in the United States.
- 30:06As you can see from the graph the rates of report it acute hepatitis C cases rose in women in the early 2000s to rates that were similar to what we're seeing a Min by 2011 the rates in men began to exceed rates women again, but over all the rates have risen in both subpopulations.
- 30:28About 75 to 85% of persons newly infected with hepatitis C develop chronic infection and among those with chronic infection about 10 to 20% develop sources.
- 30:42Once the erotic there's about a three to 6% annual risk of hepatic D compensation and about a one to 4% risk per year of hepatocytes color carcinoma.
- 30:54So what about sex and gender differences and the natural history of hepatitis C.
- 30:59hey to have led to observations of slower have had it fibrosis progression and women compared to men and that the progression of fibrosis is not linear with advancing age.
- 31:12And that the data suggests that the rate of fibrosis progression in women may be faster once they reach older age than their younger ages.
- 31:23Earlier data have reported tobacco use and iron overload as influencing the development of liver injury and hepatitis C.
- 31:34But an earlier study from France looked at rates of fibrosis progression and women, according to various stages of life and conditions in which, how would be influenced by estrogen levels.

- 31:46From this study it was observed that another Paris state or state of never having been pregnant and menopause we're independent predictors of fibrosis progression and women with hepatitis C infection.
- 32:01and additional data have demonstrated that menopause is associated with more advanced levels of fibrosis.
- 32:08And this study of 251 women with hepatitis C 122 were postmenopausal and 65 received hormone therapy.
- 32:19Although postmenopausal women were more likely to have progression to advanced fibrosis postmenopausal women taking hormone therapy were actually less likely to have progression to advanced fibrosis.
- 32:34So, given what we have reviewed about how hepatitis C has been seen with increased frequency and women and childbearing age let's briefly look at the epidemiology of hepatitis C and pregnancy.
- 32:47The prevalence of hepatitis in pregnancy varies across the world, with the highest prevalence in Africa.
- 32:53Within the United States, hepatitis C is seen and about 0.3% of women who are pregnant, representing an increase in incidence over the past several years likely related to the opioid epidemic, as I mentioned before.
- 33:10It is more commonly seen and non-Hispanic white women who are pregnant and those with Medicaid insurance and in cigarette smokers and the risk of transmission of hepatitis C from mother to child is about five to 6%.
- 33:28And it has been that most pregnancies of women with hepatitis C progress well and have positive outcomes.
- 33:37Over the years, there have been some conflicting data to suggest that there may be some association with negative obstetrical and fetal outcomes and more recent data have indeed offered some concern for increased risk of preterm birth and neonatal death.
- 33:57Interestingly, recent data have also shown that hepatitis C and pregnant women is associated with the development of intro particular status of pregnancy.
- 34:08Which is a liver disorder that is unique to pregnancy into a particular stages of pregnancy is important pregnancy related liver disease that typically presents, and the second or third trimester.
- 34:21And it presents with purpose and elevated serum bile acid levels and often there will be some elevation and liver enzymes.
- 34:31Whereas there are no significance, the color of intro particular stages of pregnancy, to the mother.
- 34:38There aren't important adverse obstetric and fetal outcomes, including preterm birth makoni and stained amniotic fluid fetal distress and still birth.
- 34:50Due to these potential negative outcomes it's important to ensure that.
- 34:56You ask if hepatitis C infected pregnant women have paralysis and that you watch for jaundice and if present you need to have a very high suspicion for intro particular stages of pregnancy and ensure that you check liver enzyme and serum bile acid levels.
- 35:17Previously, hepatitis C screening was recommended for those born between 1945 and 1965 and those with risk factors for hepatitis C infection.

