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Marianne O'Hare: Welcome to Conversations on Health Care. This week we are joined by Dr. Howard Fillit, Co-Founder and Chief Science Officer of the Alzheimer's Drug Discovery Foundation, accelerating the pace of discovery for drugs that will prevent, treat, and cure Alzheimer's and other dementias.

Dr. Howard Fillit: Repurposing diabetes drugs for the treatment of Alzheimer's disease is a very exciting field right now.

Marianne O'Hare: FactCheck.org's Managing Editor, Lori Robertson stops by and we end with a bright idea improving everyday lives. Now, here are your hosts Mark Masselli and Margaret Flinter.

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Mark Masselli: As we catch up with loved ones during the Holiday season we might notice our elderly parents or relatives have aged a bit more. The experts say the Holidays are an important time to recognize such changes.

Margaret Flinter: Alzheimer's disease is the most common form of dementia now, but more than ever there's hope, because of promising innovations. Here to share his insights is Dr. Howard Fillit. He is the Co-Founder and Chief Science Officer of the Alzheimer's Drug Discovery Foundation.

Mark Masselli: Dr. Fillit, welcome to Conversations on Health Care.

Dr. Howard Fillit: Hi everybody, nice to be here with you.

Mark Masselli: You know, I was shocked at the number 6.5 million Americans aged 65 and older are living with Alzheimer's. Why was the Alzheimer's Drug Discovery Foundation started and what does it focus in on?

Dr. Howard Fillit: Well, we are a unique foundation in the sense that we have a very clear and very fine-tuned mission, which is to accelerate the development of new drugs for Alzheimer's disease. And basically, that's all we do since 1998, when we were established by the Estée Lauder family, who saw the great need for translating basic research into Alzheimer's disease that had gone on for the prior 20 years or so to begin funding the risky effort in developing new drugs. It's obviously hard, but we're making a lot of progress.

Margaret Flinter: Well, Dr. Fillit, November is Alzheimer's Awareness Month and so often, I think both in our daily lives and in healthcare we hear elderly people say that they don't want an official diagnosis because there is no cure. But share with us why is getting a diagnosis and maybe an early diagnosis so important.

Dr. Howard Fillit: I'm a geriatrician, so I specialize in the care of elderly people. For the

past 40 years or so the majority of my practice efforts are in people with Alzheimer's disease. And I like to say that I've never met a patient or a family with Alzheimer's disease that I couldn't help. I think that despite the fact that we don't have really effective therapeutics, I do believe we're going to have them in the next five years or so, but even if we do, we're going to still need to care for people. And a good example of what happens when people don't get an early diagnosis is that very often catastrophic things happened. So people that are undiagnosed can wander, they can get lost. They end up in the hospital for a variety of reasons, such as poor management of diabetes, and hypertension and infections, and also caregiver stress. Let's not forget that. Well, there are roughly 6 million people with Alzheimer's. There' are probably 15 to 20 million caregivers. And part of our job as physicians, I do believe is counseling families on how to take care of their loved ones, so that the caregivers themselves don't become depressed and at risk for hospitalization.

The other thing is that early diagnosis is critically important for our research efforts. Less than 5% of people with Alzheimer's disease, participate in clinical trials, it's very hard to find people. But with new diagnostic tests, we can identify people with Alzheimer's disease 20 years before they become symptomatic. And what that means is that today, we can do prevention. There are clinical trials going on right now for prevention of Alzheimer's disease, studying people that have the pathology in their brain based on new diagnostic tests that our foundation has helped to develop, and then entering those people into clinical trials to prevent the onset of symptoms. So there's really a lot of excitement in the field right now over 120 drugs in development, and about over 350 clinical trials going on around the world. It's a very exciting time. We have diagnostic tests on the market.

Mark Masselli: You know your organization is an enthusiastic supporter and investor in blood based biomarker research. What exactly is that? How does it work and where is it available?

