[MUSIC PLAYING]

HEY JIN CHONG: Hi. Thanks for coming, and I think I'll get right to it.

So today I'm going to talk to you about Primary Immunodeficiency, New Ways to Diagnose and Treat. So Jeff told me to tell 'em what I'm going to tell 'em, then tell 'em, and then tell 'em what I told 'em, and I thought that was good advice.

So here's my overview today. I'm going to talk a little bit about general primary immunodeficiency, and then talk to you about when should you be suspecting a primary immunodeficiency. And so I will move on to talk a little bit about the SCID screen, and what we are doing with the SCID screen in Pennsylvania, and we are the only ones with this data because we're the ones collecting it, so you're in for a treat. I'm sure you can't wait. And then we're going to talk about the future of primary immunodeficiency, and where we're really headed in this really exciting field.

So primary immunodeficiency really wasn't even a thing until about 1953, when Colonel Ogden Bruton described a boy with recurrent pneumonias, which later was known as Bruton agammaglobulinemia. We know it now today as X-linked agammaglobulinemia. And that's really what people say started this whole field of immunodeficiency.

And then in about 1973, the International Union of Immunological Societies decided that we're going to start keeping track and we're going to report all the PIDs out there and classify them. And by 1999, they had already listed about 60 different primary immunodeficiencies in five different categories. Fast forward to 2015, there is 300 different primary immunodeficiencies in nine different categories in a very short time.

And why is that? And that's really because of the way we're able to diagnose. Now we're doing things with next-gen sequencing, whole exome sequencing. We weren't able to do that back then. The field's really taken off. Even between 2015 and 2017 I can tell you that 50 more primary immunodeficiencies have been described. So we're going to talk about all of them today.

[LAUGHTER]

So actually, why don't we just talk a little bit about general primary immunodeficiency. So the way we used to think about PID is we thought about the functional compartments of the immune system, and what's affected and what happens if that part of the immune system is affected. So when we think of B cells being affected, we think of humoral immunodeficiency. And that's your XLA, CVID sort of falls in here, selective IgA deficiency, which is the most common immunodeficiency.

But there's also other parts of the immune system. So T cells, if you have just a T cell problem, you still have humoral immunodeficiency. And so that would be something like 22q11.2 deletion, where it strictly is mostly a T cell problem, not a B cell problem. However, if you have a severe enough T cell problem, you're going to not tell your B cells to make antibodies, so you're going to end up having a combined immunodeficiency, and that's you're SCID. There's phagocytic disorders that we talk about, including chronic granulomatous disease, which I'm sure you guys are familiar with, as well as complement disorders.

So now the way we classify it, there's nine different categories of immunodeficiency, and they're really arranged based on what you, the physician, will see. I don't want to go over all of them in detail, but we kept some of those, including immunodeficiencies affecting the cellular and humoral immunity, combined immunodeficiency with syndromic features. And these are the ones that you can look and you say this baby has some sort of syndrome that comes with an immunodeficiency. Predominantly antibody mediated deficiencies, and then these are some of the, one of the newer categories, diseases of immune dysregulation. These are really interesting, because some of these patients will present more with autoimmune or autoinflammatory symptoms, even before or even without actually getting sick, and we still consider that an immunodeficiency.

Congenital defects of phagocytes number or function, defects of intrinsic an innate immunity, and these are the TLR disorders, the NEMO, some of the things that we check for, autoinflammatory disorders. I think those are interesting. Those are the NOMIDs and the ones that we usually like to tell room to handle. And then complement deficiencies as well.

The last category I think is fascinating. It's very new. It's phenocopies of primary immunodeficiency. And these are patients who present like a primary immunodeficiency, but instead of having a genetic defect they have another problem. So for instance, you can make autoantibodies against your own cytokines, which basically make it seem like you can't produce cytokines, but those patients would have normal genetic testing.

So what do we have in the United States? We have a lot of immunodeficiency here. This is the United States Immunodeficiency Network, or the USIDNET. It's an NIH funded research program, and it's a part of the Immune Deficiency Foundation. And they have a huge registry of patients with immunodeficiency in the country. And if you look and you combine the antibody defects and the agammaglobulinemia, it makes about half of all of the immunodeficiency reported in the US are humoral, or just affect antibody production. But still, there's a lot of other immunodeficiencies that don't fall in this category, including the severe combined immunodeficiency and the combined immunodeficiency.

