Emma Mertens: Good afternoon, everyone, and welcome. Today, we are excited to be joined by Jolan Walter from the University of South Florida and Johns Hopkins All Children's Hospital. We are thrilled to have her join us for an informative discussion on genetic variants in APDS. My name is Emma Mertens, and I'm the Program Manager for Education at the Immune Deficiency Foundation. On behalf of IDF, we thank you for tuning in to this virtual event.

Throughout this series, we will explore some of the rarer types of primary immune deficiency, providing diagnosis specific information and support to the PI community. In offering these programs, we aim to move forward in our vision of a healthier day, every day for every person living with immune deficiency. Today's program is sponsored by farming. It is due to their partnership and support that we can offer programs like this for the patients and families we serve. Thank you, farming.

Before we get started, a brief disclaimer. Please remember that information presented during this meeting is not intended to be a substitute a substitute for medical advice, diagnosis, or treatment. We are here today as a trusted source and friend to provide you with information. Always seek the advice to your physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice or delay seeking it based on information presented during an educational event.

And with that, I am so pleased to introduce our speaker for today. Jolan Walter is the Division Chief of Pediatric Allergy and Immunology at the University of South Florida and Johns Hopkins All Children's Hospital. Dr. Walter is the Robert a Good Endowed Chair of the USF Division of Pediatric Allergy and Immunology and serves as an associate professor of medicine and molecular biology at the Mersani College of Medicine. She also directs the Jeffrey Model diagnostics and research center for primary immuno deficiencies at Johns Hopkins All Children's Hospital.

Her extensive research focuses on identifying disease mechanisms for various primary immune deficiencies and understanding the underlying causes of immune dysregulation in pediatric patients. We are so fortunate to have her join us today to discuss genetic variants in APDS. Welcome Dr. Walter.

Dr. Walter: Thank you Emma for the wonderful forwards and introduction. I'm very excited to be here with all of you. Just looking at the names on the list of the participants. I see my patients from Boston. I see my friends from clinical care colleagues and pharmaceutical connections.

So I'm really honored to be here and educate many of you on what I think is an important matter for the past couple of years. So I'm just sharing my screen and we gonna start. So

here we are. And Emma will be helping you to make sure that your questions are noted. We will have opportunity for q and a at the second part of my talk.
So I sort of plan to give you a presentation for thirty minutes to forty minutes so we will have time to to connect. Although I'm talking about understanding the genetic variants in APDS, I do want to emphasize that what I'm gonna talk about is very applicable to the genetic testing for any other type of animal animal immunity. So don't get discouraged if you don't have APDS or if your disease is different than APDS, because what I'm gonna talk about could be still very relevant to your own care or the the care of your loved ones. So when I think about immuno deficiency, I do want to emphasize that The era that we are in is basically the era of increased awareness of genetics and immuno degraduation, and it's very different from the 1990s when the ten warning signs of human deficiencies were primarily focused on infection I would like to give a tribute to VikiModal who went to the Congress in the era of HIV and AIDS and said that she wants to talk about the other immunodeficiency, which was called coin at that point, a primary immuno deficiency disorder. And on behold, by two thousand and eighteen, we actually had universal screening for these disorders by NewVoice Cleaning.
And again, credit was to identify Park and many others in this country. So the disease that I would like to talk to you about actually just resurfaced in the early two thousand, and this is the warning sign for FPDS. And what you can see here that by this two thousand twenties, We no longer have just infections in the clinical features of the disease, but we have the so called non infectious complications such as atopic autoimmunity, inflammation, malignant cell lymphod proliferation. And EPDS is just one of the many of the five hundred plus monogenic inborn error of immunity that can have complications beyond the infections. But APDS itself has six other warning signs that are beyond infections such as lymph nodes running.
We call that lymph proliferation, enlarged liver, the patient having auto inflammation, autoimmunity, lymphoma, actually, so tendency for malignancy, developmental delay, and persistent cough. And I do want to give a shout out for Navigate Epidio as a program that can help you or your patients to go through some genetic testing to evaluate for this disease. So how to navigate this diagnostic process? When you have so many different clinical features to account for, you and your clinician will be working on different platforms to navigate a diagnosis. And some of the platform will include clinical features, laboratory testing, imaging, and tissue.
Biopsies, however, as your patient or yourself, are having more non infectious complications and the disease is becoming complex, we really have to bring in genetics to our differential diagnosis. Can you please confirm that you saw the slide and you saw this moving forward? Like, the genetics popped up for you? Yes, ma'am. Okay.

