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Announcer: Welcome to a recap of our latest Third Thursday Webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at michaeljfox.org.

Maggie Kuhl: Hello, and welcome to our webinar today. I'm Maggie Kuhl, vice president of patient engagement here at The Michael J. Fox Foundation, and I'm thrilled to be with you to discuss what I think is a really cool topic, the science of smell. We're going to talk about how it works, how it's linked to brain disease, and how people with smell loss are helping us learn more about Parkinson's and how it starts and hopefully how to prevent it.

So let me now introduce our esteemed panelists for today. First we have Dr. Ethan Brown, a movement disorder specialist and assistant professor of neurology calling in from San Francisco. He's at UC San Francisco. And Ethan is also a site investigator for our landmark Parkinson's Progression Markers Initiative, or PPMI, which we're going to talk a lot about today. And he has published extensively in the last few years on the connection between smell loss and what's happening inside the biology of our brains and bodies. So Ethan, thanks for sharing your expertise with us today.

Also joining us from the West Coast is Dr. Zara Patel. She's an otolaryngologist. We practiced that beforehand at Stanford Medicine, an ear, nose and throat doctor for us non-clinical folks, and she's also the director of the Stanford Initiative to Cure Smell and Taste Loss. Dr. Patel, thanks for joining us. We're also really excited to hear from you on some of your research into how to measure smell loss.

Don Upson is also joining us. He lost his sense of smell 15 years ago. He has not been diagnosed with Parkinson's disease, but he joined us in the PPMI study to help us learn more about how the disease starts and changes over time. So Don, thanks for sharing your experience and talking about why you've joined research with us today.

And Dave Harris also lost his sense of smell more than two decades ago, but he was diagnosed with Parkinson's in 2022. He's also in PPMI. And Dave, I think it's really cool you recently shared that while you have smell loss, you don't have taste loss. So we're also going to talk a little bit today about how those two symptoms interact and how you can treat or supplement with lifestyle changes to approach both of those. So Dave, thanks so much for sharing your own history with us.

So we're going to dive in and start with a little bit of the science, the science of smell. So Dr. Patel, maybe you can just explain to us how does smell work? How do our bodies detect different scents?

Dr. Zara Patel: Yeah, so everything in our environments outside, inside each other have smells, and those are odor molecules that are floating through the air and they enter our nose. They have to dissolve into a mucus layer and then they bind to these olfactory receptor neurons at the very top, highest, deepest part of your nose. And then those nerves send a signal to the olfactory bulb, which is just right above the nose at the very base of the brain. And then the nerves in the bulb send the signal back to the brain, and so that's the very basic way in which we smell. And as you noted, sometimes smell and taste is related. About 80 to 90% of our ability to taste the flavor of our food is dependent on your smell. Other than those very basic tastes like sweet, sour, bitter, umami, and salty, everything else about your ability to taste the flavor is based on your smell.

Maggie Kuhl: I've been in brain research for a long time and it just continues to amaze and impress me how our bodies work and how every system is connected and there's so much handoffs and interplay. So Don, I'll go to you first and then Dave want to hear from you as well. We shared that you both have lost your sense of smell. I would love to just hear more about how you started to notice that and what it's been like really. So again, Don, maybe first.

Don Upson: Okay, thank you. Yeah, I was in about my early sixties and my sense of smell just was slowly eroding away until there was really very little left. And as you just pointed out, it also really affected taste, but I had a little more taste than I had ability to smell. My ability to smell was pretty close to wiped out. Every now and then though, it's interesting, an identifiable odor will loft by and I'll have a one-off chance to actually use my sniffer again, so that's fun.

So I'm trained as a chemist. I'm a chemist by background, spent my whole career in chemistry, and without any real evidence I attributed my loss of smell to my exposure to chemicals. It was either that or it was age. It could have been that too, I suppose. But at any rate, that was what I thought of at the time.

But then 2015 came around, which I'll discuss a little later in our program here, and I got some news that caused me to wonder if Parkinson's disease could be the culprit. And so like I say, I'll leave more on that for later.

Maggie Kuhl: Cliffhanger, all right. I love it. Dave, how about you? How did you first notice your smell loss because you said that it came quite a while before your Parkinson's diagnosis?

Dave Harris: It did, and it's probably close to 25 years ago. I was in my early forties and it seemed to me like almost overnight I lost the bulk of any sense of smell that I had ever had before. There were still a few things I could still smell, but those fairly quickly faded off to where I had pretty much total loss of smell. But like Don, occasionally I will get a whiff of something very faint that I can detect some sort of a smell, but that's not real common. It's fairly rare. And like Don, I had exposure to chemicals at an earlier age, which I think may be possibly one of the contributing factors, which I'll go in a little bit later on in the presentation for another cliffhanger.