There's a lot of patients with immune dysfunction in the United States. So when should you be suspecting one? Probably the most popular or most common way that we think about suspecting an immunodeficiency comes from this, and this is the Jeffrey Modell Foundation's 10 Warning Signs of Primary Immunodeficiency.

These are the Modell's, and that picture behind them is their son. He was born with a primary immunodeficiency in the 1970s, and he passed away as a teenager. And at the time they realized that, in the 70s, there really wasn't an organization where they could reach out, meet other parents, or learn more. And so they created a charity called the Jeffrey Modell Foundation. It is a huge foundation, it supports a lot of research. And they were really instrumental in getting the SCID screen started. They worked at the CDC in the 1990s to make this, the 10 Warning Signs of Primary Immunodeficiency. And these posters are actually, I saw one at the Pittsburgh Airport. So they have these posters everywhere.

So what do we say about these posters? So through the test of time, the first four don't really stand up, and there's actually data to support that the first four don't stand up as well. Four or more new ear infections within a year, that would mean that almost every kid with ear tubes should be referred, and we don't want that. Two or more serious sinus infections within a year, two or more months on antibiotics, and two or more pneumonias.

The problem is that some of these it's difficult to tell if it's a true bacterial pneumonia, or is it a kid who wheezed 15 times and has uncontrolled asthma. And so sometimes you see an eight-month-old who comes to you with three sinusitis episodes. And it's really hard to distinguish is that a cold or is that a sinus infection? And so we like to look at the latter half of this list.

So if you have two or more of these, it can be an indication that there is an immunodeficiency. So failure of an infant to gain weight or grow normally. That is a feature that can be seen in immunodeficiency. Sometimes it's the earliest and only feature. But if they have that and something else, it's suspicious. Recurrent deep skin or organ abscesses is always one that makes you think.

Persistent thrush in the mouth or fungal infection on the skin. I don't really care that much about thrush in the mouth under the age of one. Babies just naturally have poor T cell function, we know that. But once you are over the age of one and you don't have any other factors like antibiotic use, you're not on a pacifier and you keep having thrush, that's really when it piques my interest a little bit more. Need for IV antibiotics to clear infections, two or more deep seated infections including septicemia, and a family history of PI.

So I look for other warning signs that maybe make a little more sense for us. So mild childhood disease that presents in a life threatening manner or is recurrent. I think this is a really good one, and I can give you some real life examples of cases we've seen here.

So we had a patient here at Children's. They were, it was a four-month-old. They came in with CMV pneumonitis. And you know, they needed some O2, and it seemed like the CMV pneumonitis, which isn't uncommon, was really affecting this child to the point where they were almost in the ICU. And so we talked to ID, and we decided we're going to go ahead and treat. And then despite treatment, when we rechecked, they still continued to have elevated CMV, detectable viral load in the 10,000s.

So I thought that was a little unusual. And when you look at this baby, they had a little bit of dysmorphic facial features, and when we checked the labs they had no NK cell function at all. Three times in a row, even when the child was well. They had persistent lymphopenia. At one point they had low immunoglobulins which self-corrected. It was very confusing.

And so I sent off some blood work for whole exome sequencing to Dr. Jordan Orange, who's an NK cell expert. And this is what the diagnosis came back as, immunodeficiency-centromeric instability and facial anomalies type 2 syndrome, ICF2 syndrome. There's probably about two dozen described cases in the world. And this patient had a pathogenic variant in the ZBTB 4 gene. I don't really know what that gene does, so. But it's very interesting diagnosis made

So infants and adults with HSV 1 encephalitis. So again, it's hard to know. Is this bad luck, or is this an immunodeficiency? But what we found is that TLR3 defects actually can be found in 6% of these patients. And so it's a small percentage, but it's real in that some of these patients do have an underlying susceptibility to HSV 1, and those patients are likely to recur. And so that would make a difference, because you would need to prophylax that child who has a TLR3 defect.

And then another classic example of mild childhood disease presenting in a life threatening manner is an abnormal immune response to EBV leading to HLH. And these are the XLPs or the XIAP deficiencies that we see here sometimes.

Blood counts that are low or persistently high, I think, is another warning sign. So I always look, when someone's referred to me for any reason, I look at their lymphocyte count because I can't stop myself. So I'll give you another real life case of a patient here. Two-year-old patient was seen by neurology, followed previously in DC. They had seizures, developmental delay, and when I saw them, I noticed that their lymphocyte count was low then, and it remained very low. And interestingly, they were here to see me, not for immunodeficiency, but because she thought that wheat gave her a rash and the baby had eosinoohilia.

