

Dr. Panagis Galiatsatos:

Those between their 30s and 50s, those with milder cases of COVID, they tend to make up the majority of patients experiencing Long COVID. This is a disease that is striking a population. If you think about it, 30s and 50s, that's the time you're establishing your career, you're establishing your livelihood, your true identity, whether it's at work, whether it's family, whether it's a combination of the two, your hobbies, all of that is now being robbed from patients with Long COVID.

LuAnn Heinen:

That's Dr. Panagis Galiatsatos, a pulmonary and critical care physician at Johns Hopkins Medicine. He's an expert in the diagnosis and treatment of obstructive lung disease and the care of critically ill ICU patients. Dr. Galiatsatos serves on the Johns Hopkins Post-Acute COVID-19 Team and is well-positioned to update our understanding of Long COVID as a biological illness, discuss the impact of vaccination on the risk and severity of Long COVID, and inform our personal decision making, in a time of rising infection rates and waning public health guidance.

I'm LuAnn Heinen and this is the Business Group on Health podcast, conversations with experts on the most relevant health and well-being issues facing employers. Today, Dr. Galiatsatos and I discussed Long COVID, new learnings, key unknowns, rays of hope and particular concerns.

So here in the Business Group on Health podcast, we came across this news item which appeared after this recording with Dr. Galiatsatos. The story starts two years ago when I interviewed Dr. Lekshmi Santhosh about Long COVID. At that time, back in 2021, there was no diagnostic test for Long COVID and no way to predict which patients recovering from COVID would be most at risk for Long COVID. So in my interview with Dr. Galiatsatos, I wanted to know what we'd learned in the intervening two years, what has happened, how do we now know who's most likely to develop Long COVID. It turns out that in the intervening two years, not a whole lot changed. What I learned from Dr. Galiatsatos is that clinicians are still having to address symptoms as they present.

What was exciting about the new news, these are preliminary findings just released from a new Long COVID study. Now they are pre-print, meaning they've not yet been peer-reviewed for publication. As reported in *Medscape*, researchers in the UK found that elevated levels of four proteins, which signal inflammation, were found to predict Long COVID with nearly 80% accuracy. This is exciting because inflammation is seen as a key connecting factor across all of the different seemingly unrelated Long COVID symptoms that cause various body systems to go haywire. Clinicians are especially challenged by the lack of a diagnostic test to recognize Long COVID and inform their treatment. So even these preliminary results have "gobsmacked" the research community because they offer a path toward a diagnostic tool for Long COVID. Here's my interview with Dr. Panagis Galiatsatos, and we start with talking about what's been learned in the last two years about Long COVID.

Dr. Panagis Galiatsatos:

A lot has changed and a lot hasn't changed in regards to Long COVID. It still puzzles us as physicians of truly understanding the pathology behind it, like the disease mechanism. We have these patients who come in, they have these greatly impacting symptoms, I mean, robbing them of their quality of life, robbing them of who they used to be. The challenge that we have in modern medicine still with them is we don't know the mechanism of how this occurs. The majority of our tests when we run them tend to be unremarkable. And again, we run tests for diseases we think this could be and we run tests for diseases we know, and so the fact that these tests come back unremarkable is always a bit disheartening because it tells the patient, well, it's not in my head, doc, I'm feeling this. I'm like, I know you are, I just don't have a test to test for the type of symptoms you're having. I'm saying this because I think in the last two years, the biggest things that have come out around Long COVID is a realization of what it is and what it's not. We're still not there with a unified, biological, plausible hypothesis. Many candidates have risen and why that's really important to even the next step is I can't even begin to look at therapeutic interventions, even cures until I understand what I'm combating. I'll say one more thing so I don't ramble, because this is such a passion of myself and many other

clinicians and physicians, we want to help our patients. Thus far it just feels like pulling a bucket of water out of a lake, so yeah, throw out that one bucket, but I'm drowning still. The analogy here, it's almost like the doctors battling AIDS in the early 1980s where they saw these patients get ill, but they didn't have a unified understanding of what it was. They didn't realize it was caused by the impact of viruses on certain T cells, one of the immune systems. It took years to figure that out and then even longer to come up with some level of treatments. I feel like we're stuck there with these patients where, yeah, a lot of biological mechanisms are coming up, we still don't know what's the unifying mechanism behind it.