Emma Mertens: I think we're good. Thank you.

Dr. Walter: So you have to monitor it correctly and you have to revalue the diagnosis repeatedly in this patients. So I just move to my next slide. Can you see the continuum of IEI?

Emma Mertens: Yep. We are all good.

Dr. Walter: Okay. So here, I would like to introduce two different terms that are becoming more and more important in our field. That will highlight how the continuum of inborn error of immunity is moving from infections to Alzheimer's and dysregulation. As you can see on the right hand side of this figure, there will be many patients who have more autoimmunity or immune degradation than infections. And in an umbrella term, we actually call them PIRDs or primary immunoregulatory disorders.
This can be this can have features of CVID features of iPeX as you can see it. Let me just learn later. Pointer. So you can have CVID phenotype. You can have later onset combined with efficiency or profile combined with efficiency.
Some patients will have features of ops. And basically, these disorders could present initially to other specialists, endologists and immunologists. And for that reason, I'm really welcoming the the the second terminology that I'm highlighting here for you called AlPID. So AlPID is autoimmunity and is a proliferation with primary immunodeficiency. And this was established and brought to light by step fan ill and their colleagues in Europe.
I think using Opiate could also bring hematologists closer to our discussion points, so I'm encouraging our colleagues here in on the poll and also patients to think of these two terms, PIRD and OPID when they come to a specialist and discuss their condition. An EPDS is a poster chart of PIRD or OPID an evaluation, however, what we will do for APDS could lead to other PRDs as well. Again, Emma, is this moving forward? Everything is good?

Emma Mertens: All good.

Dr. Walter: Okay. So here is the actual definition of APDS, activated PI3 kinase data syndrome. On the right hand side, I'm highlighting an important website, which is all about APDS. Where you can learn about the disease. You can learn about the disease through educators on the left hand side, read the symptoms, and then learn why genetic testing matters.
And we were discussing genetic testing more in particular in this talk. You can actually find an APDS physician and learn about the treatment options. So I highly recommend you to get familiar with with that website if you think that you have APDS or your somebody in your family. This is another information material that I wanted to highlight for you on the left hand side called the patient journey dot org, and they have very specific fliers on APDS. You

can get knowledge about the disease based on your sinus syndrome, information diagnosis and treatment.
It does give you glossary on common terms. And I think common terms in particular is becoming overwhelming for our patients. We use a lot of unusual words, a lot of definitions, and that could be somewhat helpful to our patients. And then I would like to give special thanks to I IDF to organize this symposium, and they have their own specific information on APDS. So when I look at EBITDA, I think of, again, certain infections in northern throat, bacterial viral infections, in particular, herpes infection could be of high importance in this disease.
And on the non infectious complications, We are looking for banal life at danapati, but also malignant lymphoma later in life. We see patients having really, really, right, pain and liver, which is called hepatosperamagaly. Some of our patients who will develop autoimmune enteropathy and commonly autoimmune psychopinias. So beyond these informative information about, you know, what is a common feature? You can actually go to the genetic websites by medical genetics.
We'll summarize for you some of the common terminologies that our patients could come back with such as abnormal immune system, including immuno deficiency terminology, lymphodenopathy, lymphopenia, some patients would have cellulitis, bronchiectasis, and recurrent infections. And when you read a genetic report for patients who are evaluated for APDS, they would highlight this mentioned ID number, which you can search on the medical genetic website above. So what we are learning is that our patients with APDS have a long and convoluted journey before they actually get to the root cause of their disease. Many of the patients could come with unusual diagnoses such as hyper IgM syndrome or common diagnoses such as CVID or CID. Some of our patients will have only recurrent infections with no definitive immunological diagnosis, and some of them would come through the oncologists with diagnosis of lymphoma.
Also, patients can have a prior diagnosis of autoimmune, if a proliferative disease and even exfolium. And that made me think to look for additional data on what is really causing this diverse initial diagnosis and the diagnostic journey. And what you can see here is that based on an Italian paper from twenty twenty four, twenty eight EPDS patients were reviewed for their variable delay in diagnosis. And what you can see that although the age of onset of symptoms happened below their twenties and mainly in their teenage years or earlier, most of the patient did not have an IEI diagnosis or a period diagnosis until they become adults. And why is this important?
Because if you are only getting your diagnosis as an adult and you are not grandparent or parent and unload an aunt, you still want to know your diagnosis, so you can have not only yourself but children, nephews and nephews and nephews in that family. So looking at this patient who are up here in the forty to sixty year category, many of them may not have

