

OMG Presents The Top Medical Stories of 2023



PODCAST 38

New drugs to slow Alzheimer's progression, mRNA technology used in cancer vaccines, rapid point-of-care molecular testing—tests which give results while the patient is still in the clinic, and diabetes medications turned into weight loss drugs. These are some of the topics we'll be discussing today as the top medical stories of 2023. Welcome to *On Medical Grounds*. I'm your host, Jane Caldwell.

This year, there were several new drugs receiving accelerated approval by the FDA because they were shown to **slow the progression of Alzheimer's disease** in large clinical trials treating patients with mild cognitive impairment. One of these drugs was donanemab. Patients at the Missouri Memory Center at Citizens Memorial Hospital in Bolivar, Missouri recently participated in the international clinical trial with donanemab. OMG spoke to Dr. Curtis Schreiber, Medical Director at the Missouri Memory Center to get the inside story on this new drug.

So, donanemab is a monoclonal antibody treatment for Alzheimer's disease. Forever, we've known that amyloid, a protein, a normal protein that accumulates abnormally in the brain of Alzheimer's patients is part of Alzheimer's disease. In fact, if you take it back to the very beginning, it was Dr. Alzheimer who first discovered amyloid and tau, the two pivotal proteins that are in the brain and are required for the diagnosis of Alzheimer's disease.

Donanemab is an antibody that was specifically custom designed to remove that accumulation of amyloid called an amyloid plaque that builds up in the brain of patients with Alzheimer's disease. And so it's a targeted therapy. It's targeted to remove the amyloid plaque from the brain of patients who have early Alzheimer's disease.

Dr. Schreiber summarized the results of that phase III trial:

In the phase III study for donanemab that was recently announced, the primary outcome measure is something called the ADRI. That's just an acronym for this measurement. And in the phase III study for donanemab, what was shown was that over the 18 months of the study, there was a 35% relative slowing in that outcome measure. That outcome measure meaning combined cognitive scales and functional scales; what's going on with memory and thinking as far as testing, and what's going on with how things are at home. And so this is news. This is news that we have treatments now that have clinical trial data to show a slowing of the progress of Alzheimer's.

2023 ushered in not only new drugs, but several new vaccines. **Based on mRNA technology**, new personalized cancer vaccines may become widely available. OMG spoke with Dr. Jeffrey Weber, deputy

director of NYU Langone's Perlmutter Cancer Center and a professor of medicine at the NYU Grossman School of Medicine. Dr. Weber was the senior investigator of a phase 2 clinical trial for an mRNA melanoma vaccine. This vaccine was shown to significantly reduce the recurrence of tumors in patients when combined with an immunotherapy drug. I asked Dr. Weber how the mRNA vaccine alerts the patient's immune system to cause it to attack the tumor:

Well, it's done in two ways. There's a minor way and a major way. The most important aspect of the mRNA is it encodes all of these potential protein sequences that could be recognized by the immune system in a cancer patient. And it's personalized. The genetic changes in a tumor that aren't present in the normal cell are unique to each tumor. That's good news and that's bad news, I suppose. Now, the bad news is you can't have an off-the-shelf RNA vaccine for everyone, but it has to be personalized.

The good news is, if that works, it's very personalized. So what happens is the RNA gets injected intramuscularly. It's a milligram, which is, that's a lot of RNA sequences. That's many millions. And the RNA is encapsulated to protect it from being degraded by the body's normal enzymes. And it gets into the muscle and it finds its way to what we call antigen presenting cells. And those are cells that can show the immune system an antigen.

It uncoats, it gets into the cell, and in the cytoplasm of the cell, there are things called ribosomes. Those are little factories. We call them organelles. And those little organelles will bind the RNA, and it'll translate the RNA into pieces of protein. The pieces of protein find their way into another organelle called the endoplasmic reticulum. And there they get chopped up into little bits by what I think of as the garbage machine of the cell. It sort of chops up the proteins into little bits and eventually most of them get discarded. But many of them will not get discarded and the little bits, which we call peptides, make their way in the endoplasmic reticulum onto the surface of something called MHC molecules and they get kicked out onto the surface of the cell where they can be recognized by the immune system. So the RNA encodes the protein, the protein gets made in the cell, it gets chopped up into little bits, and the little bits are what are recognized on the surface of the cell by the immune system to generate an immune response and clear the tumor.

