



Pachyonychia Congenita Project

Fighting for a cure. Connecting & helping patients. Empowering research.

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PACHYONYCHIA CONGENITA PROJECT
Transcription of the
EXTERNALLY-LED PATIENT FOCUSED DRUG DEVELOPMENT MEETING
with the FDA

JANICE SCHWARTZ: Ladies and gentlemen, can I have your attention, please? Man, you guys are obedient.

Well, welcome to the FDA Externally-Led Drug Development Meeting for Epidermolysis bullosa and pachyonychia congenita—I should know how to say it since I have it—commonly referred to as EB and PC.

Welcome to the FDA officials. To have you here, ready to listen to our voices, means the world to us. Welcome to our scientists, clinicians and industry friends. Welcome to the caregivers and loved ones of patients. Welcome to all the patients here who suffer from EB and PC. Many of you are in pain right this minute. Thank you for coming to share for what is for many of you private, personal, and maybe even a little embarrassing. Finally, to those who are watching this broadcast live through our webcast, hello and thank you for joining us wherever in the world you are, because if you're watching us live through the broadcast, you are just as much a part of this meeting as anybody sitting in here right now.

I am Janice Schwartz, the Chair of PC project, Board of Trustees, and I'm a PC patient myself. If any of you saw me earlier, you might have seen me standing on crutches, using crutches, or using a wheelchair, and now you see me standing here at this podium like I've been miraculously healed. Well, I am your first live visual aid of this meeting to demonstrate the complexities of rare diseases like EB and PC. Today, I hope you'll gain insights about the people who live courageously with PC and EB.

Working in preparation for this meeting with leaders from Debra of America, Brett Copeland and Joe Murray, I've gained a greater understanding of those who suffer from the various types of EB and the people who care for them. I've seen the love of Brett and Joe for the EB patients and their dedication to finding treatments for those with EB. I've seen the love firsthand from Holly Evans from PC Project, who has worked tirelessly for this meeting, and I've seen that love from PC Project's founder, Mary Schwartz, who began this whole charity of PC Project completely based on her love of

others. This I know, as leaders in this organization, and every act we take for EB and PC patients is motivated by our love for them.

And I just have to tell you, it's a little awkward for me to be standing here because I'm a patient myself. Throughout my entire life, I have always seemed to be able to find somebody who has a problem that's worse than mine, and so it's kind of hard for me to stand here and say please help me; please help my disease; please help my pain, when I can always find somebody who has it worse. In fact, right now I'll just tell you I'm in a lot of pain standing right here, but I can always say well, at least I have feet. But I've come to realize that we all have some kind of pain. I would say that every single person in this room, whether they have EB or not, or PC or not, has some kind of pain: physical pain, emotional pain, mental heartbreak, financial pain. I mean, you name it, there's pain out there. And when we find that somebody has pain and is dealing with hard things, we don't just go, "Oh, too bad, so sad, good luck in dealing with it." We don't because that's not who we are. We take care of one another, and we say, "let me try to understand and let me help your burden be a little bit lighter.

And I know, especially from the outcome of this meeting and this preparation, that there are many hardworking people who do care. There's enough love to go around; there's enough resources to go around; and that's why, even though there's a million different kinds of pain out there, today is the time to focus on the pain of PC and EB patients.

So, you can probably see why we're incredibly grateful to the FDA. I'm emotional already. In this room, right here, we have 24 FDA officials in attendance right now, and we have 18 additional FDA officials attending via the live broadcast. So, if you are an FDA official in this room—and I don't know who you all are—I'm learning some of you, but I want you to know that we, from PC Project/Debra of America, are just humbled that you're here. You're listening to the voices of our patients, and we're grateful for your interest in facilitating the development of safe and effective treatment for patients suffering from PC and EB. Thank you. Thank you for caring enough for being here.