Maggie Kuhl: Great, keep them on the line. I love it. So Dr. Patel, I'm going to go back to you because both of you said something, and this is maybe a two-part question. The first is where in that system that you explained around the odor molecules and the olfactory bulb and talking to the brain and sending it back, where does that degenerate when you lose your sense of smell? What part is not working correctly? And then maybe also around, you both mentioned some of these chemical factors, and we're going to talk about Parkinson's, but what causes that breakdown?

Dr. Zara Patel: So there are so many different reasons why people lose their sense of smell. And the reason why people lose their sense of smell is really what causes us to understand where in that entire process there may be a breakdown or degeneration. And sometimes it's not just one part of the smell system, sometimes it's multiple parts.

So for example, when it is a toxin, perhaps chemicals or some noxious fume or, for example, a post-viral type of smell loss like COVID-19 or other viruses, it's often at the very front end of that smell system, the olfactory nerves themselves in your nasal cavity that either they or supporting cells in that epithelial lining have become really inflamed and that inflammatory process can cause damage and lead to breakdown. And there's theories about why so much inflammation occurs, and one of those theories is actually to decrease transmission of whatever that may be to the brain through the olfactory system. But certainly there is inflammation and issues that can happen at the level of the nerves.

Now we know in neurodegenerative diseases, and Ethan will talk a little bit more about this, that the olfactory bulb and olfactory cortex, it's often where we first see the earliest signs of neurodegeneration, the tau tangles and the neurofibrillary tangles, the plaques in Alzheimer's, things like that often present in these areas first. And so in something like a neurodegenerative disease process, it may be more in the brain itself and in the olfactory bulb itself that there is breakdown.

But there are so many different reasons we can get into more causes of smell if you want, but it could really happen anywhere along that system.

Dr. Ethan Brown: I think I'd just reiterate all the possibilities. You can see how many other connections that there are between the olfactory bulb and the brain. And I think all of us know this anecdotally of how quickly childhood memories can be called up from a specific smell or emotions, for instance, and I think that the underlying neuroanatomy here has shown it how many connections the olfactory system really relies on throughout the brain in the frontal lobe and the amygdala and the hippocampus as well as parts of the brainstem. And when you're thinking about smell dysfunction, problems in any of these areas can really be associated with that.

And then I wanted to turn back to Dave. Dave, can you tell me a little bit more about your journey to a Parkinson's disease diagnosis?

Dave Harris: My journey probably began likely decades ago in my youth. I grew up on a farm and routinely handled a lot of chemicals including like fertilizers, pesticides, herbicides, insecticides. At that time, protection was not really even thought of, so I was routinely handling this with no gloves, no mask. So I think that could have possibly been a contributing factor.

I think two other things possibly could have led to my ultimate diagnosis. I had a traumatic brain injury when I was very young. I fell onto my head and was out with a concussion for four hours. And I think based upon the research that my wife and I had done, I think those two things, in addition to a family history of Parkinson's disease, could all be contributing factors toward my eventual diagnosis.

And then like we talked about, fast forwarding to about 25 years ago, I lost my sense of smell for the most part. And then most recently, I think my journey led me to go to a neurologist to get an evaluation because I was noticing some slight hand tremors, some internal tremors, plus I had stiffness in my neck and just an overall slowness and rigidity. I was having trouble getting out of my car. My handwriting was becoming very small and cramped. So I did go to see my neurologist and through a clinical observation it was determined that I had Parkinson's. So that is what where my current situation is.

I am not on medications because most of my symptoms are not the motor symptoms, other than the slowness and rigidity and a very small amount of tremors. Most of mine are what I would consider and call non-motor symptoms. I think how I'm able to slow the progression is through a very rigorous exercise program that I am participating in at different venues. So I think that has been very, very helpful for me. So that's what brought me from the beginning to my current situation.

Maggie Kuhl: Thank you so much for sharing that. Ethan, Dr. Brown, could you talk us through some of the understanding, like Dr. Patel was saying, that other causes of smell loss might be more external where some of the causes of Parkinson's might be linked more closer to the brain. So what do we know today about the Parkinson's disease and smell loss connection?

Dr. Ethan Brown: Sure. A lot of brain diseases are actually associated with smell loss, and we went over some of the anatomy so you can see how a number of different brain diseases can affect different areas that would ultimately affect smell. Parkinson's is very tightly tied to smell loss, as we're hearing from Dave and from other participants and patients too.

The way that smell is affected in Parkinson's is still not completely known, but we do know that there's actual buildup of the abnormal protein called alpha-synuclein in the olfactory bulb itself, and that can occur long before people are diagnosed with Parkinson's. It can even occur in people who were never diagnosed with Parkinson's but may be at risk. And so we think that that might be a primary driver, although there are probably a lot of other mechanisms, maybe alpha-synuclein in other areas, maybe inflammation, as Dr. Patel was mentioning as well.

And this could be the pathology or the problem in other brain diseases too. But other brain diseases, as I said, may affect other areas also.

Maggie Kuhl: If someone has smell loss but not a Parkinson's or other diagnosis yet, is it possible to tell early what type of smell loss it is and what disease they are at risk of developing?