Dr. Howard Fillit: Well, biomarkers are critical to clinical care and drug development and I'd like to take the example of cholesterol. Cholesterol in the 1950s was discovered as a risk factor for heart disease. Nobody knew how it worked. And then it took about 30 years for the first statins to come to market. And those statins actually were developed because they were designed to lower cholesterol with the theory that if you lowered cholesterol, you could prevent a second heart attack and that worked actually. So the development of the first statins would have been impossible, if it wasn't for the development and the recognition of cholesterol as a risk factor for heart disease.

We're at the same stage today. We discovered that the plaques in the

brains of people with Alzheimer's disease have a protein called beta amyloid. Beta amyloid became one of the first targets of drugs for Alzheimer's back in the 1980s. We've been working on it about 30 years, just like heart disease. And just in the last few months, we had the first accelerated approval by the FDA for drugs to modify the disease and remove the beta amyloid. What we needed was better biomarkers because the only way that we could detect beta amyloid in the brain was either by brain biopsy or autopsy, and most of my patients didn't want an autopsy just to get a diagnosis.

But we were involved in the development of the first diagnostic test brought to market and approved by the FDA, which is an amyloid brain scan. And that amyloid brain scan is used almost uniformly around the world now in clinical trials to develop new drugs. And we also have for the first time during the past year or two, the marketing of a blood test for Alzheimer's, which is incredible. If you had said to me five years ago or ten years ago, that there would be a blood test for Alzheimer's disease, I would have been astounded. The blood test is now available in 49 States. And there are many new blood tests that are going to be coming to market, making the diagnosis of Alzheimer's disease more precise, less expensive, and more accessible and less invasive to people. The blood tests will be part of clinical care of people with memory disorders and old age.

Margaret Flinter: You know, Mark and I are very engaged in the primary care space and particularly community health centers. And of course, health disparities are a front and center concern for us and we understand that there are really very significant health disparities among different racial and ethnic groups when it comes to Alzheimer's disease. I think we've read Black Americans twice as likely as white Americans to have Alzheimer's, Hispanics 1.5 times more likely, but how are you organizing the research agenda to address them within the clinical work that you're doing?

Dr. Howard Fillit: The most honest answer is we don't know how or why Blacks and Latinos for example, or Hispanic communities are at greater risk. But we do know there is greater risk. I think, probably it's related to common medical comorbidities that are risk factors for Alzheimer's disease, and cognitive decline in old age, and particularly diabetes and hypertension. We know that hypertension is clearly a risk factor for cognitive impairment and Alzheimer's disease in old age, as is diabetes. These common comorbidities and something like 65% of people over 65 have hypertension, and 30% have diabetes, and the combination of the two is particularly devastating to the brain. And in underserved communities, these comorbidities they're actually kind of difficult to manage effectively in underserved communities.

It's very clear that effective management of diabetes and

hypertension can reduce the risk of dementia and Alzheimer's disease. And so what we need to do is improve our primary care, as you mentioned, to make sure that these common comorbidities, that if we can improve the management of those then we would reduce the risk of dementia and Alzheimer's disease particularly, as we've seen in the U.S. that the declining incidence of heart disease in America has been associated with a decline in the incidence of dementia and Alzheimer's, which kind of proves that by managing vascular risk factors, we can have an impact on the occurrence of dementia. And I think another big thing is we need to better recruit underserved communities into clinical trials because you know, the vast majority of people in clinical trials have been Caucasian people.

Mark Masselli: Our organization is part of the “All of Us” research project to try to get the population that looks like the rest of America into these clinical trials. But I want to focus in on some things that have happened over the past couple of years. The FDA approved an Alzheimer's drug, but it's been denied Medicare coverage. However, another group of companies reported encouraging results for their drug. There's also some progress with a nasal vaccine for Alzheimer's. I wonder if you could take us through where we are on the pharmaceutical front, both successes and stumbles along the way.