None of us would be here today if it weren't for the vision of Dr. Julie Beitz. Dr. Beitz has had a 23-year career at the FDA involving both pre- and post-approval regulatory activities. Since 2006 she has served as the Director of the Office of Drug Evaluation III. In this capacity, she oversees the review activities of the Division of Dermatology and Dental Products, the Division of Gastroenterology and the Inborn Errors of Metabolism, and the Division of Bone, Reproductive and Neurology Products. Dr. Beitz has also served on several working groups involved in the implementation of the new regulatory authority provided for under the FDA Amendments Act of 2007 of the Center for Drug Evaluation and Research Liaison for FDA's Office of Women's Health, and as a member of CDER Medical Policy Council and Drug Development Tools Committee. I'm not even sure I'm worthy to be in the same room as Dr. Beitz after all that.

More importantly, Dr. Beitz, for us, is one of the people who identified the need to first hear from PC and EB patients in order to help her and her staff better appreciate and understand the needs of us as patients. So, we appreciate Dr. Beitz, as well as Dr.

Kendall Marcus and Dr. Jill Lindstrom, who run the Dermatology Division, and you'll hear from both of them later on today, too. We're thankful for their partnership in today's meeting.

I just want to say, before Dr. Beitz comes up, again, we are just so incredibly grateful for FDA's commitment to advancing innovation on behalf of EB and PC patients. We're so happy you're here, and we're so happy you're willing to listen to us. We'll now hear from Dr. Beitz.

DR. JULIE BEITZ: Good morning. Can you all hear very well? Okay. All right. So, good morning and welcome to today's Externally-Led Patient Focused Drug Development Meeting for pachyonychia congenita and Epidermolysis bullosa. My name is Julie Beitz. I am the Director of the Office of Drug Evaluation III in CDER at FDA. I will try to set the stage for why we are here today, what we can expect to learn, and why these learnings are so important.

First, I would like to introduce the Division of Dermatology and Dental Products, one of the divisions in my office. As you heard, several members of the division are present today, including the Director, Dr. Kendall Marcus, and the Deputy Director, Dr. Jill Lindstrom. You will be hearing from them later in the day. The division regulates drug and biologic products intended for the prevention and treatment of a variety of dermatology and dental conditions, as noted here on the slide. Among these are PC and EB, and other blistering and keratinizing disorders.

PC and EB are just two examples of the more than 7,000 rare diseases affecting Americans today. Over 80 percent of rare diseases are genetic, clinically progressive, and life limiting. Only five percent have an approved treatment. However, continued advocacy from patients and research institutions has and will continue to foster drug development for these diseases.

Why does patient input matter? First, patients may place different values to drug risks and benefits as compared to their healthcare providers, to their family members, and to drug regulators. In addition, patients themselves may have different perspectives on drug benefits and risks. Some may be willing to accept greater risks to achieve a small benefit, whereas others may be risk averse, requiring more benefit before accepting certain risks. Patient preferences may be influenced by a number of factors, including age, personal values, disease stage and prior disease management. As people living with a disease, you can provide unique perspectives.

We are here today to learn about the symptoms, the complications, the frustrations, and the impacts of PC and EB on your daily lives, both in the short and longer term. We want to hear about how your disease is currently managed, what works for you, and what doesn't work for you. We want to hear your views on risk tolerance, given that drugs have both benefits and risks. If presented with a new drug treatment option, how much risk would be acceptable to you?

I would also like to point out that even when there are drugs approved for a disease, there may still be many unmet needs. I've listed a couple here. There may be a need for a special or particular subpopulation of patients that the approved drug doesn't really address, or there may be a need for a special formulation of the drug. For example, for pediatric patients, we may want to have a liquid version of the drug that's already approved.

Patient input can be informative both before and after a drug is approved. In the premarket period, patient input can inform a company's decisions about which drugs or which formulations are developed. Patient input can inform the selection of meaningful efficacy outcomes—we call them endpoints as well—to be used in clinical trials, and what magnitude of change is important. Patients can inform us about the designs of clinical trials by tailoring schedules for clinic visits and the numbers and types of procedures to be performed in a trial. These features of designs are important to ensure participation and retention of patients in the trial. Patients can tell us which risks we should be monitoring in trials and can provide us with an understanding of the level of benefit that would be required in order to accept a certain level of risk.