This baby ended up having purine nucleocide phosphorylase deficiency. Not a baby actually, it's two years old, and they're being worked up for, with bone marrow transplant because now this patient needs a transplant. And that this deficiency is actually the cause of the seizures and the developmental delay, that was unclear why the patient had delay and seizures. So the immunodeficiency comes with neurological issues.

We had another teenage referred, rightly so, from rheumatology for elevated inflammatory markers all the time, whether they were sick or not sick. They had thrombocytosis, and the kid also had some splenomegaly, off and on lymphadenopathy. We diagnosed three generations of that family with autoimmune lymphoproliferative syndrome. The father said, oh yeah, I also have a big spleen. And the grandfather was like, oh yeah, I have a big spleen. And so it seemed like all of them had ALPS.

Family history is also really important when you're thinking about an immunodeficiency. Always ask family members about infections. Ask them about SIDS death. And so SIDS death can be, if there's a lot of SIDS in the family, that can be indicative of a severe combined immunodeficiency, or something that runs in the family.

Cancer is an interesting one. One of our patients that we ultimately diagnosed with ataxia telangiectasia, both parents were carriers of AT. Both parents had a lot of cancer on both sides of the family. Even just being a carrier of the ataxia telangiectasia gene increases susceptibility to certain cancers.

Autoimmunity is another feature we always ask about in parents, and consanguinity. So if the parents are related it really increases my suspicion. And in fact, the patient with PNP-deficiency that I talked about earlier, parents were cousins.

A good physical exam will still help with immunodeficiency. So failure to thrive is something that we look for. Looking at tonsils, so a baby who comes in with recurrent pneumonias, ear infections, he's a boy, he has no tonsils on exam, that's the baby who's going to end up probably having XLA. So looking in the mouth and looking for tonsils is an important part of a physical exam.

Retained baby teeth, I want to show you this. So these are some of the pictures. The first one is a baby, a boy with DiGeorge, who has low set ears, a classic facial features of DiGeorge with a large nose, bulbous tip. And I will tell you that even, I was in Johnstown, I picked up an eight-year-old just for asthma after the pulmonologist there moved away. And when that kid came in to see me for asthma, I looked at him and I realized that he had DiGeorge. He had palatal issues, but he had never had a heart problem so he wasn't picked up at birth. We sent off testing, and that 8-year-old had DiGeorge.

Looking in the mouth, the middle picture are the cone shaped teeth that are characteristic of an immunodeficiency called NEMO. This last picture is one of our patients here. If you look, you can see that she didn't lose her baby teeth in the front. So the retained baby teeth is actually a very unique feature for hyper IgE syndrome. It's not seen in any other immunodeficiency. And it's unusual to see someone with so many baby teeth that they haven't lost.

Looking at skin can help you. Looking, always look at the hair, the nails. This is a picture of one of our patients with a really significant fingernail onychomycosis, a fungal infection in the nail. And these are pictures from the internet of a baby with this beautiful silver gray hair. That is characteristic of Chédiak-Higashi. Even if you just take a piece of their hair and you look at it under a light microscope, you're able to see that there's abnormal pigmentation. And I have actually done that. I've taken a piece of hair up to hem/onc on the ninth floor. So thank you, hem/onc, for letting me pretend I was on an episode of *House* and I was looking at hair in the microscope.

So that seems a good way to suspect it. But how are really going to diagnose it, and, and when should we diagnose it? So I want to talk to you about one of the most significant and severe immune problems that we see. And this is what we actually call the one true emergency in our field, and that's severe combined immunodeficiency. You guys might have heard of this as the Bubble Boy. And this is the original, this is the Bubble Boy. His name was David Vedder. He actually was born with X-linked SCID. His diagnosis was known because his brother previously had X-linked SCID and passed away. And so when he was born, they immediately, after birth, placed him in this bubble, tested him, and he did have X-linked SCID as well.

They kept him in isolation, in a bubble. They made, like, a spacesuit for him when he would walk outside. Until finally, at the age of 12, they decided we should do something. And they transplanted him from his sister who is the donor, but unfortunately he died four months later due to complications from EBV.

So SCID, there's 20 monogenic causes of SCID, so it's really more of a syndrome, right? And it presents, and not every case is the same, but usually it presents with some failure to thrive, candidiasis, chronic diarrhea. When they have opportunistic infections that makes it a lot easier to diagnose. Some have significant dermatitis or eczema depending on the gene defect that you see. And we, there's so many types of SCID, but we characterize it based on the genetic defect, which can be thought of as either defects in lymphocyte survival, gene rearrangement, or cytokine-mediated signaling.