Dr. Ethan Brown: Yeah, I think that's a great question. There are some ways. First maybe we should take a step back and talk about testing. I don't know if we've had an opportunity yet. So there are a number of different ways to test someone for smell loss. And maybe Dr. Patel, can you talk a little bit about those various ways? I know some but not nearly as many as you.

Dr. Zara Patel: Yeah, I'd love to. So there are actually so many different ways to test smell. In a recent compendium of all the clinical knowledge we have on smell loss, there was a table that was 20-pages long on all the different smell tests that are out there around the world. That can show you that none of the tests that we currently have are actually really wonderful.

So the most common one that we use here in the United States is called the University of Pennsylvania Smell Identification Test, and that's a scratch and sniff booklet that has people identify different odors, pick from a list of four, and there's 40 options to go through. And there's a Sniffin' Sticks test that's the most commonly used test in Europe. This is pens that have an odor and there's different ways to test not only identification but discrimination and threshold. And there are many, many other tests that can test those different facets of smell.

However, as you can imagine, all of these tests at the end are really subjective measures of smell. You're asking someone can you identify this, where is the threshold, can you discriminate between these, and none of them are truly objective. If you think about the way that we test for vision loss or hearing loss, we have much more rigorous, much more objective tests, and you can imagine the barriers that come up when we do subjective testing.

For example, we don't know whether or not someone is smelling the smell or not. We are really just testing whether they're familiar with a particular odor, which can change based on the geographic location of where someone is born, whether they live in a rural environment or an urban environment. And then on tests like the UPSIT, for example, that scratch and sniff one, we're testing literacy, and we know that patients often won't actually tell their doctors if they cannot read, they're too embarrassed, so they'll just guess. And you're testing things like language when you're doing other types of testing.

So for all the tests that we currently have, although we have been able to find a lot of good data based on these objective tests, we are leaving some people out and probably not getting the most vigorous, most scientific way of testing smell, and that's part of my research actually. I'm currently developing a device that I hope to be a truly objective test of smell, an endoscopic device that we could easily just place in someone's nose, record directly from the neurons themselves and really understand not just their amount of loss, but probably patterns of loss, which goes back to the question to Ethan about can we tell what is the cause of loss. Sometimes we can tell right now just based on a really good history taking, but I suspect that if we get an objective smell test, we may be able to discover patterns of the neuronal nerve activity that points us in one direction or another also.

Maggie Kuhl: So what I'm hearing is there are some issues with the accessibility of our current tests. We actually are funding an update or a change to the UPSIT in Africa given that a lot of the smells that we use are not familiar in that area and we do our PPMI study there.

And then also, back to my original question, it's not discerning as to what disease someone might be more at risk for. It's really at this stage, I think, and this is the way that we treat it currently in some of our studies, is an initial step to then do additional testing afterwards.

So smell loss as a monolith cannot tell you what disease, but with smart researchers like you on the case, we might soon have not only more objective, but also perhaps more discerning or differentiating tests that could help us send someone down a specific lane, so to speak.

Okay, we have a couple of questions that I want to bring in, and maybe this is related as well. Dave and Don, you both commented that you can still smell some things or some things come up. Dr. Patel, what's behind that? Is it just you're like a surge maybe after you exercise, the neurons are just firing really well and things are working again, or are there certain smells that are more likely to be lost versus others? Can you explain?

Dr. Zara Patel: Yeah, there's probably a combination of factors that go into that. It's a very common thing that people with smell loss will tell me in my clinic, and part of it has to do with the fact that not all of your six to 10 million smell nerves that you have on either side of your nose up at the top, not all of them die off or regress at the same rate. They're not just suddenly all gone. And so the reason that some people can smell some things but not other things likely has to do with the type of olfactory receptor neurons that they still have and the amount of redundancy that the system has in those different types of neurons. And the combination of different neurons is really what often allows us to truly smell a full smell.

So for example, coffee is a good example. That's not just one molecule that's binding to one nerve sending a signal back. It's many different molecules binding to many different types of olfactory receptor neurons, and that combination is the signal that we recognize, that our brain recognizes as coffee. And so missing just a few of them may make that coffee just smell off, like what we call paraosmia or distortion of smell or missing all of them. You might just not be able to smell at all. Or if the problem is more of a central processing type of issue, that can also lead to these things.

Now being able to smell something that you weren't able to smell yesterday may have more to do with the fact that you may have some level of inflammation in the lining of your nose. That changes based on your environment and what you may be more or less reactive to. So not just allergens, but there's so much particulate matter in the air now that can affect the inflammation and swelling of the lining. And so if you are on a particularly not inflamed day and you have a lot of really good blood flow and you have the right amount of mucus layer in your nose, that might come together to create the perfect environment for that nerve to be able to pick up on that smell.