In the postmarket setting, patients can provide us with perspectives on new safety risks should they arise. For example, we would want to know what the acceptability of a new risk might be given what we know about the drug already as far as benefits. Patients can also help facilitate communication about new safety risks.

While there have been many opportunities for patient engagement over the years, a more formalized process for obtaining input from patients was initiated in 2013. In that year Congress enacted what's called the Fifth Reauthorization of PDUFA, or PDUFA V. PDUFA stands for the Prescription Drug User Fee Act, which was the law passed in 1992, allowing FDA to collect fees from drug manufacturers to fund the new drug review process. In 2013, with PDUFA V, FDA launched a Patient-Focused Drug Development initiative or PFDD initiative for short, and this called for us to convene several public meetings with patients, with caregivers, and patient advocacy groups. A total of 24 meetings were held on a variety of conditions over a five-year period to hear patient perspectives on the burden of their disease and on available treatment options.

Looking to the future, patient organizations such as PC Project and Debra of America, can expand on the PFDD initiative in several ways. For example, convening a meeting just like today's, or they could participate in other FDA meetings and workshops that we convene. They can coordinate with other advocacy groups, and I'm happy to see the coordination between these two groups today. They can perform communication and outreach. They can educate patients about the drug development process in the United States. They can submit what's called proposed guidance to the agency for our consideration, and this could include information about the disease or how the disease might be impacted by certain drugs; what matters most to patients that we should be looking for to try to assess in trials; or they could take a look at we already published in terms of guidance and provide comment.

Under the sixth reauthorization of PDUFA, which we're now calling PDUFA VI, FDA has committed to developing systematic approaches to collecting patient input, so that what we learn can inform future regulatory decisions. Over the next five years, FDA will convene additional public workshops and publish additional guidance. Working together, we can expect to see innovation in a number of areas: in venues for patient engagement such as this, and in the systematic collection of patient preference information; innovation in clinical trial designs that incorporate patient preferences; innovation in development strategies for drugs in rare diseases, so that every patient counts and every measurement counts. And most importantly, innovation of approvals in new drugs, new drug combinations, and new drug delivery systems.

In closing, I would like to share this portrait of Clara. Clara is a two-and-a-half-year-old living with EB. Her portrait is part of an art exhibit called *Beyond the Diagnosis*. This exhibit is traveling around the world to medical schools, hospitals, and even to the FDA campus in Silver Spring, Maryland. Her smile speaks volumes about her spirit to live with, and overcome, EB.

Thank you.

JANICE SCHWARTZ: Thank you, Dr. Beitz.

The PC session of the meeting will now be moderated by James Valentine. James works at the law firm Hyman, Phelps & McNamara, where he assists medical product industry and patient advocacy organization clients in a wide range of regulatory matters. James is considered a leading expert in patient engagement and drug development and approval. Before joining his firm in 2014, James worked in the FDA's Office of Health and Constituent Affairs, where he facilitated patient input in benefit risk decision-making, and served as liaison to stakeholders on a wide range of regulatory issues. One of the last things James did or worked on before leaving the FDA was to help launch the Patient-Focused Drug Development or the PFDD program like this. James is aided with seven of ten of those meetings, six of which he has moderated, so he's an expert right here, and we love having him lead us and guide us as we prepared for this meeting. I have personally seen James in action. He led a focus group at the PC Patient Support meeting last summer. James is sharp and he's bright. He's right on point, but I know James genuinely cares not only about the success of these meetings and this meeting, but he also cares about making a difference for PC patients and EB patients. So, with that, I'm happy to turn now the rest of the morning session over to James.