Dr. Howard Fillit: Well, we've had many failures since 1980. And the last full drug approval that we had for Alzheimer's was in 2003. The drug you're referring to aducanumab or Aduhelm from Biogen did go through a controversial review process. It ultimately received what's called an accelerated approval from the FDA, which is kind of an interim decision based on the idea that the drug clearly showed that it could remove the amyloid plaques from the brain and so we showed that the Biogen, for example, showed that the drug actually worked to do what it was supposed to do, which was to remove the amyloid plaques from the brain, as measured on these brain scans, and the other drugs that are in development drugs from Lilly called donanemab, drugs from Eisai and Biogen called lecanemab, drugs from Roche called gantenerumab, they all do something similar, which is to remove these amyloid plaques from the brain. The big question about what's called the Amyloid hypothesis is if you remove the plaques from the brain, does it slow the rate of decline of cognitive impairment? And it's looking to me like it does. The question is the slowing of the rate of decline that we're seeing with these drugs is clinically meaningful. And for that reason, I think the drug got accelerated approval based on the idea that removing the plaques reasonably predicts that patients would have a slower rate of decline, but it's not a definitive answer. And I think what we're going to see is these other drugs coming down the pipeline that I mentioned, probably getting accelerated approval and maybe if the results are even more robust, maybe will get a full approval.

This is, imagine where cancer was in 1950. You know, we didn't have any approved drugs. We were experimenting. We didn't know what to do, and today, cancer is a chronic disease that's manageable in most cases. We're just on the cusp of a new era of drugs for Alzheimer's disease, these approvals are really exciting because, you know, if we slow it down by 30%, well, we want to slow it down by 100%. But that's where we're going. We're going to be using Biomarkers, what we call precision medicine, like in cancer. I think the Medicare that the Centers for Medicare and Medicaid did not approve payment for the drug is somewhat unfortunate, and somewhat understandable. I think the issue that Medicare had was one about, as I mentioned, clinical meaningfulness when it wasn't clear how effective they were and there were side effects. I think gave caution to Medicare to give what's called the coverage with evidence development. They're saying to the companies, we want you to prove that these drugs really work and that they're effective, and they're safe enough for us to pay for it. It was unprecedented that Medicare refused to pay for a drug that was FDA approved, but that's a whole another discussion that we need to have.

Margaret Flinter: Well, Dr. Phillip Mark mentioned the “All of Us” project a few months ago, and you just referenced precision medicine. So want to talk about genetics a little bit. We understand you're investing in a unique treatment approach that targets the underlying genetics of Alzheimer's disease, and that this approach could generate levels of a gene that might be protective for those with a pre-existing genetic risk for Alzheimer's. Share with us the latest on this research.

Dr. Howard Fillit: Sure. Well, it's been known for many, many decades that if you have a close family member with Alzheimer's, then you have increased risk of parent or sibling and it wasn't really understood till about 30 years ago, a gene and a protein called apolipoprotein E was discovered to be a major risk factor and remains today really the major genetic risk factor for what we call Sporadic Alzheimer's disease and there's three kinds of this gene APOE2, APOE3, and APOE4. About 70% of people in the community have APOE3. So that's thought of as the neutral risk of this gene, which by the way, plays a critical role in cholesterol metabolism, and does a whole host of other things modulating inflammation in the brain. About 20% of people in their community have an APOE4 gene, either one from mom or dad, or two one from mom and one from dad. And the people that have one APOE4 have about a five times increased risk of Alzheimer's disease in old age. And people that have two APOE4s have about a 15 times increased risk of Alzheimer's disease in old age and that's huge. So even though only about 20% of people in the community have an APOE4, about 60% of people with Alzheimer's disease have an APOE4.