LuAnn Heinen:

But don't we now believe, and we didn't two years ago, that this is truly a biological illness. It's just, I guess you're saying we can't describe it.

Dr. Panagis Galiatsatos:

Yes, 100%. It is a disease and we are finding abnormalities in these patients, but on a research level, not on a clinical level with tools that we constantly use. It is a disease. Our challenge is just trying to figure out the right tests and the right mechanisms to evaluate it in order to find biomarkers that signal the disease is happening, to find objective testing, to say, aha, look, there is active organ damage and dysfunction, because our current testing doesn't do that. If we do find it, it's usually not a traditional Long COVID. It's more of a post-viral complication that isn't unique to COVID. A lung scar is not Long COVID. Many viruses leave scars in the lungs. It is a disease. I don't doubt that at all. I think sometimes you may get a dismissal in modern medicine around Long COVID and that breaks my heart, but the dismissal is just because these clinicians fail to find an objective thing that they can intervene on. I tell my colleagues, remember, medicine didn't get born out of chasing biomarkers and chasing tests. It was born out of our patients. They give us our identity. No one fakes being ill. That really should be the emphasis of recognizing this is a true biological disease. We just haven't realized what it is that drives it.

LuAnn Heinen:

And there are still many, many variations of Long COVID. Would you agree, as we heard two years ago, that there's no one Long COVID experience?

Dr. Panagis Galiatsatos:

Oh, 100%. Because like any other disease, this is true of any disease, if I say cancer, you would say, okay, what type, what stage, what are its symptoms, right? That's to me also Long COVID where it's recognizing that there's a variety of symptoms from fatigue to cognitive dysfunction to breathlessness to palpitations, variety of aspects of it, and those certain symptoms, a lot of them are more aggressive than others. So yes, you're spot on. It is a disease, but what I am imagining we'll see in the future is that Long COVID will be more of an umbrella term and underneath it you'll see specific categories or in medicine called specific phenotypes where it'll be somewhat different. There'll be a Long COVID fatigue, there'll be a Long COVID breathlessness or dyspnea. You'll probably see that play out as we try to really harmonize the definition around Long COVID.

LuAnn Heinen:

Are we any further along in estimating prevalence of Long COVID than we were a couple of years ago?

Dr. Panagis Galiatsatos:

I think we are. There's a science behind it that's really good. It's just the estimates are going to likely be under-reported. I think the best that we can figure out is that 10% of patients who survive COVID experience Long COVID. That 10% is an estimate. It's got to be an estimate because first it's a little bit more biased to the countries that can keep a tab on COVID cases and then follow patients who are ending up seeking out medical care for it. Countries like the U.S. or the United Kingdom, yes, we're going to be doing better of the epidemiology around understanding the Long COVID prevalence. But my heart goes out to countries that don't have that kind of organization or ability to capture such data, and it's going to really affect the socioeconomically disadvantaged countries and nations and individuals, because if you can't capture the

disease prevalence, then you can't allocate resources to those populations. The best estimate is about 10% of those who survive COVID will experience Long COVID.

LuAnn Heinen:

What do we know about the individuals who are most likely to be in that 10%?

Dr. Panagis Galiatsatos:

I was one of the physicians who kind of wore three hats during the pandemic. One was my clinical hat. I ran an ICU, an intensive care unit, like my other colleagues. Many of us ended up at some point in time just transitioning to a COVID intensive care unit. So I wore that hat. The second hat I wore, more kind of unique to myself and a few others, was the community engagement around COVID, where we go out there to help our populations really streamline the right information for them to make the right decisions to care for themselves. Then the third hat was brought in by one of my colleagues, Dr. Ann Parker, who said, hey Panagis, we're going to get a lot of post-COVID survivors from the intensive care unit, we should have a post-ICU COVID clinic. I thought that was a brilliant idea. Myself and a few others, Dr. Alba Azola and other clinicians, we all teamed up with Dr. Parker. It was probably true the first 6 months we saw majority of ICU, intensive care unit, survivors, patients who went on life support and we were helping them through this. Then all of a sudden we began to get emails from other patients, emails from other primary care doctors wanting to refer, hey, I have this young patient, they had a mild case of COVID, but they still seem to not be back at a 100%. Then those few emails turned into dozens, turning into hundreds, turning into thousands, where we suddenly realized that in our clinical experience, those seeking out care for Long COVID were not survivors of an extreme version of the disease known as COVID. The majority of them in our clinic were people who were young, 30s to 50s, they experienced a mild case of COVID, something that they will tell you was a really bad cold, but they never got back to their baseline. And the epidemiological data, the data that the population health studies are looking at, kind of displays the same thing. Those between their 30s and 50s, those with milder cases of COVID, they tend to make up the majority of patients experiencing Long COVID. This is a disease that it's striking a population. If you think about 30s to 50s, that's the time you're establishing your career, you're establishing your livelihood, your true identity, whether it's at work, whether it's family, whether it's a combination of the two, your hobbies, all of that is now being robbed from patients with Long COVID. That's what a lot of my clinical experience has shown in addition to the current published population health data as well.

LuAnn Heinen:

Wow, and leaning female, I've read.

Dr. Panagis Galiatsatos:

Yes, I'm going to use that point to kind of give you my thought on this because Long COVID, it robs people of who they were. It's unlike your polio where you can physically see their lungs failing them and they threw them on the iron lung back in the 50s. Long COVID is so individualized. That's what's scary about this. It doesn't rob people in such a disease spectrum that everyone has the same symptoms. Long COVID can still be the same symptoms, it's just how much that affects you. If you're an astrophysicist who's calculating the rockets being sent up into space and you are working on an intellectual level way above your peers, Long COVID's cognitive impact on you may decline your IQ back to kind of the average population. But the thing is, you weren't working in that average state; you were above average, right? You needed that extra cognitive insight to allow you to do the job that you do.

The reason why I'm painting it in that context is this is what makes Long COVID so diabolical. It robs people of their individuality of who they were. And so why I think it leans towards more females is because I think more women begin to signal the bell to say, I need to seek out care for this faster. Even in our clinic we saw that bias. Women tend to have come in within a year of their symptoms. Men tend to have come in two years after their symptoms, dragged in by family members being like, something's wrong with dad. So the female leaning, I think there might be a bit of a clinical bias. We'll see how this plays out. But again, the devil of Long COVID really is that individuality. There might be symptoms that are very similar to everyone, but how people experience them begins to make them say, oh my gosh, I need care more urgent than waiting.

LuAnn Heinen:

Well, that is frightening. It's frightening. Diabolical. What a descriptor.

Dr. Panagis Galiatsatos:

Yes, well, I've seen many diseases rob people of their individuality, but it robs them pretty uniformly and in a way that most doctors can predict and prepare. But when my nursing colleague comes to me and says, I can't be a nurse anymore, I think I'm a safety risk to my patients, and they're in their 30s, that's what breaks my heart. These are people that want to continue working, want to continue to maintain an identity, and all those years and decades of building up who they were, suddenly they've lost it. As a clinician, I can tell you it is heartbreaking, especially when I don't have a cure and without a biological understanding of the disease, without a cure of the disease, and it's still novelty, I can't even tell patients what to predict. This disease robs us of what we have been accustomed to as being doctors.

LuAnn Heinen:

And it's sort of the first cousin or early cousin of dementia, almost.

Dr. Panagis Galiatsatos:

Yes, exactly.

LuAnn Heinen:

Pivot to prevention, we know about vaccination. How effective do you think vaccination is against Long COVID?