- 35:30However, recently updated recommendations now state that hepatitis C screening should occur at least once in the lifetime of all adults.
- 35:41aged 18 years or older acceptance settings where the prevalence of hepatitis C is less than 0.1% and that hepatitis C screening should occur in all pregnant women during every pregnancy.
- 35:57For those who have identified risk factors for hepatitis C, they also should be tested and this testing should occur regularly.
- 36:06Regarding concerns about mother to child transmission the earliest time to test infants born to mothers with hepatitis C is two months.
- 36:16hepatitis C antibody can be checked at 18 months of age or later and for those children who have been identified as being hepatitis C antibody positive, they should be checked for hepatitis C RNA at three years of age, which would be the earliest age for treatment.
- 36:36So, thankfully, we have multiple very effective hepatitis C therapies that clear infection and greater than 90% of patients tend to be a short duration and the very few side effects.
- 36:50We don't have enough safety data at this time to support a recommendation for hepatitis C treatment and pregnant women, which really underscores the importance of screening women of childbearing age for hepatitis C and hopefully being able to treat them prior to conceiving pregnancies.
- 37:13Regarding hepatitis C treatment outcomes overall existing data have suggested that sustained virologic response with hepatitis C therapy may be associated with important.
- 37:26Extra hepatic outcomes, including lower risk for type two diabetes acute coronary syndrome ischemic stroke and end stage renal disease and patients with pre existing diabetes.
- 37:41We know that data from outside of the hepatology realm tell us that the risk of cardiovascular disease increases and postmenopausal women and that women, older than 60 years of age have higher rates of cardiovascular disease than men.
- 37:59Interestingly, chronic kidney disease without end stage renal disease is more common in women, women are less likely to start dialysis and more likely to die in the pre dialysis period of chronic kidney disease.
- 38:14With these gender differences in cardiovascular and kidney disease and earlier observations of sustained virologic response lowering the likelihood.
- 38:25Of these extra hepatic endpoints and hepatitis C infected patients it's important to really understand if there are gender differences and how sustained viral logical response might impact these co morbid conditions.
- 38:40newer data just recently published identified a reduced risk of acute coronary syndrome and stage renal disease and ischemic stroke and hepatitis C patients but she'd svr with treatment.
- 38:56This risk was particularly significant in female patients compared to male patients.
- 39:02Interestingly, the lower risk for acute coronary syndrome is particularly significant or female patients who achieved svr on interferon based therapy.
- 39:13Compared to male patients who achieved svr on interferon based therapy or direct acting antiviral therapy.
- 39:24The reasons for this are not yet clear and please keep in mind that, nowadays, hepatitis C treatment is usually done with direct acting antiviral therapy, rather than with interferon based therapy.

- 39:38But what was interesting and what was also noted in the study is that the observation of female patients with interferon treatment failure having a marked response, excuse me a mark increased risk of cardiovascular and kidney disease.
- 39:57These data highlight the importance of diagnosing and treating women with hepatitis C.
- 40:05So now let's focus on non alcoholic fatty liver disease.
- 40:10Non alcoholic fatty liver disease is now got to be the most common liver disease and it's thought to be seen in about 25% of a global population.
- 40:20Its associated with obesity, diabetes dyslipidemia metabolic syndrome and polycystic ovarian syndrome, it can progress to advanced liver disease and it represents the third most common cause of hepatocytes killer carcinoma.
- 40:38The second most common indication for liver transplantation as well.
- 40:44The most common cause of death in patients with non alcoholic fatty liver disease is actually not liver disease itself but cardiovascular disease.
- 40:55The prevalence of Napoli is lower in women than in men, however, among those with napoles women are as likely as men to have non alcoholic Seattle, hepatitis, which is fat with inflammation or Nash.
- 41:13And, excuse me, and among older patients, women are 37% more likely than men to have advanced fibrosis.
- 41:24This is concerning and that severe fibrosis actually predicts increased liver related mortality and these patients.
- 41:34Data have demonstrated that among novel patients I brought us to severity is greater and men than premenopausal women but it occurs, at the same rate and postmenopausal women with natural.
- 41:50Data have shown that postmenopausal women are at an increased risk for the development of mash and advanced stages of fibrosis.
- 42:01And it is believed that contributors to this include observations of decreased energy expenditure increase visceral fat with increased body weight.
- 42:12and greater likelihood of development of dyslipidemia and women who reach menopause.
- 42:18These changes and subsequent development of a more severe fatty excuse me, have more severe fatty liver disease and postmenopausal women are likely related to estrogen loss and age related changes that lead to increases in pro inflammatory cytokines.
- 42:40As we continue on the theme of liver disease across the spectrum of a woman's health we'll turn our attention briefly to a few notes about fatty liver disease and pregnant women and in women of childbearing age.
- 42:55obesity affects about one third of women of childbearing age in Western countries, and these obese pregnant women are at risk for preeclampsia and for gestational diabetes.
- 43:09The metabolic know you a pregnancy is altered with increases and triglycerides and cholesterol levels across pregnancy, as well as increases and free fatty acids, leading to a decreased ability of insulin to suppress my policies.
- 43:28Justice snaffled is of increasing importance as women age there's also concerned about metabolic disturbance and pregnancy, as it relates to that old risk.