Now people that have an APOE2 actually have a reduced risk of

Alzheimer's disease. So it's telling us that something really important is going on in this biology of apolipoprotein E. But because APOE plays so many different roles in the brain, targeting any one of those roles is probably not going to be good enough. So we worked with investigators, particularly Dr. Ron Crystal, who's the Chairman of Department of Genetics at Weill Cornell here in New York and he is an expert in developing gene therapy and they're developing gene therapy to treat this APOE4 problem by putting the APOE2 gene which is protective into a non-infectious virus, and then injecting that non-infectious virus into the brain of people who are APOE4 and seeing if that injection of that virus stimulates the production of APOE2. So the theory is that if we could turn these APOE4 people into being able to produce APOE2, we would offset the risk of APOE4. And this has been approved by the FDA, a small number of people have been treated with this virus gene therapy, and it's been shown that these people actually make APOE2 in their spinal fluid. So it's a really exciting approach, and we're very hopeful that this will move forward and have a big impact on preventing and treating Alzheimer's disease.

Mark Masselli: Well, that's very exciting. And I know there are probably more exciting things coming up because there's a major conference coming right up after Thanksgiving, the Clinical Trials on Alzheimer's disease conference. Tell us about what you'll be presenting and if there are additional outcomes of this conference that you're looking forward to.

Dr. Howard Fillit: Being a geriatrician, I've been interested in aging, and I thought early on that Alzheimer's disease is a disease of aging and all day and we've known, there's been research going on about the biology of aging for over 100 years, but we didn't ever really translate that knowledge into developing therapeutics for Alzheimer's. So things like inflammation is also seen in the aging brain and in Alzheimer’s disease, and indeed, inflammation is recognized as one of the causes of the progression of Alzheimer's disease and for the first time we're going to start seeing at this conference, a result of that therapeutics research, and I'm chairing a section for example, called Beyond amyloid. We want to go beyond the drugs that had been tens of billions of dollars in development to remove the amyloid, which is one theory beyond the tau, which is the other pathology and look at things like neuro-inflammation and vascular problems, and metabolic problems like diabetes that we mentioned and how we can improve that in the aging brain. We're going to hear at this conference coming up with these novel trials and the results, the early results trying to reduce the amount of neuro-inflammation in the brain. There's a gene called TRIM2, which has been recognized and so that's one I think, exciting reports that we're going to start to hear about metabolic disturbances, repurposing Diabetes drugs for the treatment of Alzheimer's disease is a very exciting field right now. The brain is dependent on glucose. If we have reduced glucose availability in the

brain, then neurons get sick and die. There's insulin resistance with aging. It's part of aging, and so drugs like Metformin, for example, which is the leading drug for diabetes is now being repurposed for the treatment and prevention of Alzheimer's and heart foundation is supporting a large prevention trial out of Finland, where lifestyle intervention, comorbidity management of diabetes, hypertension, and the addition of Metformin as a drug sort of parallels the way we prevent heart disease, these days, lifestyle and exercise, diet and sleep and so on reduce stress, manage your diabetes and hypertension, and take a statin, using that model will be a randomized clinical trial of prevention thing that Metformin adds on to that by reducing insulin resistance.

So for the first time, it's going to be a meeting where we're going to have positive results from clinical trial, we're going to see a lot of clinical trials that are non-amyloid, non-tau, non-traditional interventions from many different companies, small biotechs, and academia. There's a lot of excitement in the field and we're going to see a lot of reports.

Margaret Flinter: Let me just ask you about one group early onset. Is the search for solutions any different for this group than it is for the older population? Is there a different biomarker that we're looking at? What is different about this group?

Dr. Howard Fillit: It's rare to see Alzheimer's disease under 65 and I had families from South America come visit me where everyone in the family got Alzheimer's in their 30s and 40s, and these are genetic mutations. They're rare. But in many of the mutations are in the beta Amyloid gene. So they're teaching us that these proteins play a role because alterations mutations in the genes that code for these proteins cause Alzheimer's disease, but it's not the same illness as sporadic illness in old age, in my opinion, because the sporadic form of the disease have multiple causes, particularly lifestyle and comorbidity whereas you're taking the healthy 30-40 year old and seeing them develop the cognitive decline. There's one issue there, which is the mutation. So you can't necessarily translate what's going on in these genetic mutations. But I think we have learned a lot from people that have these mutations around the world, and so it is unfortunate and I've seen people in my practice in their 40s and 50s with Alzheimer's, it's very, very tragic, but it's actually quite rare.