Respiratory Syncytial Virus has received growing awareness in the media due to its prevalence and reoccurrence in infants and toddlers. **A new vaccine for RSV** was approved and recommended by the FDA for pregnant women and persons over the age of 60 years. Vaccinations given to pregnant women have been shown to protect their newborns from the disease. We spoke with Dr. Joseph Domachowske, professor of pediatrics at the New York Upstate Medical University in Syracuse in 2021 prior to approval of the RSV vaccine:

I think it's always impressed me that influenza is very well known across the general population inside and outside of medicine everywhere and I'm not sure why it gets that much attention, although, the morbidity and the mortality can certainly affect us at any age. And we do have vaccines and antiviral treatments available to either prevent or to treat it. But if we take the young infants, children in their first year of life, RSV is six times more likely to lead to hospitalization compared to influenza. Why is it that so few people really know what this respiratory syncytial virus is? We have to get the word out and increase awareness for how dramatic this virus can be and how pervasive it is every year. We have between one and two percent of our entire birth cohort hospitalized with this infection every year. Any other infection that did something

like that would get loads of attention or we have long had a vaccine to prevent it. RSV is that one that sort of lingers. And I think that we really need to increase awareness and make folks understand why it's so important to try to prevent this infection.

Point-of-care testing refers to tests that are performed in or near the medical clinic where a patient is being diagnosed. Using point-of-care molecular DNA/RNA or protein methods allows clinicians to get results while the patient is still in the clinic. Point-of-care tests may use polymerase chain reaction, also known as PCR, to detect and even quantify viral or bacterial pathogens. PCR can also be used to quantify human biomarkers. Biomarkers are mRNA or proteins released in our bodies in response to infections. Scientists have correlated certain biomarkers to different types of infection, either viral or bacterial. Viral infections do not respond to antibiotic treatment. Differentiating between types of infections helps the health care provider quickly diagnose an infection and choose the proper treatment.

In-home testing was normalized during the COVID-19 pandemic. COVID detection kits were free and readily available through federal government programs. They used lateral flow devices, the same kind used in in-home pregnancy tests, to help with early COVID detection. We predict that medical kit companies will create more at-home tests in the years to come.

During COVID we moved to telehealth for medical care and remote meetings such as Zoom and Teams for work. Medical monitors have also gone remote. I have a family member with diabetes. Her management of the disease was greatly improved in 2023 due to the use of a telemetric sensor that she wears on her arm. It sends her blood sugar levels to her physician in real time, so she is constantly monitored and no longer has to stick her finger daily. For the first time in many years, she is able to control her blood sugar levels.

And speaking of diabetes... diabetes medications that reduce HbA1c levels such as dulaglutide (Trulicity®), liraglutide (Victoza®), and semaglutide (Ozempic®), have been shown to achieve weight loss in patients due to appetite suppression. Please note that mention of these products is not an endorsement. Here's a fun fact: These drugs are based on the metabolism of a desert lizard, the Gila Monster. The Gila monster is a venomous critter that has a unique ability to maintain steady blood sugar levels—even when it hasn't eaten for a long time. Venom from the Gila Monster inspired the development of this class of drugs used to moderate blood sugar. The FDA has already approved one semaglutide for the treatment of obesity. We anticipate that more drugs from this class will be fast tracked for FDA approval next year.

Last, but certainly not least, Sexually Transmitted Infections or STIs are on the rise once more. We spoke with Dr. Yukari Manabe the director of the Johns Hopkins Center for Innovative Diagnostics for Infectious Diseases to get her perspective on this alarming trend.

Dr. Jane Caldwell

Okay. All right. What do you feel are the major drivers for the recent increase in STIs?

Dr. Yukari Manabe

STIs have actually been increasing since 2016. So, if you're considering that recent, really the last five to 10 years, they have been increasing over that period.

I think overall, the early surveillance data from 2020, (usually they lag about two years), are also discouraging. I think this is all still going the wrong direction. Major drivers, I think are, because we don't

detect enough infection, particularly asymptomatic infection. I think that we probably need to do a better job communicating the risk of STIs to the general public here in the United States.

Dr. Jane Caldwell

Isolation, masks, and social distancing during the COVID pandemic helped reduce outbreaks of influenza and RSV. Why not STIs?