Dr. Panagis Galiatsatos:

I think it's effective, though it's not foolproof. So what do I mean by that? Here's the challenge. One is who was driving Long COVID? Was it the earlier variances, alpha through delta, even versions of Omicron? Was it the lack of an immunity? Keep in mind, this is what makes our immune systems amazing. Our immune system is amazingness to me, and I don't think I'm alone in this camp, is its memory. The fact our immune system can form a memory. Right now you may feel great while it's battling a virus that made you feel miserable years ago, because of that memory you don't even feel it. It's gone. So was Long COVID a consequence of both the variances or lack of immunity? That's hard to tease out, because right now, while this virus has mutated countless times and while it's stuck in the Omicron variant family, Omicron keeps having more and more grandchildren, right now with a new one emerging called HV.1.

So is it the variant? Is it the immunity now that we've gained? I think there's a combination of the two, but what I'm seeing is the patients that we know that have been vaccinated are less likely to experience Long COVID, yes. Are less likely to experience severe symptoms of it, yes. At the same time, even if they experience severe versions of it, many of them have come forward as if Long COVID has resolved or it's become more manageable. But because the virus SARS-CoV-2 has adapted so well to invade a very specific receptor in our bodies that's found really everywhere, brain to heart to kidneys, once it's been able to get into the bloodstream and get its way into the nerves of all of these, it's going to result in some level of a viral reservoir that it allows it to stay there and continue making its impact. If you have an immune system that recognizes it already, I think you're going to be able to fight that off. I do think vaccines is a strategy that we have found impacting Long COVID, whether it's occurrence or it's severity or it's chronicity, I do think there's a role in it, yes.

LuAnn Heinen:

But if I understood correctly, you were interviewed by *Statin News* and essentially the bottom line was each time we're reinfected with COVID, we're rolling the dice again on Long COVID.

Dr. Panagis Galiatsatos:

Yes, 100% agree, and keep in mind, this is also new. Three years ago, I never had a patient that was infected more than once. Now a lot of patients I get, you're right, this is their fourth infection of COVID. A side note to your listeners, this is why I really encourage patients to test for COVID. If you have symptoms, you may be like, well, look, I'm trying to get back into 2019, COVID is just a cold, yada, yada, yada. Alright, fair enough, but listen, if we don't have a diagnosis of COVID, I can't allocate Long COVID treatments to people, and at the same time, I can't rely on antibody testing anymore, because I don't know if you got it from a vaccine or you got it from an infection. Test, because if you can test and prove you had COVID, suddenly that unlocks the health care doors to making sure you get the right Long COVID allocation resources.

LuAnn Heinen:

Does a home test work for that or does it need to be done in the clinician's office, PCR?

Dr. Panagis Galiatsatos:

Home tests work; just notify your doctor. That's what I plead with patients, because once the doctor can enter it, you're good to go. Relying on the PCR now is challenging, because there are less sites doing it. I don't want you to be like, well, I'm sick on a Friday and I can't go in until Tuesday, because of its availability. We've kind of returned to a world where it's normal operating of a health care system. So PCR is great, but get a home test. And our government as of now, the government is given our free covid tests again for the foreseeable future. So get those tests when you can.

LuAnn Heinen:

Right, four per address.

Dr. Panagis Galiatsatos:

Yes.

LuAnn Heinen:

Let's just digress again back into these viral reservoirs, because I've also heard you speak about the fact this is a known biologic model that works exposed to many viruses and something like chickenpox can come back later as shingles and HPV can come back as cervical cancer. I think you had a couple more examples. I'm kind of stressed by thinking about that, all of these viruses we have in our system, how does that all play out?

Dr. Panagis Galiatsatos:

And Epstein-Barr Virus can come back as multiple sclerosis. This is concerning. How this coronavirus adapted so well to this, I mean, just showcases that mother nature, she's never really done, this is a whole new world. I'll unleash it to this and bring it back to this, the way viruses mutate, we shouldn't be surprised, as mother nature finds more and more viruses that become more contagious and result in long-term complications. It's a massive advantage to the virus. Whatever we can do to prevent the infection or to provide our immune systems with a memory to it should always be seen as advantageous. I will say if the data with the vaccine continues to hold out, that it does help prevent Long COVID severity or Long COVID itself, you may even begin to see this vaccine repurposed, not just to help prevent severe COVID, but for that as well. Just kind of like HPV vaccines, they're not really promoted to prevent the infection, they're really promoted to prevent the cancer from the virus. That's key here. Or it might be more something inclined to like hepatitis B where the vaccine there is inclined to keep the infection from being severe and at the same time prevent hepatitis B complications like liver cancer or cirrhosis. From my standpoint, I think we need to recognize how the vaccine's role may also help us with some of its complications. But getting to your question, yes, I think the virus, its reservoir impact kind of as you said, HPV to Epstein-Barr Virus (EBV), but it also can do other things as well. It seems to have a micro circulatory dysfunction against the cells that align the blood vessels called endothelium in a cascade that doesn't really shut off. This is where people were talking about micro clots and so forth. These studies about the biological plausibility of the driving mechanism, there's many of them, but there's few patients that they recruit because it's challenging and there's many people that will drive down one hypothesis that in of itself seems still distinct from the other one. So we're waiting for that holy grail of a unifying

hypothesis and it may be minor ones throughout, but when we unify it, ideally what I hope comes of it as well is a biomarker. Some objective test that we can reproduce over and over and over again to allow patients a confidence in our diagnosis.

LuAnn Heinen:

Let's segue to another topic, which is I've been thinking about pediatric exposure to COVID. What from your perspective are the potential neurological or pulmonary effects when sometimes we don't even know our kids have had it. They may be asymptomatic. I'm aware of many parents in their 30s and 40s with young children who previously were vaccinated once or twice for COVID, but don't think it's necessary anymore.

Dr. Panagis Galiatsatos:

It's a great question. I would say, listen, I recognize the resiliency of the physiology of a young child's body. At the same time, we should take advantage of that young immune system that is thriving to learn and create immune memories. This is the way you help children and it's not just a focus on saving their life, it's also a focus on saving their quality of life. I'll put it this way, one of the strongest reasons that the chickenpox vaccine came out, because you may say, look, we've all had chickenpox. I had chickenpox. It's not life threatening for the majority of children, but you know what it is, quality of life robbing. Even if it's just for a week, the child is out of school, the parent's usually with them, so they're not making an income, they're not going into work, the child is missing some days of school. We've put a stop to that, because also that really impacted a lot of low socioeconomic families where if they don't show up for their work, they're going to miss a paycheck. We have focused on viruses that will just rob an individual of their quality of life. So with that same impression, I think COVID needs to be recognized for that as well and having them vaccinated and preventing severe COVID, the probability is on their side that it wouldn't have been life-threatening, but more importantly, we want to know if we can prevent Long COVID, because if your child develops that, the developmental impact on that kid is going to be lifelong, at least for the foreseeable future. I don't see patients resolve this disease quickly enough for me to give people the confidence to say it may not be with you in a few years. The more likelihood is it's probably going to be here to stay. Maybe there's some level of a decrease in its amplitude of symptom severity, but I've yet to see that.

LuAnn Heinen:

Well, let's talk about recovery from Long COVID. I've heard and seen most Long COVID patients are better in a year. Then more recently a study regardless of variant, half of Long COVID patients fail to improve after 18 months. What's your perspective on recovery?

Dr. Panagis Galiatsatos:

I'll pull from my clinical management of patients. I think I have a few handful of patients who can tell me, doc, I feel back to baseline. I will tell you those patients who say that, something in their Long COVID management was interesting. Either their thyroid disease that they had got worse and we fixed it over time, meaning there was something objective that we chased down to help them with it. But the majority of patients who tell me they recovered really mean to say, I've learned to live with it, right. I've learned to adapt.

LuAnn Heinen:

That's different, isn't it? Yeah.