- 43:41For women who developed gestational diabetes, they are at risk for subsequent type two diabetes and the metabolic syndrome is a marker of early atherosclerosis and of development of NAFTA later in life.
- 44:00The incidence of map old is rising, with the largest rise incidents occurring and young adults underneath your 40.
- 44:09That snaffled and it's increase incidents and young adults has implications for its impact on reproductive health.
- 44:18This table provides data from a recently published study on the impact of math hold on the tunnel and prenatal outcomes in data from the nationwide Inpatient sample database.
- 44:33And this study the prevalence of napa to pregnancy nearly tripled between 2007 and 2015 accounting for an increase from 10.5 per 100,000 pregnancies to 28.9 per 100,000 pregnancies.
- 44:52Researchers also found that Napoli was associated with an increased likelihood of hypertensive disorders of pregnancy.
- 45:01When comparing baffled and pregnancy to pregnancy, in the absence of liver disease researchers found an increased likelihood of postpartum hemorrhage maternal death.
- 45:12And preterm birth and pregnancies affected by baffled when comparing snaffled in pregnancy two pregnancies affected by other liver diseases researchers found an increased likelihood of feel worth restriction and large for gestational age presentations and pregnancies affected by snaffled.
- 45:36It is therefore extremely important that efforts are made to determine if pregnant women are at risk for Naf old.
- 45:44Whether an apple does identified in pregnancy for pregnant women who are presenting with obesity or preeclampsia it is really important to ensure that they undergo metabolic assessments.
- 45:57and monitoring postpartum in order to ensure that there is not progression of metabolic disturbances in the postpartum setting given concerns about the longitudinal effects of metabolic disturbance on feature pregnancies and on long term health in general.
- 46:16Furthermore, if there are opportunities to make these assessments prior to pregnancy, even in women without known obesity, diabetes, or history or preeclampsia this may offer opportunities for interventions that could help to improve metabolic health prior to pregnancy.
- 46:39The main intervention or napoles that has been associated with success is a lifestyle intervention with weight loss.
- 46:47noting that weight loss of three to 5% has been associated with improvements and statuses and weight loss of up to seven to 10% has been shown to improve hepatic inflammation and necrosis.
- 47:03Here I will also make note of vitamin E, because this actually comes up frequently in practice prior research data suggested benefits of vitamin E use in the management of nonalcoholic Seattle, hepatitis and non diabetic patients, this is a part of the very important pivots child.
- 47:24However, more recent data Hashem concerns for increases and all cause mortality with vitamin E use, and therefore its use in the management of Nash, as actually been more controversial.

- 47:38So we still do not have FDA approved medications at this point for nap older for Nash, but there are numerous clinical trials that have been.
- 47:48In various stages of development, and these have been exploring various pharmacologic therapies for now, and so, at this time, the main thing that you should really underscore with your patients is lifestyle intervention and dietary interventions.
- 48:08To help with promoting weight loss in a way that can impact the disease positively.
- 48:17And with that i'll bring my presentation to a close, I like to thank each of you for your time and your attention and I guess if there's opportunity for questions i'll take them at this time, thank you.

UVA IMR Chiefs

48:36Will you folks a moment to leave their questions in the chat or asked to be unmuted.

- 48:44I will start, let me just do something online.
- 48:56i'll start with a question from.
- 48:59From the question I have is you know I'm understanding, you know you know leveraging some of these insights about how estrogen seems to.
- 49:11have been a research, and you know, identifying therapeutic estrogen derivatives to help.
- 49:18You know sort of you know not you know sort of postmenopausal women or men sort of slow the progression of their fibrosis when they have liver disease.

Carla Brady, MD

49:30that's an excellent question part of the issue and difficulty with that is, as you may be aware, there's a lot of controversy with estrogen therapy and whether it may have some negative outcomes regarding cancer risk thrombosis and bollock disease.

- 49:53And so therefore it's been very difficult to determine whether or not you could take an estrogen based therapy and actually use that for the specific purpose of slowing fibrosis progression.
- 50:07Certainly, it would make sense right to think about that physiologically based upon some of the data that I showed you.
- 50:14But again, you know part of the concern and the lessons that we learned from hormone therapy on that to us and.
- 50:21postmenopausal women is that there can be potential negative outcomes um, so I think you know there's a lot that remains to be seen as to whether or not this can be utilized in clinical practice.

UVA IMR Chiefs

50:37unmuted Dr Henry so he can ask you a question.

Zachary Henry

50:41Hello and I'm wonderful to kind of see you on the screen um.