Maggie Kuhl: So there's hope that you may smell again. And Don, maybe I'll toss it to you from your own journey, and we got a question. Is smell loss usually more gradual or more sudden, and would love to hear from your own experience. And then Ethan or Zara as related to disease, is this something that is it more of an awareness thing you don't really notice and then, oh wow, that's all gone, or do you lose one thing after another and it's again more of a slow roll towards hyposmia?

Don Upson: It's a little hard to say. I think a lot of it happens very gradually to the point where you almost don't even consciously understand that it's happening, and then all of a sudden you go out for that nice pizza or something that you've enjoyed a thousand times and all of a sudden it's not the same, and you realize that something has changed. And so I think it's, I know Dave said that his came on fairly suddenly. I'd say mine came on rather gradually. It probably took it several years to go from what I would consider a very functional smell ability to very little smell ability.

Dr. Zara Patel: There's a good study actually that came out in 2017 that shows that up to a quarter of patients with smell loss are not aware of their smell loss. And that's because often in patients, especially as we get older, it is not necessarily obvious to people themselves. And it is often their significant others or their family members that are the ones that eventually let them know, "Hey, that dish that you've cooked this way for so long, it just doesn't taste the same." Or, "Hey, the garbage has been sitting out there and it's been reeking for the last week. Can't you smell it?" Very often this sudden change that the patient themselves then realize, but it's been in a long process and that's why they haven't noticed it.

Maggie Kuhl: Well, and it sounds like also much like Parkinson's disease. It can be a heterogeneous journey, a bespoke individual experience. We've referenced a couple of times this big study that we have PPMI and how we are using smell loss as this initial risk factor screening to then learn more. And Ethan, maybe you could talk us through what this study is about and really why we're using smell loss as this first line of screening.

Dr. Ethan Brown: Of course. The PPMI is a large study, international, and has been going on for a long time. Some of you out there may be participants. I've met participants that have been in since the study started in 2010. And an overriding goal of PPMI, although it's contributed in many different ways, is really trying to find a biomarker for people with Parkinson's disease that can represent disease diagnosis and severity.

Right now we don't have a great way of tracking progression in Parkinson's disease or in people who are at risk, and we really think that that's essential to develop therapies that can slow progression and to understand mechanisms more about how Parkinson's progresses. And with some of the realization that, first of all, we also don't really know when Parkinson's disease starts. We know that people have symptoms long before they're diagnosed, and we know that people even experience some, many different types of symptoms before they're diagnosed, such as smell, but other symptoms as well, and we can see elements of disease in people before they're diagnosed.

And so with that kind of recognition, PPMI has really tried to enroll more people who may have some markers that suggest they're at risk of a Parkinson's disease diagnosis or may have some markers similar to people with Parkinson's disease.

And the way that we're recruiting people that are in that group is through this smell test. So what we use is what Dr. Patel mentioned, not perfect, but it's what we have and it has been very effective at enrolling a ton of people. Thanks to people like Maggie and many other people at PPMI, this scratch and sniff has been sent out to over a hundred thousand people I think at this point, and is really what we find people basically complete this at home and then send it back to us, and if they have a low sense of smell, they're eligible to come in and have further evaluation.

Maggie Kuhl: I want to cover something that we've been getting a lot of questions on. So as you said, a lot of people have received this test and a lot of people are asking if they get their personal results returned back to them. PPMI is not yet returning your UPSIT results, and I want to share a couple of reasons for that.

One is that the answer is a little complex in that we look at not just how many you got out of 40, but also your age and your sex and how much we expect someone with normal smell ability to score on this, and so it's a percentage of your expected normal. It's not a certain cutoff, so it can be a little challenging to explain.

We also don't know yet exactly where the, I think you used Dr. Patel, the threshold is, like what does it mean to have this level of smell ability right now? And maybe it's a good day, a bad day for you, again as we've discussed, that you might ebb and flow depending on your inflammation levels, for example.

And so we are considering how to do this in PPMI, also again how to do it with a hundred thousand people in a way that we feel like we're providing the right education and the right context for sharing those results. It is taking us a little bit of time. We want to make sure that we're getting it right. So right now you won't get your results.

We do return some other results in PPMI, which might be enticing to you if you want to continue on after taking this test. But I've heard anecdotally, and Don and Dave I would love to, you both had already recognized your smell results, but Dr. Patel, as you said, if you fall into that 25% where you might not even really be aware, the act of taking the test I think could be really illuminating and it could, if nothing else, spark a conversation with your primary care doctor or your ENT or another specialist about your concerns and they could probably provide more objective and again, the time to sit with you and really talk to you about what that result means.

So I did want to clear that up since I know we've gotten a lot of questions on that. But Dave and Don, maybe Dave, hear from you first, you are both in PPMI and what it means to be in PPMI is a lot of different things. You can take the smell test. We're going to talk a little bit more about who can do that. You can join online. You can go to myppmi.org and fill out these online surveys over time and help us understand health and aging and wellness. Or you could also, if eligible, join at a medical site and have other tests and scans and help us really look below the surface a bit to understand how all these things work together, how what's happening on the outside is linked to what's happening on the inside.