immediate access to genetic testing or the clinician would assume It is not worth going after genetics at this age, but I do encourage you in that age group to to speak out for genetic testing, not just on your behalf, but on behalf of your family members. This is sort of eye opening to me that APDS has such a a delay diagnosis against the fact that now we have genetic testing available, and I'm hoping that these curves will change with time. So why is it important to understand whether you have a a gene defect for APDS? Because this disease is out of some dominant in inherited in inheritance.

So autosomal dominant means that one copy of a mutated gene is sufficient to cause an passed on disease. So let me give you an example of this. If you have a family, mom, and dad, and the father has this one copy of effective gene. He have a fifty percent chance of passing Idan to his children. And there is an equal opportunity to pass Idan to a male or a female child.

So in this figure, we are highlighting that both the son and the daughter have a fifty percent chance of inheriting the father's genetic disease. And in fact, what I'm learning through my own patient cohort here in Florida is that the likelihood of inheriting the APTS gene is actually relatively high. So many of our families would have several children in the family inheriting the gene from the parents. However, we also know that one in five cases, the APDIS patients will not have an inheritance from the parents, but they have it as a new, we call it, their noble variant, so we have to keep that in mind. That not every patient will be inheriting genes.

They may have a new variant popping up in their own genetic material. So how could we improve the early diagnosis of APDS? You would, of course, look into patients who have chronic infections, frequent hospital admissions, if they have autoimmune presentation and a compromised immune phenotype. You also could look at patients who have history that should be genetically screened even all these circumstances. And this is a report from Germany just from two years ago when they basically recommended that increased susceptibility for infections with the combination of autoimmunity leave a preparation or fail to drive, should, indicate a need for genetic testing for APDS.

Or if you have a workshop that is a possible IEI and that has a CVID like or CID like presentation, you should consider genetic testing for APDS. And in addition to this flowchart that was created by Dr. Katherine Schuster and her colleagues, I do want to mention that immunize segregation such as autoimmune cytopenia and liver preparation may precede infections. So in my mind, this arrow could go either way. You could sometimes have patients who actually would present the liver preparation or autoimmunity and then develop susceptibility infections and still would require genetic testing to look for the underlying cause of possible APDS.

So what do we know about APDS and the genetic cause of this disease? I'm gonna use a couple of very, very crazy long terms, but I want to make sure that you make sense of it by

highlighting the important letters in these genes. So pathogenical disease causing variants of two different gene, p I k three CD or p I k three r one can result in APDS, and I would like to highlight the c and the r in these genes. Because c will will mean that it's a catalytic domain and r will mean that it's a regulatory domain. And any of these gene defects, if they have a pathogenic or disease causing out of soma dominance, single or very end, take a result in both immuno deficiency and immuno degraduation and APTS.
And what we learned so far is that as of two thousand thirteen, when the disease was described, they estimated around one to two people per million And as knowledge is increasing and there is more awareness, we are finding more and more patients with this condition. Here in our centers, we have over fifteen patients in our care currently. So I'm sort of circling back to these two genes that I mentioned to you before. The one with the c is actually the catalytic domain, and it is the one when you would push the gas. So this catalyzing the activation of this pathway And when there is over activation or over driving of the pathway, with a gain of function variant is when you have disease, whereas the other variant is called r or regulatory variant, which is a loss of function variant.
And as you are losing function of regulation, then the pathway again will be overactive. And the result in this sort of highly active end to our pathway. So both the increased function of c or the decreased function of the arginine will reside in APDS. On the right hand side, I'm distinct for you, a couple of the known genetic variants linked to this syndrome, and the e one zero two one k is the most common method made this is causing variant in APDS. So if you have the syndrome, it is likely that this is gonna be your very end or at least is the most at the very end.
I do want to emphasize that this variant is a missense mutation. So what I mean by missense is that the mutation in the novel guide will change a single amino acid in the protein change of this molecule. And I'm highlighting here that this blue protein on the left hand side is not changing to a red protein. But this is the blue amino acid is changing to a red amino acid on the right hand side. And you would think why is that important?
Because if the function, the characteristic, of this protein protein is now differently folding, differently changing, then it can affect the function of the protein. So even a single tiny amino acid change can result in a very important functional change of these of these molecules. So examples of testing, when you do genetic testing for this variant, you can have a very clear cut answer when you get back a result, a positive testing. So for example, this patient had a pathogenic variant identified in heterozygous form, one allele, but it's autosomal dominant. And therefore, this is pathogenic and relevant for the patient.
You can also have a positive testing when you will not have any result that would be meaningful for your patient's underlying disease. And then you can also have a very end up uncertain significance, which is this wicked v u s. It's hard to know at that point whether you should advise your patient whether they have a period death or not. So you have to go