Dr. Yukari Manabe

Though people were very good about wearing masks, particularly early on in the pandemic, I think that that the same was not true in terms of social distancing and sex. What's really interesting is if you look at the lockdown period around March of 2020, maybe through June of 2020, in fact there probably were fewer STIs, but we made up for lost time in the latter part of that year, and we continue to see more cases.

Part of it also though was that there was less detection as well, so I'm not sure the numbers were as accurate. People didn't have good access to getting STI testing. The data from 2020 are varied because you can see that there was much less testing during the lockdown period. For example, chlamydia looks like it might have gone down in 2020, but if you look at the actual testing rates, there was much less testing, particularly during the lockdown period. What's interesting about chlamydia, particularly in women, is it can be asymptomatic. So (for people with) symptomatic infections, people tend to look hard to try to get testing and treatment. Whereas when you're asymptotically infected, you have less of an opportunity then to detect that asymptomatic infection.

Dr. Jane Caldwell

I see. What are the classical STIs of concern right now?

Dr. Yukari Manabe

The reportable ones are obviously gonorrhea, chlamydia, and syphilis. HIV is also a sexually transmitted infection, although sometimes we categorize it separately. I think those are sort of the classical STIs of concern right now because they're reportable and they're tracked, and so we can see how they go year on year.

Other infections that are probably important but are not reportable are things like Trichomonas vaginalis can cause bacterial vaginosis in women, but also men can get infected of course, because it's transmitted between men and women. As I said, HIV is treated as a separate category, and overall I think that HIV trends are starting to go down.

But again, different money goes towards HIV control than sometimes STI control. And of course, that's part of the crux of the problem. We need to put more, we need to invest more, if we want to get STIs under control in the United States. And our public health system, as you know, has been very stressed over the last three years because of COVID.

Many of the people that actually work on STIs have been flipped over to COVID. Many of the machines that are used to diagnose STIs have been flipped over to COVID, and as a result, many of the infrastructure elements necessary for us to both diagnose and treat STIs have really been moved over to deal with the current pandemic.

We really need to develop deeper infrastructure in our public health system if we want it to address things that are basically a problem instead of always having to move to the next thing. Monkeypox also, similarly, took a lot of the focus of public health officials and practitioners away from STIs.

Dr. Jane Caldwell

How are STIs diagnosed?

Dr. Yukari Manabe

So most often you get a swab or a urine specimen for people who have genital STIs and you would do a molecular test. That's the most reliable way. Of course, in some resource-limited settings, and even here in the U.S., you might do what we call a Gram stain, someone has a drip, you would put that onto a slide you would stain it and you could see, for example, gonorrhea. Chlamydia is not easy to diagnose that way. Gonorrhea can also be cultured. Chlamydia is very difficult to culture, so molecular testing has really allowed us to diagnose many more STIs than we had in the past. Nonetheless, when someone comes in, those tests don't often come back quickly. It may take six to 12 hours, maybe up to 24 to 48 hours in places that are more rural, that are sending their testing to some central reference location. Therefore, if someone comes in with symptoms consistent with an STI, they will go ahead and get empirically treated for everything while waiting for the results.

So though we test and treat, sometimes we treat and then wait for the results of the test, and that's something that I think we should try to address.

Dr. Jane Caldwell

Are there any new technologies for more rapid test results?

Dr. Yukari Manabe

That's the thing that I think we've been most interested in trying to develop here at Johns Hopkins in our Center (for Innovative Diagnostics for Infectious Diseases).

So, point-of-care diagnostics mean tests that can be performed using the instructions for use by any paraprofessional. You don't need to be trained. You can just read the instructions and do the test. That kind of point-of-care testing is really necessary. There are three tests that are currently available. They take anywhere from 40 to 90 minutes and most people know, when you've been to a doctor's appointment or seen a clinician, rarely does your appointment last an hour or an hour and a half. You might not be in the office. So we'd really like to develop tests that can be done, say in 15 minutes, because most people are willing to wait 15 minutes.

If I were to choose two words to describe medicine in 2023, they would be REMOTE and FAST. It's a busy world we live in, but we're glad you took the time to consider the medical trends of 2023. Please go to our website **OnMedicalGrounds.com** to hear the full interviews we referred to in this show.

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