So I'd love to hear from you Dave first, and then Don about your decision to join PPMI, to raise your hand for research. Again this is something that the foundation is really behind, but it is a very individual journey and there's a lot to consider when you think about joining a study. So Dave.

Dave Harris: Right, when we first learned about the PPMI program through research on the internet, it was very appealing to me until, now this is about a year and a half ago or so, until I realized that at that time the program was not sharing any type of results from the tests. So I decided to forego it at that point. But recently, I'm not sure how far back, but a little, probably nine months ago, the program changed the protocol to where many of the test results are released back to the participant if they so choose. You have the ability to either get the results or not get the results.

So in my case, so far I've gotten the results back on three of the tests. And to me that is very important. I had my baseline evaluation this past December, and for me, I am very interested in being able to get the results on an ongoing basis. The primary tests are done on an annual basis with interim six-month visits where it's not as detailed on the tests. So for me, I think the more information I can get on my progression or lack of progression, in some cases, is very important to me.

Plus I'm also being altruistic, wanting to be able to contribute toward future research to ultimately hopefully find a cure at this point. So it's the PPMI program that I go to on site is at Northwestern Medicine in Chicago. And the staff there that I've dealt with, I mean, you couldn't ask for a more positive, proactive approach. There's always time for questions. They explain things very thoroughly, and it's just been an overall great experience. So I highly recommend it. To those in the audience that are eligible, it has been a very good program, and I think that you would benefit directly from it.

Maggie Kuhl: Thank you for your partnership. Don, how about you? What led you to take the smell test and then continue on in PPMI?

Don Upson: Okay, well, this is the easiest question for me to answer because I mentioned at the beginning with my little cliffhanger that I got some news in 2015 that was quite disturbing, and that is as our then 37-year-old son was diagnosed with early onset Parkinson's. And we were pretty devastated by this having watched a brother-in-law go through Parkinson's and pass away from it and so forth after about 15 years.

Anyway I started, once I knew what his problem was, I went on to the Fox website and first thing I did was I decided to get financially involved, so I do the monthly contribution and that sort of thing. Then I did the sniff test, which I believe I probably out of 40, since there were four possible answers in each one, I probably got 25% because I couldn't smell any of them, not a single one could I discern.

But anyway, I decided at that point I was going to go all-out to do whatever I could to give my son, or if not him, people in the future a little more opportunity to hope for relief and eventually cure. So I went ahead and took the smell test. I guess it qualified me to be a PPMI contributor, and I went to the New Haven site at Yale, or near Yale, for my testing and did every test I think known to man. I'm not sure. It seemed like it, but it was the DaTscan and the EEG and this and the that. Oh, and don't forget the spinal tap and all of that, which of course yielded the alpha-synuclein clue, very, very important.

So anyway, I've been doing that now since 2021. I went to New Haven every year in the fall and got all these tests done, and now I'm switching over to Phoenix because it's a lot closer to where I live. And so I'll be doing that actually later this week. So that'll be good.

But anyway, I'm pretty passionate about doing whatever I can do. So in the future, I've donated my brain and all, I mean just about anything that you can think of. And so I'm pleased I've done that and we'll see, and done all those things. And of course, I get all the questionnaires and everything every three months or so, however often it is.

Maggie Kuhl: We do certainly ask a lot of people in PPMI, but we also, as you said, have found a lot together. And so again, thank you, and we're so sorry to hear about your brother-in-law, but it sounds like you're really honoring him by joining PPMI and leaving a true legacy for both of you.

You commented that you were in Connecticut, you're now in Phoenix, Dave, you're in Chicago. There are 33 sites, 32 sites I think actually in the US with PPMI, and we provide travel for the participant and a study companion, so there's a lot of ways to get involved. There's also 17 external ex-US sites, so it is a global study, so a lot more about that on the website that is linked in the resource list.

And I also wanted to share, so we've been talking about the smell test, we just lowered the age of eligibility, whereas Ethan said we wanted to know how early this Parkinson's process is happening. And so previously you had to be 60 years old or older without Parkinson's to take the smell test as part of the study. We've recently changed that to 40. And I will say as someone who is now eligible, that is an interesting shift in thinking about, okay, all right, Parkinson's study.

But especially it's helping us also, I know obviously likely many people on this call, young onset Parkinson's is also something that impacts a lot of people and so we want to be really learning more about the full spectrum of disease and these different disease profiles. So if you are age 40 or older, you can visit mysmelltest.org and request one of those today.

We also though have found out of PPMI this interesting relationship between sustained smell ability. I think we got a question or two about this. Not everyone with a Parkinson's diagnosis does lose their sense of smell. And Ethan, I'm going to ask you to explain. I know that whenever you put up a scientific graph, people can start to get a little overwhelmed, but I love the slide. I've shown this at support groups, and I do think that it can be pretty graspable of what we've learned and what we are trying to do now. So with that, I'm going to leave it to you to try and explain this graph and what we're looking at in Parkinson's, people who do have smell ability.