I think the important thing about SCID to know is that it is universally fatal without treatment. So these patients need to be diagnosed and these patients need to be treated.

And this is a picture of a chest X-ray. So an infant, a very young newborn or infant, should have a mediastinum that's about 50% of their chest, because they have a big thymus. And so you can see in the first one that that mediastinum is really skinny, because the thymus is absent.

So what is the diagnostic criteria for SCID? So the Primary Immune Deficiency Treatment Consortium, that's the PIDTC, it's about 40 immunology centers in North America. We are one of those centers, thanks largely to Paul [INAUDIBLE] at BMT. And it's a network of experts who do research and clinical trials together. They came up with a diagnostic criteria for SCID.

The first criteria is that you have to have a negative HIV. You also have to have absence or very low number of T cells, so fewer than 300 CD3 T cells. In addition, you have to have low T cell function. You can't just have low T cell numbers. And that is either due to mitogen response, or if you can't do that at your institution, then you should demonstrate the presence of maternal T cells which would indicate engraftment.

And I just want to point out that there is no genetic testing as part of the diagnostic criteria of SCID. Why is that? Because we don't want to delay the diagnosis and treatment by waiting for genetic testing. So if someone meets the diagnostic criteria, you should treat them sooner.

So what is treatment? So classically, the treatment is hematopoietic stem cell transplant. But now we do have some gene therapy treatments for certain types of SCID. This is a picture of Dr. Rebecca Buckley. She is one of the world's experts in SCID, and has been treating hundreds and hundreds of SCID babies and transplanting them at Duke. She showed data that if you treat these babies with transplant less than 3 and 1/2 months of age, you can see that the survival curve is a lot better than if you wait until they're over 3 and 1/2 months of age. And a lot of this is because when you are treating someone with transplant under 3 and 1/2 months of age, they're usually not sick. And if you were transplanting someone after that, you're transplanting a baby who presented with illness, and that impacts survival.

In addition, she presented data that showed that it was, cost of care was higher with later transplants.

So we should be identifying these babies as early as possible before they're sick. But how can we do that? So she first suggested that we could screen them with CBCs. But CBC is not a good screening test for every baby. It's not cost effective. But she's still one of the earliest pioneers for SCID screening, but at that time it really didn't seem feasible.

And then it became, actually, a little more urgent to SCID for screen. Why is that? Because rotavirus vaccine came out. And this is a live vaccine that we give two month olds. And so what happens when you give a live vaccine to a baby with SCID? They actually get rotavirus. And this report came out in the *New England Journal* of two babies who ended up having SCID. Both of them received rotavirus vaccine, both of them had significant diarrhea and shed rotavirus vaccine. One of them, even after a transplant, continued to shed rotavirus vaccine and required Tpn. So this was, this was a problem.

So why, how can you really add something to the newborn screen? So the Secretary's Advisory Committee of Heritable Disorders in Newborns and Children have some criteria. So the disorder should be serious, check. Should be prospective pilot data, so we needed to get some data to show that it worked, the spectrum of the disorder should be well described, the screening test characteristics should be reasonable, including having a low rate of false negative results. That was really the hang up. We didn't have a good way to screen these babies yet. The spectrum of the disorder is broad, and you should be able to identify those who will benefit, and there has to be an effective treatment, and Dr. Buckley show that.

So if we can't really do CBCs-- this is another picture of Dr. Buckley, because no talk and have too many pictures of Dr. Buckley. So if we can't really do CBCs, then what can we do? We need an assay that can be done on the dried blood spot that we already send on newborn screening.

And so this scientist figured out how to do that, and this is Dr. Jennifer Puck. She's at UCSF. So she developed an assay that can be done, it's RT PCR which can be done on a dried blood spot.

So what is she measuring? So she's measuring T cell receptor excision circles. And so what is a T cell excision circle? When the T cell, a naive T cell comes out of your thymus, it rearranges its DNA in order to mature, and that T cell will then go on to proliferate. The DNA that is not necessary and the T cell receptor gets stuck together in this episomal, circular piece of DNA that is only in that naive T cell and it doesn't get passed on, because it's not needed. So she developed a PCR assay that goes right across that signal joint. And so it would only recognize, the primer would go here, a primer would go here, so the PCR would only work if this signal joint existed. Otherwise, if you don't have this piece of DNA, the PCR won't pick it up.