through with your doctor or as a physician with your patient. If I fill a discussion of this variant and discuss whether you want to pursue it for further studies.
So let's talk about this resolution of a very end up uncertain significance. And I'm highlighting here in their paper, one particular of the US that is, again, a missense variant when the volume is still falling in, you know, one week, two and a half years. Does it really mean that patients have APDS? So this variant of the solution is a complicated process. It will get better and better each year.
So I'm giving encouragement to our patients and clinicians. Don't give up on the US's. You really want to understand is that the US is going to lean more toward benign. So you you sort of can ignore it, or do you have evidence leaning toward a pathogenic variant? And to collect evidence, we are at actually looking at several details at the very end in our reports. We look at a protein change. As I saw you, protein change can actually start in folding three dimensional change and eventually impact the function. This required population frequency and also reports in the daily target disease. And then we also want to know if the family has other patients who could be affected by this variant and any distribution within the family could help us to determine pathogenicity or leaning towards pathogenic variants. So when you are ready for genetic testing and you will have a conversation with your physician, you have to think through the logistics of obtaining DNA testing and navigating the report with your physician.
So this is a big commitment from both you and your doctor. And it is not an easy decision to pursue genetic testing. But I also want to emphasize that your physician could be any other specialist wired around you So although we are talking to the allergist immunologist in our field, since I am an allergist immunologist, I do want to mention to you that your physician can be a hematologist, hematologist, g I specialist, genetics is pulmonologist and neurologist, and they can all send out genetic testing. So I don't have to worry about being followed by rheumatologists for a condition that is concerning for an underlying imaging. You can talk to your rheumatologist and bring it to their attention that there are few genetic programs and bring them to on par with where the times are and make sure that they understand that you would like to look for the root cause of your disease.
So I'm gonna give you a scenario for this consenting process of what would happen when you decide to move forward with genetic testing. Your physician will discuss this opportunity for you if you think that your condition is unusual, there's a worsening clinical course. If there are several specialists in your care and certain medications do not work, if you have both infectious and noninfectious complications, if there's family history that is concerning, you could pursue this genetic testing in conversation with your physician, and the consenting process is as a serious part of that conversation. In this consenting process, you are consenting to a certain genetic testing, a certain terrific information, but the strong decision making is is has to be thorough. So you have to understand what are the

sequencing?
Are we doing panel sequencing or beyond? Are we looking at certain genes that are going to cause immun deficiency or other genes included now that can even look at your cancer body's position. So make sure that this concerning process is becoming clear to you with your doctor and you feel comfortable moving forward to the genetic testing. After the consent is obtained, there will be a selection between different panels for sequencing. Most commonly in our practice at USF, Diego is in the MBT, import error of immunity and cytopenia panel.
Which has over five hundred genes. But we can also move to all sudden three genetic testing such as APDS, Navigate, and other programs. I also want to highlight some additional genetic testing through other companies. Prevention genetics have a six forty gene panel for human deficiencies and similar to Invitae, they're using a whole genome whole exome sequencing, and they are looking at the panelists within that by only analyzing panel data. We have a PCD, immuno efficiency panel available with looping phonetics, which is covering three hundred eighty three genes.
And GeneDx is also looking at custom sizes for in whole exome sequencing for immuno disorders. Initially, they had a hundred and fifty genes and they just made an announcement. That are going to sequence over five hundred genetic disorders for immuno deficiency. So depending on your assurance and your conditions' availability for testing, that could be very different platforms used for your evaluation. And then eventually, you they have to decide how to get the specimen to this genetic company.
So this specimen is have can be obtained multiple different ways. It can be obtained a sample class verb or a saliva sample. Both of these on the left hand side and the right hand side are very easy to access even from home. The glucose wavs could be used from infancy to adulthood and very helpful if your patients have received bone marrow transplant. The saliva samples need a bit of a more involvement of the patient trying to, like, spill into an antiviral, and you cannot have any food or drink thirty minutes before obtaining that that sample.
And then if your patients are unable to get the vocal swab or the saliva sample, I recommend considering the blood blood room, which can happen at any age.
Unfortunately, we have ability to do it either in the office or at in the in home setting with a phlebotomy service. So again, when you get the genetic testing, it's sent out and you get the results back, the result can be positive. And getting a positive result is always exciting because now we know that we have some action items to do. And some of the action items for a positive result include even closer monitoring for certain disorders such as herpes infections.
Looking at autoimmunity, making sure that the patient doesn't have any signs of cancer, we would do probably even more detailed immune phenotyping to understand if the disease is