Mark Masselli: As we started off the show, we mentioned that we're in the Holiday seasons, what’s some good advice for noticing and dealing with any changes we might see in our relatives around the Thanksgiving time.

Dr. Howard Fillit: You know, of course, memory, but the way it manifests, for example, at Thanksgiving dinner is that mom might ask you like, what are we doing tomorrow? And you'll say, Well, we're getting together over

sister's house tomorrow and then 5 or 10 minutes later, mom might say, what are we doing tomorrow? You know, that's kind of out of the ordinary. That's, you know, very obvious sort of memory problems, particularly short term memory, mom will remember when sister was two years old, and that wonderful day that they had, but she might not remember what you told her five minutes ago, mom might be the person who's hosting Thanksgiving dinner and now suddenly, she's having trouble cooking, these kind of functional deficits that we see they're so obvious.

Another thing is loss of emotional control and executive function, which is very common in the early stages of the disease at a stage where we call -- that we call now mild cognitive impairment or MCI. And MCI is characteristically a stage where there's memory disorders, but also loss in what we call frontal executive functions, loss of emotional control, change in personality. So in the past, mom might have been the peacemaker at the dinner table when everybody else is fighting. And now she's kind of lost control of her own emotions. And that's a change in personality for mom or dad.

And I think that would be another sign that I would be worried. And if you combine them, usually these things occur together. Word finding is common with old age, remembering names is common, but forgetting the name of your daughter, who would not be common. So there's a difference. People always ask me, Well, I'm having trouble retrieving words, that happens with old age. But when it gets into the ability to recognize or remember the name of a loved one that you've known for 40/50 years, that would be a problematic sign for me.

And I think under any of these circumstances, a person should probably be brought to primary care or to neurology care, just to get some simple cognitive testing that can take 10/15 minutes and see if there's something going on, so we can get the early recognition. We can do the advanced care planning, but most importantly, we can understand what's going on with mom and help her to get through this horrible disease.

Margaret Flinter: Well, thank you, Dr. Fillit for your very important work. You can learn more about Conversations on Health Care and sign up for our updates at www.chcradio.com. Thank you again, so much for all that you're doing and for joining us today on Conversations on Health Care.

Dr. Howard Fillit: Nice to be here with you.

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Mark Masselli: At Conversations on Health Care, we want our audience to be truly in the know when it comes to the facts about health care reform and policy. Lori Robertson is an award winning journalist and Managing

Editor of FactCheck.org, a nonpartisan, nonprofit, consumer advocate for voters that aim to reduce the level of deception in U.S. politics. Lori, what have you got for us this week?

Lori Robertson: COVID-19 vaccination has been shown in multiple studies to reduce the risk of stillbirth by protecting pregnant people and their babies from the Coronavirus. There is no link between COVID-19 vaccination and an increased risk of stillbirth despite such claims being made online and on social media. These posts have been circulating a leaked memo from a Fresno California Hospital to incorrectly suggest that vaccination increases the risk of stillbirth.

The memo reportedly came from a staff member at a Fresno hospital, who claimed that the stillbirth rate had skyrocketed after the COVID-19 vaccine rollout. The employee shared an e-mail from a managing nurse that referred to an apparent uptick in the number of so called demise patients, including 22 demises in August, but the memo makes no mention of COVID-19 vaccination and is primarily focused on informing nursing staff how to properly handle the demise specimens.