JAMES VALENTINE: Thank you, Jan, for that kind introduction, and thank you Dr. Beitz for those really insightful remarks. It is now my job to get us to work for the day. We have a lot of work to do, and to start I'm going to introduce you a little bit to how the meeting is going to work and how exactly we're going to bring the voices of pachyonychia congenita and Epidermolysis bullosa to FDA officials, industry stakeholders, research stakeholders, and many others in the room and on the web.

We have a unique joint double header PFDD today. As you're aware, we're going to be spending the morning session covering PC, hearing from PC patients and their loved ones and caregivers, and then we're going to hit the reset button over lunch, and we're going to come back in the afternoon and work with EB patients and their loved ones and caregivers to explore their experiences and preferences. The two sessions, the morning and afternoon sessions, mirror one another, so the framework that I'm about to explain to you now will apply to both the morning and the afternoon.

We've organized our sessions to cover two topics, which were alluded to by Dr. Beitz. First, we're going to explore the health effects and daily impact of your conditions. So, we're going to ask you questions about what health effects have the most significant impacts on your life; what things in your life, activities or otherwise, that are important to you, are you either not able to do or not able to do as fully because of your conditions. We're going to ask you about how these effects might vary from day to day, as well as over time, and we want to explore what worries you most about your conditions.

The second topic we're going to approach as a group is going to focus on approaches to treatment, both current approaches and potential future treatments. So, we're going to ask you questions about what you're currently doing to try to treat your condition and its symptoms. We're going to ask you how well those treatments work, what are their downsides, and then we're going to turn to the future and ask you what it is that you would look for from an ideal future treatment, short of a cure. We've developed a program that, hopefully from our experience, will be able to bring out your experiences and preferences on those topics.

So, for both the morning and afternoon, we're going to begin our discussions with a clinical overview. Both will be provided by Dr. Anna Bruckner. Once we have that kind of baseline framework of both PC and EB for each of our sessions, we're then going to turn it over to the real experts in the room, all of you, the patients and the caregivers. We're going to kick off each of our topics with a discussion from panel members, members of your own communities, that have graciously agreed to provide some prepared comments and remarks about their own experiences. At the conclusion of the panel discussions, we're then going to open it up to the audience for your participation, both in the room and on the web. You'll be able to participate in polling questions. If you haven't already when you registered, you should have received an email with instructions on how to download an app that will allow you to participate in polling. And the programs in front of you, if you haven't already, please go ahead and look at those directions and download that app.

Once we finish with some polling questions, just to get a sense of who we have in the room and kick off some of the discussions on each of those two topics, we'll then open it up to a broad audience discussion. This will be an opportunity for all of you that have traveled here today to participate and provide comments to those questions that we are asking of you. For those of you who are viewing on the web, we will be following up with an email that will provide a survey with those same discussion questions and ask for your written comments. We will be including those comments, along with what we hear

today in the room, in the summary report for this meeting, which, for both PC and EB projects, and Debra of America will be drafting *Voice of the Patient* reports, which are the summary reports of this meeting to provide to the FDA and to the public at large.

So, before we move into our clinical overview for PC, I do want to lay out some discussion ground rules. There are many of you in the room today, and we do only have so much time to have a discussion, to make that as fruitful as possible, we do encourage all of you to participate and contribute to the dialogue. You're going to hear from panelists first, but it's important for us to know both similarities and differences in your experiences from what we hear on the panel. So, please contribute even if you feel that your experience has already been presented. It's important for us to know commonalities within your own community. FDA is here to listen, so we won't be posing questions to FDA, although if FDA has questions, they can certainly raise their hand and ask a question during the audience discussion, but today you are the experts. We're here to ask you the questions and try to learn from you.

We know that today can be very personal. We're asking you to share your personal stories. So, please be respectful of one another, knowing that you all have different experiences and preferences. When we get to the audience discussion, what I'll do is I'll just ask if you would like to speak. We're going to have microphones that will be brought around the room to you, and please wait for a microphone so that way our webcast participants will be able to hear you, as well as others in the room. But we'll just ask that you wait to be called upon, and then once you do, please state your name and we can have a discussion.