progressing immunologically, not just clinically. And then there could be some need for therapy besides immunoglobulin and antiviral therapy you may be able to prescribe ample inhibitor or PIC highness inhibitor therapy such as annualizib. And furthermore, by knowing the genetic variant in a positive testing, open up the door to consider testing for family members as well. You have a negative testing on a panel sequencing, I recommend that you don't get discouraged. We still would be monitoring the patients repeatedly.
And if we are very concerned, we can go up higher from panel sequencing to a full whole exome or whole genome and consider research study on AMPAP pathway evaluation. So never feel that that you are left behind just because your result is negative. There would be other avenues to evaluate you for APDS or other immunities or this is again a genetic report of a patient from a teaching case that we are using repeatedly for our colleagues. And what you can see here is that this PI patient had a PIK3 CD missus Varian at position three thirty four for one amino acid to another. It was heterozygous and an uncertain significance.
So why is this important? If this patient comes back with this support, and he had it done in the past with the four hundred seventeen panel. It may be worthwhile to send the five hundred plus anyway to make sure that you cover your grantments for other type of imaging. That's for miss with the four hundred seventeen panel. But you also want to go after this PRK3 CD variant and do your diligence as a clinician whether this is meaningful for your patient's disease.
So similar to what I have shown to you, you would be going through this variant classification and steps for resolution of the US, which can be pretty tedious or requires a lot of diligence from the condition side. And it would also probably require in some cases actual functional validation. So I wanted to highlight you an important paper that came out as an abstract recently in one of our meetings when farming actually published a navigate APS platform. And what they have shown is that in the year of twenty twenty one to twenty twenty three, between two years, they could have to sequence almost four thousand patients. And after four thousand patients, three hundred and four patients actually had now APID diagnosis because of the genetic testing.
That's a very impressive ten percent rate in the general population. And I want to congratulate farming in helping to bring diagnosis to patients even beyond APDS. Forten patients actually were diagnosed with APDS, but sixty three patients had APDS with WUS. So that means that the majority of the patient that you may see in these reports may come with WUS. And please don't get discouraged when you have a VUS because you have opportunity to resolve this with the help of the company and your colleagues.
So how to resolve this VUS? We can actually not do functional essay to determine what adenicity by testing the PICK kinase pathway. In this pathway, we'll be able to stimulate in the three sides of your patients, PICK3, PICK, and look at the phosphoacitin presence. If AKT is footfalled for in a prolonged manner, that means that the pathway is overactivated.

And this validation assay is under clinical development, but research or research basis, you can already collaborate with doctor Manish viewed his and he has the ability to send phlebotomist to your patient's home and bring the patient's sample to his laboratory to test this pathway.
So in my in the conclusion of my talk, I would like to say that your diagnostic journey for IAI can help us several layers. And especially in this regulation, you have to have the diligence of many specialists working together and using diagnostic tests, depleted clinical evaluation and genetics. Since the penetrance may vary, especially in autosomal dominant variants, I do recommend that you repeatedly evaluate your patient with your diagnostic workup you aim for targeted therapy and you monitor these treatment response and for all of that genetics is becoming a key part of your journey. If you would like to learn about variant resolution. I do want to highlight Heather McLaughlin from Firming who has been a great advocate for the US resolution.
There is a scientific consulting through Firming that can help you to understand your genetic variant Shaooping is a main leader of our field in APDS by leading the antibody deficiency variant creation expert panel when they are looking into VSS solutions. And again, for functional assays, please reach out to doctor Manish Food and his team. I wanted to share with you a short story before I I closed my presentation. In two thousand and twenty two, I actually recorded my first video with farming on APD F evaluation. And as of now, there are almost three thousand views of the report.
So I went back like to it today just to get a sense of where are we with this presentation and happy for react to it. And I found this very interesting discussion on the website when somebody was asking for the report, they asked if they could get a VUS resolution report because they wanted to use a template for their assignment. And and another person responded to to them saying, just give up as my advice. You have to give up. It's not worth pursuing various resolutions.
And I want to tell you, just never give up. And not never give up on your own health, on finding the right specialist and on various resolutions. So with that in mind, I wanted to thank for your attention. Very sorry for the initial glitches, technical glitches, and I hope we can be of help to you. Thank you so much for your attention.