Dr. Ethan Brown: Sure, yes. So what this shows is this is a scatter plot and on the X axis, the one on the bottom, the horizontal axis is the UPSIT percentile. So that's the smell test results adjusted for age and sex. And then on the Y axis is the value of something called a DaTscan, which is an image that we use that can tell us if there's a loss of dopamine projections in the brain, which is something that we see get lower and lower in people with Parkinson's.

And this is a group of people with a diagnosis of Parkinson's. This comes from a publication from a couple years ago from the PPMI group. And what you can see is the filled dots have basically alpha-synuclein detected in the cerebrospinal fluid, which right now is one of the only and most successful biomarkers we have of actually confirming that there is alpha-synuclein in people with Parkinson's. And you can see a lot of empty dots here or not-filled dots that show that that test is negative. So there are people with a Parkinson's diagnosis that do not have the underlying alpha-synuclein protein, and we are trying to understand exactly what's going on in those people. That's an active area where PPMI and other studies are looking into.

But what you can see here is that smell loss is really tightly tied to people with the alpha-synuclein biomarker, which we call SAA here. You can see that on the left side there are a number of people who, most of the people who have the filled dots are on that left side, so they have a very low sense of smell. But there are a number of people with Parkinson's and with that alpha-synuclein who are extending out into the normal ranges of sense of smell.

There were a lot of questions before about what does it mean if I have loss of sense of smell in Parkinson's disease? Does that mean that things are worse? Does that put me at higher risk of certain things, like problems with thinking? The answer is we don't really know. In the past, there were a number of studies that looked at sense of smell and found that it was a poor prognostic marker in people with Parkinson's. Like if your smell was worse, it meant that you are at higher risk of certain things, but that was before we had this SAA biomarker. And so what those studies may have just been identifying people that were more likely to have this alpha-synuclein biomarker, and therefore more likely to have true Parkinson's disease. Sometimes a clinical diagnosis of Parkinson's disease is not always accurate.

So we don't know what sense of smell does for people. Among the people who already have the alpha-synuclein biomarker, we don't know if it's a bad risk factor or not. I will say the vast majority of people with Parkinson's have low sense of smell, so there's still going to be a lot of variability among people who have a low sense of smell in Parkinson's, but this is one area that we're really trying to study more PPMI.

Maggie Kuhl: It's important to know what's happening biologically because that helps us have better measures and diagnostics. It also helps us match people to the right treatments at the right time. So if we have a therapy that is trying to prevent or break up those alpha-synuclein clumps and you're an individual without a filled circle, that therapy may not work for you. But we have to figure out what is happening so that we can develop and test in populations like yours treatments that would solve whatever type of PD you have.

So right now, PPMI is screening people with Parkinson's for normal smell ability. We've been talking about smell loss so much, believe me, as the one who has to explain this, I'm trying to keep it all up in my mind too. If you do not have Parkinson's, we want to know if you have smell loss. If you do have Parkinson's, we want to know if you can still smell, if you have sustained smell ability.

So if you have Parkinson's and you've been diagnosed within the last seven years, we've expanded it a bit because as Ethan said, there's a lot fewer people on this side of the graph and we know it's going to be harder to find them, you can also go to mysmelltest.org and request a smell test, but we'll be looking for smellability versus smell loss. So again, it's confusing. We have a nice little screener on the website that's just going to ask you a couple questions and tell you yes or no so you don't have to keep that in mind, but you can go to mysmelltest.org for that information.

Okay, I want to spend a little bit of time talking about smell loss today. If you are living with Parkinson's or if you don't, but you've found your way here, like Don, and want to know how do you deal with this day to day, are there treatments to come, PPMI very focused on Parkinson's. But by studying these distinct symptoms like smell loss or sleep disorders, we're also learning a lot about that symptom itself, and so what we're finding in studies like PPMI and others could also help treat or improve smell loss and other aspects of the disease.

So with that, we're going to move on. Dr. Patel, maybe you can just tell us more about treating. If a person comes to you with smell loss, how do you approach it, both any treatments or lifestyle factors or supplements or really what should people know?

Dr. Zara Patel: Yeah, I'd love to. And because we want to leave time for questions at the end, I'll try to run through these options very quickly. I'll hit the highlights. The only options I will talk about are ones that have high-level randomized control trial evidence. There's a lot of different things out there and not very well run studies, very low-level evidence so that we don't offer our patients in my clinic, but just to run through and then we can put resources to links of these studies if you guys want later.

Olfactory training is probably the most widely heard about or accepted in more primary care and general ENT and neurology circles. Olfactory training is really basically just a structured smelling protocol. It's like if you had a stroke and you lost function of your arm, you'd go do physical therapy over and over to get that function back to make those neurons fire and reconnect, and that's really what olfactory training is doing for your sense of smell. We start with four different odors. They're in different categories of smell and that's why we choose to start with those four. The typical ones are rose, lemon, eucalyptus, and clove.