And so it worked. So in 2008, Wisconsin started the pilot newborn screening for SCID, and in January 2010 they had enough data to say that this really should be done nationwide. So in June 2010, Wisconsin identified their first SCID baby based on the newborn screen. These are the Modell's from the Modell Foundation I showed you, and that is the baby, the first baby ever identified by newborn screening with SCID. They threw a gala. I don't know he's not happy about that.

[LAUGHTER]

Most babies love galas. So then in fall of 2010, they had enough data to start the national pilot SCID study. And they screened almost a million babies in this national pilot. They had 364 positives. Does that mean they had 364 SCIDs? No. So 14 of them were classics SCID, six were SCID variants, and 40 were non SCID. What's important about the SCID screening though is that there were no cases of missed SCID on this screen.

So if a lot of these babies don't actually even have SCID, then what are we picking up? So we're picking up a lot of things on the SCID screen that are not SCID. And this is just a partial list of some of the things that we're finding. DiGeorge Syndrome, we get a lot of DiGeorge, 22q11 deletions, CHARGE syndrome, Jacobson, even trisomy 21. I think this really changes what we thought about trisomy 21, because we don't consider that to be something that comes with significant immunodeficiency. But some have had such low T cells that they get picked up on a SCID screen.

RAC2 mutations, DOCK8, cartilage-hair hyperplasia has been picked up, and then we've also been picking up a lot of secondary T cell lymphopenias. So cardiac babies, if you do the newborn screen after a cardiac surgery, they will often have a positive SCID screen. Neonatal leukemia, gastroschisis, third-spacing, and extreme prematurity will all cause a positive SCID screen.

And so I also want to point out that just because they're SCID screen, you're not catching everything. Life threatening immunodeficiencies can still be missed by the SCID screen, so you can't relax too much, even if it's normal. So if the T cell function is abnormal but the numbers are normal, the screen will miss it. Also pure B cell neutrophil defects will be missed.

So MHC class II deficiency, this is a defect that doesn't cause abnormal t cell function, and we actually had twins here with MHC class II deficiency that we transplanted. This was before the SCID screen, they would have been missed on the screen. They still would have shown up in clinic with PCP the way they did.

ZAP70 can be missed, ADA and PNP deficiency can also be missed. So you can still have a very serious immune problem and a normal SCID screen.

So now that we've learned, now that we've done the screening, what have we really learned about SCID? So prior to SCID screening, we thought the incidence of SCID is one in 100,000. Now, it seems like it's closer to one in 58,000. So clearly we were missing some of these babies. The distribution of SCID genotypes have changed. For years, I was taught to think that X-linked SCID was the most common. It doesn't seem to be the case anymore. X-linked SCID and RAG1 deficiencies are just, they're both just as common now. And so it's interesting that, that even what type of SCID we see is not the same.

So is everybody SCID screening? Well, 90% of births in the United States are now finally SCID screening. And you can see there's still a couple states that have pilots that are coming, and then there's two states that still are not screening and haven't planned screens.

So what about us in the state of Pennsylvania? So thanks to Dr. [INAUDIBLE] I was part of the work group that really tried to get the SCID screen started in the state of Pennsylvania. And so we were able to add the SCID screen to the newborn screen in July 2013.

And this is really how we do it, through PerkinElmer, which is the lab that does the SCID screen. I don't want to go into in too much detail. But basically, we look for tracks first. If that's normal, we're done. If it's abnormal, then we do verification with a beta-actin, which is a control. It's a housekeeper gene. And if beta-actin is normal, tracks are absent, we call that a positive. If beta-actins are not normal, we repeat. If the baby is under 37 weeks, we do not report that out to the physician. This caused a lot of debate. But there are so many, there are so many pre-term babies who have abnormal SCID screens that we decided that if it was abnormal they would have to repeat it weekly until the baby hit 37 weeks. So the NICU has a lot, and they continue to just keep checking these babies.

So we also came up with a list of the designated immunology centers in Pennsylvania. I highlighted us, because obviously we're the most important.

[LAUGHTER]

But what we thought were, we split this into SCID specialty centers that transplant, and SCID specialty centers that don't transplant. And that was also something that was up for debate. But this list is actually given to pediatricians when there is a positive SCID screen, and they tell the parent to go to one of these places.

So I've got some data from the Department of Health for the past year of 2016 just for our state. And you could see that about 140,000 babies were born. And that about 85% of the babies were, screened for SCID. But what's interesting to me is look at how many of the babies born to midwives that aren't SCID. 79.6% of babies born to midwives are not getting screened for SCID.