Emma Mertens: Wonderful. Well, thank you so much, doctor Walter, for your wonderful talk. There we go. Give me just a moment while I pull my slides back up, and then we'll get into Q and A. We have some really exciting questions all ready to go in the box.
Alright. Alright, Dr. Walter. So kicking it off, our first question, this individual says hello and thank you for your presentation. My son has APDS one and was deemed de novo.
Yet, my husband has battled similar symptoms such as respiratory infections his whole life

and was surprised that he was not a carrier of the mutation. Based on his latest research, should he retest, might he have another variant that contributes to an offspring with APDF?

Dr. Walter: Thank you so much for the question. And it is possible that your husband may have a different type of immuno deficiency. So I recommend that beyond testing him for the variant, being a carrier of the variant that he has full immunogenic evaluation for his own condition. So I recommend that that it's gonna be reviewed one more time, and he he has his own medical journey with the full evaluation.

Emma Mertens: Thanks, Dr. Walter. All right. Next question, so I know that the majority of this talk was focused on variants of uncertain significance and their role in diagnosing APDS, but we also got a couple of questions that are kind getting back to the basics of APDS, so I wanted to ask those as well. This first person asks what types of lymphoma are associated with APDS?

Dr. Walter: So many of many of the lymphomas that we see are Hodgkin or non Hodgkin lymphomas and the fact that these patients have problem with EBV clearance, we think that EBV and CMV could be triggers or potentially contributing to some of these lymphoma tendencies. So in Hodgkin and Hodgkin lymphoma and EBV is of high importance to be monitored for.

Emma Mertens: Thank you so much. And getting back to genetic testing, is that usually covered by insurance?

Dr. Walter: Yes, mortality testing are covered by insurance. And if there is a problem with insurance that are also or payment assistant programs that are present in EBIT companies. And I have to mention that EBITDA is navigate, for example, is a free genetic program. So there are several avenues to help you to make sure that you don't have any financial burden with your genetic testing.

Emma Mertens: Wonderful. Thank you, Dr. Walter. All right, next question. This individual wants to ask, they say thank you for the lecture.
I would like to ask for variance of certain significance and serous limits or lineal sub decision, how do you act in your practice?

Dr. Walter: But for the variant of uncertain significance, I really want to make a determination whether my variant is leaning towards pathogenic before I would go for the treatment journey. And you you have to get into this functional essay that attribute is recommending and really very uncarefully. If I see that there is evidence that it is leaning towards pathogenic, and I recommend the patient to get on an anti inhibitor, which could be cyridienosoloneologib. But we have patients not only one but more who actually had

more leaning towards the nine and I advised against that in therapy because I thought that their medical journey required a different approach.

Emma Mertens: Thank you so much. Alright. And next question, can you tell us a little bit about what is the quality of life that you expect for an individual who's been diagnosed with APDS?

Dr. Walter: This is a hard question, and we hope that the diagnosis will actually bring to you and your family, maybe even other members in your family, a much higher quality of life because we know how to minimize immunosuppression, but still have to take care of immunosuppression. What I think is the hardest hardest condition or hardest complication of our immune deficient patient at this point beyond cancer is immunization. We are not our colleagues in on mycology and he mycologist sometime I hesitate to use immunosuppression because they worry about tenancy for infections. And if we can come up with a targeted treatment, we all could do better. So I think five years actually improve with targeted therapies.

Emma Mertens: Thank you, Dr. Walter. And we have time for a couple more. This individual wants to ask about penetrance of disease. And to get your opinion on, are there any patients that have pathogenic variants that you've seen without or with mild symptoms?