And then you do it for a really long time. You smell it. When you do it in each event, it doesn't have to be long, just 15 seconds. What is important is that you focus your memory on what that smell used to smell like to you or should smell like, and then you just rotate through those four. It's best to do that at least twice a day. When I say a long time, I have patients do this for at least six months.

If you keep in mind that each olfactory neuron out of those six to 10 million I noted on either side, each one has a natural regenerative life cycle of every three to four months, one is dying off and should be repopulated by a new one. That's not all happening at the same time for all those neurons. And so in order to cover and support that entire system of regeneration for as many neurons as you can, that's why I have people do it for so long. Lots of people try it for a few weeks and say it didn't work and they stop, but that's not enough time to see a difference. So that's the first thing.

The second thing I'll say, and that has been studied in lots of different etiologies of smell loss, these other things have been studied in other etiologies outside of Parkinson's or neurodegenerative disease, but they may be helpful for patients in that category, so I'll tell you about them. Adding a high-volume steroid irrigation can bring down inflammation within the olfactory epithelium itself, and we know nerves don't function very well when they're in an inflamed environment, and they certainly don't regenerate very well, and therefore that's another option. So twice a day, again, high-volume steroid irrigation.

Then Omega-3 is something that we ran a randomized controlled trial on, and again a different patient population and a post skull-based surgery patient population. It was just replicated in a COVID-19 population in Germany and was also beneficial. So a high-dose Omega-3, as long as you don't have a bleeding disorder or are on other blood thinning medications, that can be helpful based on this trial.

And then finally something that we've just started doing, PRP, or platelet-rich plasma injections into the nose. Some of you may be familiar with that in relation to orthopedics. Some people get joint injections for a mild arthritis in the shoulder or hip. And we have studied it mostly in postviral patients, but we have opened it up as a treatment option for all smell loss patients, and we have been seeing some interesting results in other etiologies like post-traumatic and other unknown etiologies of smell loss, and so that's another option. You need at least three to see a significant difference, and we're still studying that and understanding more about it.

And so that, I suppose I'm going to stop there. Those are all the things with high-level randomized control trial evidence that can help with smell loss. Maybe Don and Dave, you can tell us about things that you have already tried and whether they've been helpful for you at all.

Don Upson: Well, I would say in terms of strategies to cope, the smell loss, to me I don't worry about it. That's the main thing. To me, Parkinson's disease is something to cope with. Smell loss is a minor problem in comparison to that. And so my main strategy really is to stay as involved as I possibly can be with PPMI. I want to do whatever I can to help my son, and if he can somehow be lucky enough to have a treatment that works in his lifetime, that'd be wonderful.

Dave Harris: Yeah, I agree with you, Don, that for me, it is not a really big deal. I think in my case, especially since I still have a really good sense of taste still. I think if it would have been turned around that I had lost my sense of taste, that would be much more devastating. But for me, I think in the overall scheme of things, that is a minor annoyance, I guess for lack of better words. So yeah, I've dealt with it.

And a little funny side story here. I went to a wine tasting about 10 years ago with my wife and some friends not realizing that there was going to be a competition for tasting notes as well as smelling notes. I did fine on the tasting. I completely bombed on the smell. I didn't have any connection at that time between loss of sense of smell and Parkinson's and I did not tell the people that we were with, so they probably thought I was just a very untrained wine non-connoisseur. But anyway, I did fine on the taste.

But going back again, I think the sense of taste makes up for the loss of smell in my case.

Dr. Zara Patel: So I'm just going to pipe up and make a couple of comments on that. So interestingly, if you were able to taste actual flavor in the wine, that likely indicates that you still have some olfactory nerve functionality, and that often we make a distinction between orthonasal smell and retronasal smell. Retronasal means that the posterior aspect of the olfactory epithelium often has intact olfactory neurons that allow people to taste the flavor of their food, even if they're blocked from being able to smell from the very front of their nose. And so that may be playing a role in your ability to taste true flavor, not just those very basic tastes, but not having the ability to smell it.

And then one other thing I'll just mention is that it's really wonderful to hear that both of you are coping so well and that you're keeping it in perspective. But I will say a lot of patients that I see in my clinic are highly impacted by their loss of smell and taste, especially if they felt like they were super smellers before, or they depend on it sometimes for their job, like chefs or sommeliers, but even people just who like to cook or who feel more closely bonded with their family and environment through their smell.

And so I just want everyone in the audience to know that that feeling really emotional about your loss of smell is normal, and I think it's totally fine for you to find someone to talk about with that, find support groups and things like that that can help you deal with that part of the impact.

Maggie Kuhl: I love that you brought that up, Dr. Patel. I think especially we classify Parkinson's as a movement disorder. We talk about functional impairment as it relates to someone moving or living independently, but as you said, some of these symptoms perhaps less appreciated or tied to the real core of how we define the disease have real impacts on your socialization and on your sense of enjoyment in life and just quality of life. So we certainly echo that.