This is the list of shame. These are the 21 hospitals still not screening for SCID. And every time they put out this report, we keep trying to get more and more hospitals to screen for SCID. In fact, Dr. Sullivan at CHOP had to write a letter to one of the hospitals after a baby was born at their hospital with SCID, was not screened, and presented four months later with PCP. And that hospital now SCID screens.

So some more data that they were able to provide us from the Department of Health is, how many abnormal screens have we had here in the state? So from 2013 to mid-2016, we had 414 abnormal results. But when they double check them, only 57 of those get referred out back to the pediatrician. And they said that eight of those had SCID. And they gave us a couple other categories, but this is all reported data in that the Department of Health was depending on the pediatrician sending them a fax saying, this is the outcome of the screen. So this isn't perfect data.

We wanted to have more information. We wanted to know the outcomes of the SCID screens. And since they couldn't provide the data for us, we start, we decided that we were going to get that directly from the institutions. So I worked with one of our Fellows, Dr. Steve Rosenberg, and a medical student at Pitt. And we got IRB approval at Hershey, CHOP, and CHP to collect deidentified SCID screen data for two years of SCID screen. And so I want to present some of those findings today.

So this is collectively the data on 28 patients that were reported to us that had positive SCID screens from CHP, CHOP, and Hershey. The majority of the positive SCID screens actually were at CHOP. So we had about six during that time, Hershey had maybe three or four, CHOP had the rest. So it seems like a lot of these are going there.

So what did we find? So eight of those patients had lymphopenia. Unexplained, did not find a diagnosis. And this has been reported. There's actually PIDTC study coming out right now following these patients with this lymphopenia to see why, why some of them resolve and some don't. One of these babies with lymphopenia did get whole exome sequencing that found a novel mutation, and that's getting written up right now by CHOP. So, so this is interesting data.

22q11 deletion was found in five patients. So we are picking up a lot of DiGeorge. Five of these patients had true SCID. One of the patients after we followed for months and finally received the diagnosis at five months of ataxia telangiectasia, which is a devastating diagnosis. Two of those babies had CHARGE. One of the baby's had CHARGE and was found on the newborn screen, and they realized the baby was born with no thymus whatsoever. That baby ended up having to go to Duke to get a thymic transplant with a thymus from another baby's getting who was getting cardiac surgery. They take that thymus, and they put it in your thigh.

There were five that we confirmed later to be false positives. Meaning that when we did all the blood work, that baby actually didn't have the lymphopenia. Two had congenital anomalies that were quite severe, and ended up having positive SCID screens.

So what about the five patients with SCID? One had an unknown atypical SCID. They did receive a cord blood transplant and they are alive. Four of them had the IL-2 receptor, common gamma chain. This is the classic X-linked SCID. Two unfortunately died post-transplant due to infection. One they reported from CHOP died of RSV. The other one, they reported to us died of Rocky Mountain Spotted Fever, so I find that really interesting. One left the state of Pennsylvania to seek transplant elsewhere. They were lost to follow up. One was transplanted here with a perfectly matched sibling who's alive and well.

So when we calculated the Pennsylvania incidence of SCID it was 1 in 53,000. That's remarkably close to the national average of one in 58,000. I think the caveat to our data is that we are not including SCID that's been diagnosed outside of the newborn screen. So the Amish patients that come to us are picked up not typically on SCID screen. They're, and so we've had at least two SCID babies not screened. And I know that CHOP has had at least two or three SCID babies not screened.

So what is the role of the primary care physician in SCID and in SCID screen? So this is what we came up with when we were working on SCID screen in the state of Pennsylvania, that the Department of Health is actually going to contact the PCP. They're going to send you a fact sheet that says, "Facts About SCID." And then you're going to, the PCP is then supposed to call the patient, tell them they have a positive SCID screen, and tell that family, here's a list of the immunological centers in the state of Pennsylvania. Pick one and go. After a while, we changed that to make sure that the Department of Health contacts the immunology center directly, so that there's no missed communication.

This is actually something that was created with the American College of Medical Genetics, and it's just a sheet that tells the pediatrician what to do if you get a positive SCID screen in your office. And so I thought I would review that a little bit with some of the other data from other institutions on what to do when you get the call that one of your babies has a positive SCID screen.