Dr. Walter: Absolutely. And it is not with not just with APDS received with NFKB1 and CTLA-four. We now know who could be in the family, even a baby, who can have a potential journey of medical problems because we find them through genetic testing. And asymptomatic cases are very interesting because we don't necessarily treat back we monitor very closely. And something that was monitoring helps us to prevent and organ damage, lung disease, disease of deliver the spleen.
So, yes, we see as symptomatic patients with pathogenic variant, early life, and this is, I think, very helpful to plan the patient's journey.

Emma Mertens: Thank you, Dr. Walter. Alright, a couple more questions. I think we have time for two more. This individual asks, have you seen improvements cognitively or in mental processing speed for APDS patients treated with leniallisib who initially experienced multiple learning disabilities or delays in their early development?

Dr. Walter: This is such an important question, and I want to thank the person who asked this question since we, for the first time, see condition like APDS where beyond the immune system, we are noticing neurological, like, cognitive complications. It's very early to say how we can have that with this therapy especially when a patient is already more advanced in their age. And these are the questions that we don't know how to answer, for example, should we have somebody even at the younger age if they don't have infections or

immune dysregulation, but maybe they have already some sign of tendency for cognitive delay. It is unclear what to recommend, but these are very important questions that we have to answer throughout natural history and post marketing surveys.

Emma Mertens: Thank you, Dr. Walter. And our last question, how do I find the best immunologist in my area to treat APDS?

Dr. Walter: On the website that I highlighted, which was APDS Navigate, all about APDS. There's actually a find your doctor in the area link. So I recommend that you go there and look for the the key opinion leaders in your area for APDS.

Emma Mertens: Wonderful. And I'll add to that answer IDF also has a clinician finder tool similar to the one you just described that you can also use to find a treatment in your area. Alright. Well, that is going to wrap up our Q and A. Thank you so much to our audience for these great and engaging questions.
Thank you so much, Dr. Walter. For joining us today and for addressing these very important questions. I know you have somewhere to be now, so I I will let release you and let you go on about your day, Dr. Walter, but we are so appreciative for this presentation.
Thank you for hanging in with us with those tech issues initially. We are just so appreciative for this critical information for for you sharing your time today and sharing your expertise. So thank you so much.

Dr. Walter: Thank you, Emma. Have a nice one.

Emma Mertens: Thank you. Take care.

Dr. Walter: Bye bye. Bye.

Emma Mertens: Alright, everyone. Well, we are gonna get ready to close out. But before we do, I'm gonna share some information and our latest resources and upcoming events. Alright. So applications are still being accepted for IDF's twenty twenty five research grant program.
This program supports research initiatives focused on improving patient outcomes and expediting the time to diagnosis for individuals affected by PI. To submit your project for consideration, download the application, which we have linked on screen, and I'll share that link in the chat here shortly as well. Did you know that the walk for PI fully funds our IDF research grant program, gather your family and friends and start a walk team to be a part of the impact? By participating, you are making PI research possible. And helping to improve the lives of those impacted by primary immune deficiency.
For more information and to register, visit walk for PI dot org. Are you looking for ways to connect with others who are also navigating life with a PI? You might be interested in joining one of our many get connected groups. These groups are free, virtual, volunteer led

opportunities to connect with others with PI all over the US. We do offer location based groups, so in your city or state, and we also have nationwide groups.
And because we meet over Zoom, you can really join any group, time, leader, or category that works for you in your schedule. We even have groups for seniors, young professionals, folks in healthcare, and more. We also offer facilitated support groups for young adults, parents, spouses, and partners. Here at IDF, we are so proud to offer educational programming each month and various in person events throughout the year. Here's a look at some of our upcoming events this spring and summer.
And before we conclude, we want to thank you so much for joining us this afternoon. We appreciate your participation. And your patience today. And we do hope to see you back for more programming in twenty twenty five. A big thank you again to Dr.
Walter for leading this talk and a huge thank you to farming. We are so appreciative for your generous support of all the IDS educational programming and for today's lunch and learn.
Thank you so much. I'm going to leave the platform up for just a few minutes in case anyone wants to revisit any of the links that we shared in the chat. Otherwise, Take care.
Thank you for joining us, and enjoy the rest of your day. Thank you so much.