Moreover, the e-mail never states that its figures are only for stillbirths. Fetal death or a fetal demise refers to death at any time in pregnancy. Deaths before 20 weeks of gestation are miscarriages, while deaths after 20 weeks are considered stillbirths, conflating stillbirth with fetal death erroneously exaggerates the number of stillbirths. Among 16 studies that have assessed COVID-19 vaccination safety with respect to stillbirth, none has found an increased risk of stillbirth following vaccination. On the contrary, a meta-analysis reviewing some of those studies found that vaccination reduces the risk of stillbirth.

A Centers for Disease Control and Prevention study looked at 1.2 million delivery hospitalizations in the U.S. between March 2020 And September 2021. It found that women with COVID-19 had nearly double the risk of a stillbirth compared with those who did not have COVID-19. And that's my fact check for this week. I'm Lori Robertson, Managing Editor of FactCheck.org.

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Marianne O'Hare: FactCheck.org is committed to factual accuracy from the country's major political players and is a project of the Annenberg Public Policy Center at the University of Pennsylvania. If you have a fact that you'd like checked, e-mail us at www.chcradio.com. We'll have FactCheck.org's Lori Robertson check it out for you here on Conversations on Health Care.

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Marianne O'Hare: Each week Conversation's highlights a bright idea about how to make wellness a part of our communities and everyday lives.

Heart disease is the leading cause of death for both men and women in this country. And while it's known that women often present with cardiac disease differently than men, the standard treatment protocols are based on studies done mostly on men for whom blockages are the primary cause of heart attacks. But not so for women whose cardiac events often have different causes and different symptoms. Not just chest pain, but often pain in the jaw or in the stomach.

Dr. Samit Shah: When women come in, it's not always so clear and women are less likely to have blockages in their blood vessels and so we see heart attack without blockages in the blood vessels.

Marianne O'Hare: And according to a recent study done by Yale New Haven Hospital, Interventional Cardiologist, Dr. Samit Shah, an accurate diagnosis can sometimes take years.

Dr. Samit Shah: The average time to diagnosis is more than six years, most people have had two heart catheterization without a diagnosis multiple stress tests, and it reflects how you know what the patient is going through.

Marianne O'Hare: Dr. Shah's findings showed that when a woman presents with a cardiac event in the ER, the standard testing protocols to look for blockages in the large vessels. But that baseline test does not pick up on problems in smaller vessels were the cause of heart attacks in women may lie.

Dr. Samit Shah: And it's all part of what we call the comprehensive coronary physiology program. What we want to tell our patients is that we have more testing that we can do, that can really get to the bottom of these problems were otherwise it's like chasing a goat.

Marianne O'Hare: Shah found it by doing a second more comprehensive scan, you may identify what's causing the heart attack in women taking the skin deeper into the smaller vessels where more nuanced problems can be detected.

Dr. Samit Shah: So, you know the conditions specifically that I look for is something called coronary microvascular disease and then the other big one is coronary vasospasm. There are problems that aren't related to cholesterol plaque.

Marianne O'Hare: Dr. Shah is expanding his study to nine teaching hospitals around the country to include this comprehensive coronary physiology program in their treatment protocols to automatically progress to the next scan if a blockage isn't found. He believes the larger national dataset from multiple hospitals will yield the necessary impetus that should

lead to a change in the national protocol for diagnosing heart disease in women, which he says will not only save lives, but insurance companies will see the wisdom of saving money in the long run. The Comprehensive Coronary Physiology program, seeking to standardize a new protocol for cardiac care for women that will yield a healthier outcome from this leading killer of women. Now that's a bright idea.

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Mark Masselli: I'm Mark Masselli.

Margaret Flinter: And I'm Margaret Flinter.

Mark Masselli: Peace and Health.

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Marianne O'Hare: Conversations on Health Care is recorded in the Knowledge and Technology Center Studios in Middletown, Connecticut, and is brought to you by the Community Health Center, now celebrating 50 years of providing quality care to the underserved where healthcare is a right not a privilege, www.chc1.com and www.chcradio.com.

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