Dr. Panagis Galiatsatos:

That's what I tend to see. For example, I have a young college patient, straight A's, Long COVID hit, barely could pass. Now they're doing great again. They're passing, they're getting straight A's, but they're doing it because their teachers are accommodating their disability from Long COVID, doing it because of the medications that help them with their symptoms. They've been able to adapt, but adapt in the same way that an amputee adapts to a prosthetic. That's what I tend to see. With the studies that talk about recovery, that's the part that I really still struggle from the researchers is do you mean they're back to baseline? Here is the kicker, remember we said in the beginning, there's not an objective test where I can really understand the biological mechanism of a disease. It's not like they can show me lung function test came back to normal. It's

not like they can show me a biomarker that was elevated is now gone. What you're relying on patients is kind of this subjective quality of life reviews, which is fine and appropriate for where we're at, but what I can't decipher or some of the studies hint more at this than others is, it's patients more or less have learned to live with it and their new adaptation is a recognition to them that will say, yeah, I get it's my new life.

LuAnn Heinen:

Any recommendations for employers on management of COVID and prevention of Long COVID?

Dr. Panagis Galiatsatos:

Actually two things. This is one that I said earlier that I will really stress to employers now. If your patients don't feel well, they're sick, really make sure to make a point of emphasis of just testing yourself for COVID, because I don't have a biomarker. Your clinicians have to do so much to convince an insurance company that they think it's Long COVID without that definitive test. As an employer, my first recommendation is if your employees are not feeling well, they got a cold, still encourage getting tested for COVID, because goodness forbid if it does become Long COVID, at least they have that objective testing that can help them get the right resources immediately for Long COVID. Then the second part is understand that, as I said earlier, the age group that seems to be really affected is those between 30 and 50. This is your workforce, right? This is your workforce. To the employers out there, I would say these people want to work. Every single one of them loves what they do, loves their job, they want to get back to it. So to the employers out there, I would just say work with us to work with the patients in order to make sure we can have the appropriate accommodations. That's what I think is key here. You're going to see a workforce that wants to still do what it can, but they just need a lot more resources to help them adapt. Just like I brought up that young college kid, it's back to getting straight A's, but he's doing it because the teachers are giving him more time, they're giving him more resources or allowing him to adapt to the classes.

LuAnn Heinen:

Well, thank you for that. Last question, looking ahead, predicting the future, how far away do you think we may be from a biomarker or a diagnostic test for Long COVID and any other predictions about Long COVID and its ongoing impact on us?

Dr. Panagis Galiatsatos:

I will say here's my hope. My hope is within the next two years, we have an objective marker, something that every clinician can order to evaluate for Long COVID. I do think we're two years away from it, if not sooner. But with that in mind then, we're probably another five years away, again if not sooner, for true therapies to modify the disease, if not for some cure. At the same time, I'll tell you my biggest fear. My biggest fear is if that cure or those therapies are time sensitive. What I mean by that is, I reflect back on the patients with polio. When they're in the respiratory failure of it, I can't bring that back, and so waving around a therapeutic cure for them is almost, not that it's insulting, but it's such a horrible irony that I can cure some, but not them anymore. So my biggest fear is for the patients currently suffering, when does their suffering transition into something irreversible that even if a cure comes out, we find that it's time sensitive. Kind of like Paxlovid, right? Paxlovid is time sensitive. I got to intervene at a very specific moment in order for that medication to be effective. After five days of your symptoms of active COVID, it's no longer able to do what it can do. I will tell you that's my biggest fear. I'm hoping that doesn't play out. I'm hoping the therapeutic finding that we find can help Long COVID at any stage of the timing of it, but I will say that out loud and hopefully that out loudness being mentioned also motivates people to do the right thing to prevent Long COVID or to keep it from being as severe.

LuAnn Heinen:

Thank you so much, Dr. Galiatsatos, for sharing your time and expertise with us today. I'm really impressed with all of the many hats you wear from the community to the outpatient clinic to the ICU and keeping your sense of humor and humanity. It's wonderful to meet you.

Dr. Panagis Galiatsatos:

It's my honor and thank you so much for allowing me to do this. Thank you. To your listeners out there, if you know someone with Long COVID, just make sure they get the right care so they can at least start feeling somewhat like themselves again.

LuAnn Heinen:

I've been speaking with Dr. Panagis Galiatsatos, a triple board-certified physician in critical care, internal medicine and pulmonary disease, about Long COVID. For more information about his work, go to <https://www.hopkinsmedicine.org/>.

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