That's how things will run. We're going to start now with the PC portion of the agenda, and so I'd like to introduce our speaker for the clinical overview, who is Dr. Anna Bruckner. Dr. Bruckner is an Associate Professor of Dermatology & Pediatrics at the University of Colorado School of Medicine, and Director of Pediatric Dermatology at Children's Health Hospital Colorado. She attended Northwestern University as part of the honors program in medical education, earning her MD in 1997. She completed residencies in pediatrics and dermatology at the University of Colorado, followed by a fellowship in pediatric dermatology at the University of California San Francisco. She maintains Board certification in dermatology and pediatric dermatology. Dr. Bruckner is passionate about proving outcomes in quality of life in children with skin disorders through patient care, research, education and advocacy. Her academic interests include genetic skin disorders, vascular anomalies, atopic dermatitis, and complex patients. In PC she's actually helped the PC Project by taking biopsies from a number of PC patients back in 2012, which were then sent to four different scientists in order to help advance PC research. So, join me in welcoming Dr. Bruckner.

DR. ANNA BRUCKNER: Good morning. Thank you, James, for that introduction. It really is a pleasure to be here representing patients with pachyonychia congenita and EB. As James mentioned, I will be providing a general overview for each of these disorders, just to make sure that we're really all on the same page. I know we're talking about the same thing, but the stars of the show really are going to be the patients that

you're going to be learning from later on. Without further ado, just as a formality disclosure, I do have some relationships with industry, none of which would be pertinent to this presentation.

I'm going to start with a case presentation. This is a two-year-old child who was referred to me, actually from out of state from another dermatologist. His history was that he was born with funny looking toenails, which progressively worsened over time. Around the age of one he started to develop blistering on his feet, and this generally progressed to thick areas of callous, or what we would call keratoderma in the medical literature. He also was fairly active but did sometimes complain of pain, and his mom reported, in general, he really did not like for her to bother with his feet at all.

Some additional findings that were subtle on his examination included some focal callouses on his palms, as well as a sort of white thickening of his tongue, called leukokeratosis. Also, interestingly, his mother reported that he had started to develop teeth at two weeks of age, which is unusual. So, based on this constellation of findings, I was suspicious that this child had pachyonychia congenita, and I did refer him to PC Project, to where he was able to undergo genetic testing to confirm that diagnosis.

So, what exactly is pachyonychia congenita or PC? It's an autosomal dominant genetic skin disorder, and it is quite rare, so we estimate that there are approximately only 5,000 to 10,000 people in the whole world that are affected with this condition. So, we are all unique in our own ways, but if you have PC you truly are one in a million. This is the prevalence of this disorder. In speaking tongue in cheek, you have more or less won the genetic lottery you did not choose to participate in.

The onset of symptoms for this disorder can vary. In some cases, it does present at birth. The mean age is typically four years, but there are certainly reports that it's starting—or the symptoms starting—later on, even in adulthood. If you read a typical dermatology textbook, they used to classify PC in two forms: P-1, PC-2, but really, based on the work of PC Project, which has been remarkable in terms of genotyping affected individuals and cataloging their symptoms, we now know that there are really five affected genes, and the classification of PC corresponds to those particular genes. The genes more or less encode what are called keratins. We're going to talk a little bit about that in the next slide, how those keratins and the abnormalities in the keratins will lead to the symptoms that are seen in PC.

So, in all of the cells in our epidermis, the keratins more or less form a scaffolding or a structural network. There are different keratins that are expressed in the bottom layer of skin, keratins 5 and 14. Higher up in the skin in most cases, keratins 1 and 10 are expressed. In PC the keratins that are affected are keratins 6, 16 and 17, and those are typically expressed sort of in the middle-ish part of the skin, but more highly relevant in areas such as the palms, the soles, the hair follicles, the oral mucosa, and the nails. But in this example here you can see how on those slides, the green structures are more or less the keratin filaments forming this scaffolding that should give them their shape.