So first thing is that you are going to be the first person to call that parent and say that, that the baby has a positive SCID screen. But I think it's really important that you remind them that this is a screening test and that doesn't mean that they have SCID, and that this test is really geared to pick up low lymphocyte counts, and that further testing is really needed for diagnosis. I think it's nice for you to maybe do that in a face to face or talk to them, and also that way you can really examine the patient. Because some of these features can get picked up just through exam. You would probably be able to recognize a 22q11.2 deletion. You might recognize a CHARGE. You could recognize a trisomy 21. That can help you think about what to say.

This is a really controversial one, but we, but most places say stop breastfeeding. We ask you immediately when you tell the parent that they have a positive SCID screen that they can't breastfeed and they have to store the milk. This was a very heated debate at the last PIDTC meeting I went to. And so some institutions will check the mother for her CMV status, and if she is negative they will let that child, they will let that mother resume breastfeeding. But there was two cases of CMV post-transplant in California. They thought that was due to maternal breast milk transmission. So that one is still a little controversial, but at least at the time you can say don't breastfeed until we get more information.

We ask that you tell them to stay out of day care, of strict hand washing, family members should be up to date on all the killed vaccines. And then there have been some very rare cases of powdered bacteria, powdered formula carrying a bacteria that is totally fine for normal guts and can cause infection in SCID babies. So we say to use pre-mixed sterile formula if that's possible. If you're using the powdered formula, try to use boiled water. No vaccines for that child, and if there is a fever, you call that parent and the child seems febrile or off, you need to admit that kid.

And then we say see the immunologist ASAP. And we ask that you facilitate this process. One of the first positive SCID babies, positive SCID screens that we saw here was a PCP saw the SCID screen, told the mom make the first ID appointment at Geisinger that comes up. It was months in the future. She got worried, so she called Children's ID to get an appointment, and then ID called me and said, I don't think this baby should be waiting months to see ID. And we ended up having to get their baby in to see someone at Geisinger right away. Fortunately, it wasn't SCID. But if that mom had waited months and months to see ID with a positive SCID screen and it was SCID, that would have been a poor outcome.

Also, a baby at DuPont with a positive SCID screen was told to make an appointment. They never showed up. They ended up having to call the police to find the family to bring their baby in for testing. Sorry. I was pausing for dramatic effect.

[LAUGHTER]

All right. So now we know how to, now we know that SCID screen is important, and how to act when we get a positive SCID screen. And we see that it's been working here in the state, and the results we get are similar to what we see in the nation. So I just want to take the last couple of minutes just to talk about the future of primary immunodeficiency, because it's changing so much and it's so exciting. So I want to talk. I'll go really quickly through these slides.

But I have a patient here who's just very dear to me. He's in his 20s, and I first met him, like, five or six years ago. He had recurrent ear infections his whole life. At age six, he almost died of his pneumonia. And during that hospitalization, he was found to have splenomegaly, severe anemia, they thought it was for cytosis. He tested negative for that on genetic testing. And he followed with pulmonology for a while. He had recurrent sinus ear infections. He had tubes, it didn't help. He was first seen in immunology in 2003. He had a very elevated IgM of 593. But interestingly, that's someone who would smell of a humoral immunodeficiency, but their IgG is 813, so that doesn't really seem right. He had low complement, and he had low T cells as you can see here with the CD4-CD8.

He developed recurrent pneumonias continuously. He was found to have bronchiectasis on a chest CT. And finally, despite normal IgG, because of the recurrent illnesses, he was started on IVIG. At that time in 2005, and because he was so lymphopenic, they did a PCP prophylaxis bactrim. He continued to have, so what started really coming out is that now that he wasn't getting all those infections because IVIG helps with that, it didn't help his giant spleen. He would get these huge lymph nodes that would require hospitalization and work up. He would get a giant swollen eye every single year.

And so something was really unusual about him, and he didn't really fit into anything. So we sent off whole exome sequencing. For a while we waited, and this is what he has. I'm sure you guys probably figured it out already.

[LAUGHTER]

But he has p110 delta activating mutation causing accumulation of senescent T cells, lymphadenopathy, and immunodeficiency. This is a disease called PASLI. It was first described in 2013. So even if he was checked as a six-year-old, it wouldn't have existed then. This is autosomal dominant, and it leads to recurrent sino palm infections with bronchiectasis, lymphopenia, splenomegaly, lymphadenopathy. Half of these patients have an high IgM, just like our patient did. Half of them will end up getting EBV, CMV viremia that's really difficult to control, and, and there have been cases of lymphoma from this.