- 50:48I have, I have.
- 50:50I have a very specific question.
- 50:53about managing autoimmune hepatitis and young women who want to get pregnant um I have a number that are you know well controlled on is a firebrand at pretty low doses.
- 51:05And I believe is a buyer personas still listed as pregnancy class C or D I can't remember which but they're also studies of IB patients.
- 51:18kind of staying on his authority through pregnancy, where they actually do well, and they haven't noticed much fetal harm, do you have a specific approach to young women with autoimmune hepatitis and managing that during pregnancy.

Carla Brady, MD

51:32Absolutely and I certainly could have spent some time talking about autoimmune hepatitis as well, I chose to spend time on I believe our three top liver diseases but.

- 51:43You know let's talk a minute about that so I'm indeed a sapphire pran which is for the general audience part of our.
- 51:54Therapeutic regimen for patients with autoimmune hepatitis historically has had a negative FDA classification in terms of its ability to be used safely and pregnancy, historically, it was given a classification of D.
- 52:14Which for those who may not be familiar with suggest that you probably should not use this drug and pregnancy that certainly based upon much, much older data.
- 52:25However, as Dr Henry mentioned, we have a lot of data from the ID patient population as well as from the rheumatologist population that suggests that as a firebrand can be used very safely and pregnancy.
- 52:42And it is typically expect or recommended that in the setting of autoimmune hepatitis, if you have a woman who becomes pregnant on.
- 52:54As a fine print, it is best in this thought that the risk benefit ratio suggest continuing on is a fire print during the course of pregnancy, rather than to stop it.
- 53:07If a woman ends up say developing flair on requiring immunosuppression you know manipulation or changes is a failure print could be considered or even introduced during the time of.
- 53:24The pregnancy, if necessary, um and therefore you know I think the main lesson or the take home point is that you don't want to stop it there be.
- 53:37In the setting of autoimmune hepatitis, because there are clear data that demonstrate that there are worse outcomes with layers of autoimmune hepatitis during the course of pregnancy and in the months leading up to consumption of pregnancy.
- 53:54So, therefore, the thing that you want to do is just keep them on stable therapy, the entire time.

- 54:02prednisone can be used as well as as a fire print on, there are some concerns about association of prednisone with.
- 54:12cleft palate formation, however prednisone has been used in pregnancy in a number of settings and situations, I be D population, the rheumatologist population it's used.
- 54:24For asthma management and I didn't see, so there are plenty of data that was suggested that would be an alternative or a complimentary strategy as well.

UVA IMR Chiefs

54:37Great we've got a question in the chat from whatever residence is Calvin say hi Dr Brody thanks so much for the presentation what pharmacologic therapies are closest to FDA approval on the horizon for an apple.

Carla Brady, MD

54:51Yes, so um there are some therapies that have been studied and.

- 55:00thought this potentially being close one of them that's been looked at and has gone through a number of clinical trials, is a beta colic asset which we actually use for primary biliary colon titus.
- 55:18There are a number of Fr X agonist therapies and as well that have been looked at and study.
- 55:30However, nestled is a pretty complicated liver disease metabolically and so trying to identify the appropriate targets for therapy.
- 55:44That would lead to beneficial outcomes has been quite difficult it's a complicated complicated metabolic disease and the ability to find the right targets to be able to treat.
- 55:59or manage the development and progression of fat and inflammation and liver have been quite difficult, so I think we'll have to stay tuned and see what's on the horizon.

UVA IMR Chiefs

56:12As a as a follow up to that question has there been any research and identifying kind of like.

- 56:18You know, easily identifiable sort of Sub sets of patients with snaffled based on either metabolic profiles, or even you know more like advanced you know sequencing so I'll take it is it a much more heterogeneous disease and we sort of given credit at the moment.

Carla Brady, MD

56:34it's probably a bit more heterogeneous than what we once upon a time.

- 56:42There are concerns about genetic.

- 56:46components to the disease, as well as just you know the metabolic expression of the disease itself and so part of the question is.
- 56:56Is there something that you could target genetically Is there something that you target metabolically is it something that you target in terms of fibrosis progression or inflammation you know these are all things that make the disease much more complicated.
- 57:11And that's the reason why I think that it's probably difficult to be able to you know that one drug that might actually work, and it may be the case that we may be looking at.
- 57:26A complimentary set for a suite of drugs, over time, that may be the most beneficial in terms of treating the disorder.

UVA IMR Chiefs

57:35Right excellent or really appreciate your time and the presentation and also your answers to our questions, and we wish you could have you here in person and hopefully we can pretty soon and yeah just I really appreciate it oh it's just Calvin SEC thanks.

- 57:52So much great.

Carla Brady, MD

57:54Thank you very much.