We do have time for a couple questions, and we got one earlier that I thought was really interesting. A couple people brought up phantom smells, either smelling something that is not, they're not near or smelling something differently. Is this part of Parkinson's? Is this a phenomenon that happens with other conditions or aging, and what might be behind that? Dr. Patel, I'm not sure if you're more familiar, and of course, Dr. Brown pipe in as well.

Dr. Zara Patel: I can start. And then Ethan, please add on anything you want. I think that phantosmia we think about slightly differently than the anosmia, hyposmia, parosmia, the loss and distortion of smell, but it can be part and parcel of the same phenomenon. So some patients will have phantosmia again just because of an increase in inflammation in their nasal lining. So sometimes just getting people on that high-volume steroid irrigation that I was talking about is enough to make their phantosmia go away.

But in other people, it's more of a central processing thing. So for example, patients with epilepsy sometimes will have phantosmia, phantom smells. Some people with migraine will sometimes have a phantom smell as part of their aura. So there are central processing things that can cause phantosmias, and so often we try to treat the peripheral potential issue. And if that's not enough, then I'll send it to someone like Ethan to investigate any potential central issues.

Maggie Kuhl: People with Parkinson's, the hallmark, the go-to medication, carbidopa levodopa. Any impact on smell ability, either favorably or unfavorably?

Dr. Ethan Brown: Yeah, I saw that question. It's a good question. I have not seen any impact on from levodopa on smell, certainly not unfavorably, and there may be studies that I'm not aware of about this. I've heard of some, so I don't think that levodopa certainly wouldn't worsen sense of smell for any reason.

I think some people, I think there was a question before about deep brain stimulation actually improve someone's sense of smell. And I have heard that or seen that sometimes anecdotally. I think the question is if one therapy improves a sense of smell as opposed to what Dr. Patel is talking about where we're directly trying to, is whether it's really improving something in the brain that can help us discriminate smells or remember smells. And we know that sometimes levodopa or DBS could have improvements in some people with attention or thinking, which these are not reliable and not reasons to get deep brain stimulation, but whether or not it helps in those areas in certain people is possible. So I think that the, like we said, the possibilities for smell loss really are throughout the brain, and I think the possible for improving certain aspects of it may also be different mechanisms. But in general, no PD medications should not worsen the smell.

Maggie Kuhl: Question, Zara for you on the timeliness of the treatments that you shared. If someone lost their sense of smell 10, 20 years ago, would retraining help them, or similar to how we talk about Parkinson's, when dopamine cells are gone, they're gone. Is there a sense to get it back, and if so, what's that window?

Dr. Zara Patel: So my answer to this has actually changed over time. So I used to tell people that the longer out you go, just the much less likely it is that anything we do will bring back your smell. And I still think that's true, it is less likely the longer you go. We know that for most parts of your nervous system, if you don't use it, you lose it. Nerves can regress back if they're not stimulated, things like that.

Also, your age, that it is much harder to regenerate any part of your body, especially nerve if you're older versus younger. However, I have been surprised pleasantly recently with some of our treatment options. For example, we just published a case report because it was so shocking to me, a patient with post-traumatic smell loss 45 years after his initial injury and going that long amount of time without any smell, both subjectively and on an UPSIT quantitative measure of smell. After three injections of platelet-rich plasma into his olfactory epithelium, he came back to my clinic sobbing with joy, a whole list of things that he was able to smell and taste again, and actually on the UPSIT had increased almost double the minimal clinically significant difference that we want to see for improvement. So that really shocked me. It's the first case report I've ever published because I was so surprised about it.

But so I would say for anyone that I don't think it's impossible. I never say it's impossible anymore, but I think for each individual person, we really don't know. We don't have enough information about your specific amounts of neuronal loss or your specific amounts of neurodegeneration and so it's really hard to know individually. But I will say that all of these treatments are actually quite simple and easy to perform, and so you might as well try.

Maggie Kuhl: Great. Well, I want to thank you. I feel like we covered today, we hear often the biggest questions from people are if you have a risk factor, am I going to get Parkinson's disease? If you have Parkinson's, what's going to happen to me, on what timeline? And it's interesting that through that smell loss and through research like yours, Ethan and yours, Zara, and of course the participation of research volunteers like you, Don and Dave, are really helping us answer some of these questions. And that's I started off by saying, I think this is such a cool, interesting topic because who would have thought that smell loss could really be the key to this?

So if you want to help us unlock these mysteries of disease and answer these big and very personal questions about what's going to happen, certainly help us by joining PPMI. And it sounds too like if you are living with smell loss or a loved one, there are things you can do today and so talk to your Parkinson's doctor, talk to a specialist. I hope that those who are listening today or later on, on-demand felt like the conversation was helpful for them and hopefully empowering and inspiring to do more and that's because of our panelists, so I thank all four of you for joining us today.

Again, I'm Maggie Kuhl from the Fox Foundation. Lots more on our website, michaeljfox.org, and thank you for spending your time with us.

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