And so I just want to show you that p110, PI-3 kinase, p110 delta, why is it so important? It is downstream of very important cytokines for the immune system, as well as the B cell receptor and other important receptors. And so when you activate PI-3 kinase, p110 delta through phosphorylation, that will then in turn go and phosphorylate other signaling, other molecules in the signaling cascade. These patients continuously have p110 delta phosphorylation. So they are overstimulated. Instead of other immunodeficiencies where you think of loss of function, they have too much function.

So why is that a problem? Because then you're pushing all these cells to maturity quickly, even when you don't need all these mature T cells. You're getting these giant lymph nodes because your immune system is overacting. Those T cells, they don't want to be activated so much, and so they become senescent. Basically, they're not working properly.

So having this diagnosis, how did this change the management of our patient? It changed a lot, because Novartis created a molecule called CDZ173. It actually inhibits p110 delta, the exact problem that our patient has. It was, this drug is actually marketed for scleroderma, but it seemed totally appropriate for this rare immunodeficiency. He was entered into the clinical trial at the NIH. His spleen has shrunk for the first time ever. He's had no episodes of lymphadenopathy. He stopped his IgG replacement on his own. I didn't tell him to do that.

[LAUGHTER]

And he hasn't needed it. He's had no more infections. His IgG levels have remained steady. His cough completely resolved. And he told me, for the first time in his life, he walked four miles without stopping because he loves Pokemon Go now. And he tells me he feels full of life. So for him, the quality of life, you could say, oh, IVIG kept him out of the hospital. But he didn't really have the quality of life that he does now just by taking a pill every day.

So conventional treatments. We've done immunoglobulin replacement for years and years, for over 60 years. But now we have new ways of giving it that make it easier for the patients. So we can give it subcutaneously. And in fact with HUYQVIA, you can give it subcutaneously only once a month at home which is great.

Stem cell transplant's being done. It's been done for a while, but now we're doing it for other types of immunodeficiency that we wouldn't have done 20 years ago. Retuximab steroids have been done for a while. But we need to get more precise now with medicine, right? That's, feel like that's where medicine is headed. And so that's where immunology is headed.

So with herpes simplex encephalitis, you can do interferon therapies with CGD. You don't have to just give prophylaxis, you can also give interferon-gamma therapy now.

And then with this, really interesting gain-of-function STAT3 mutation. I won't talk too much about it because we're almost out of time. These patients will come in with over, a gain-of-function mutation usually cause hyperactivity. They have over activation of STAT3, and this can cause a lot of autoimmune problems. And so this patient had serious arthritis that was not better on every arthritis treatment they tried. They gave tocilizumab to this patient and you can look at his hand on the bottom after therapy and he had resolution of arthritis that for years nothing else touched.

CTLA-4 and LRBA deficiency can be treated with abatacept, which is a CTLA-4 molecule. It inhibits T cells, and so a lot of their autoimmune features can be solved with a drug that's available today.

STAT1 gain-of-function mutations, these are kids who have chronic mucocutaneous, chronic mucocutaneous candidiasis, very refractory to treatment. They have a lot autoimmunity. This woman had chronic mucocutaneous candidiasis as a child, started developing autoimmunity, lost 40% of her hair due to alopecia areata, failed retuximab, failed numerous therapies, failed intralesional steroids. And when they started her on a JAK1/2 inhibitor, her hair grew back, she had complete resolution of her mucocutaneous candidiasis during the time of therapy. I think that's fascinating, because if you had just called her CMC, you wouldn't have given her a JAK inhibitor, and you wouldn't have been able to treat her that way.

IPEX and PASLI can be treated with rapamycin instead of just fixing their immunodeficiency and as an alternative to transplant.

This is another fascinating disease. It's called XMEN. It's a loss-of-function mutation in the X-linked magnesium transporter 1 gene. This causes EBV susceptibility. Because this is a problem in magnesium, literally you give these kids magnesium and their immune system improves. I mean, that's such a simple therapy. That's the X-Men,

[LAUGHTER]

because why not.

So the take, the take-home points is that sometimes, on rare occasion, it really is a zebra, it's not a horse. If you suspect an immunodeficiency in an infant, check the newborn screen to make sure that they were SCID screened. And even if they were, remember that it could still be a life threatening immunodeficiency, so you still might need us anyway. If you get called about a positive newborn SCID screen, reassure the parents. Don't tell them you definitely have SCID. And then feel free to refer to our clinic anytime if you are suspicious, because as hopefully showed you today, a precise diagnosis really changes the care for these patients.

Thank you for your attention.