The mutations that we see in PC basically lead to structural weaknesses within those keratins, so that they're really not able to withstand stress like they should. If you have a nice, strong scaffolding, that's sort of analogous to your Eiffel Tower. It stood the test of time, right? But if you have a weak scaffolding, that's sort of like having a house of cards, more or less. It's going to fall over very quickly, but as a result of that structural fragility in those keratins, the body sort of actually sends out distress signals and compensates by making the skin thicker in those affected areas. So, you can imagine what's basically happening is that you have sort of a weak foundation, but in order to compensate for that, the skin grows up thicker, so you have this sort of pillar, more or less, of skin cells growing on top of a weak, unstable foundation.

The term pachyonychia means thick nails, and you can see here there are several examples of thick nails. Thank you to Holly Evans of PC Project for helping me with some of these clinical pictures. The classic pachyonychia is this U-shaped nail where there's quite a bit of thick nail underneath this hyper curved nail, but this is not necessarily typical for all patients with PC. I do think that the name PC or pachyonychia congenita doesn't really encompass all of the findings that we see in this disorder.

This is the typical triad of findings that is seen in the majority of patients with PC: plantar pain. So, a significant pain mainly involving the feet occurs in 95 percent or more of patients with PC. In addition, that is combined with these callouses. You could also call it hyperkeratosis or keratoderma focal, involving the feet, and in some cases, involving the hands. Also, nail thickening predominantly involving the feet, but in some cases, involving the hands. This triad of finding is seen in over 90 percent of patients with PC. It's very important to recognize that the pain is very characteristic.

Other findings that are seen in PC include cysts. These are more or less sacs or dilations that come from the hair follicles or other glandular structures in the skin. Also, follicular hyperkeratosis or plugging in the hair follicles is another finding, more often seen in children and adolescents. It does tend to improve over time.

Finally, is leukokeratosis, this white change in the oral mucosa, particularly the tongue. This is, again, a result of thickening of the epithelium of the mouth. In addition, some other oral findings that are less common include natal teeth, or teeth occurring very early in infancy; chelitis or sores on the mouth; a hoarse voice or hoarse cry due to involvement of the airway and larynx. Interestingly, what's been described by the work of PC Project is also this "first bite" syndrome or this intense pain that people will feel when they first eat or drink.

I'd like to conclude by pointing out that there are no approved therapies for PC, and you are honestly going to be hearing more about treatment in the upcoming sessions. Patients will rely on nonspecific modalities in order to help them manage their callous, in order to manage their nails, and also to help control their pain. What I'm hoping that you all will share with us and what we will learn from you, what is really the impact of the manifestations on your life? What do you need to do in terms of managing this? I know that you are going to share these experiences, but hopefully we will also see that what

you are currently doing is really not perfect, is it? So, we really do have a true gap in terms of developing better treatments for PC, and I know that you will convey that the impact of this condition on your life is very real. So, with that, I will stop there. That was my overview, and I'll turn it back over to James. Thank you.

JAMES VALENTINE: Now we do get to turn it over to you. We're going to go into our first set of polling questions, which is a set of demographic questions, just to get a sense of who from the PC community we have in the room. We do ask that only PC patients and their caregivers participate in these polls throughout the day. If you're here for the afternoon session and you're observing, and you're from the EB community, please hold off until the afternoon polling. If you are another stakeholder here, whether a clinician or a researcher or a member of industry, please also do not participate in the polling, as we would like to limit it to PC patients and caregivers.

So, with that being said, if we could go to our first set of polling questions. We have six demographic questions. Our first is:

Are you a patient or a caregiver, or both?

Respond to:

- A. If you're a patient
- B. If you're a caregiver of a person with PC
- C. If you're both a patient and a caregiver

If you're having any technical issues trying to respond, please raise your hand and we'll send someone over to you to help you out with that. We have one hand over there. Holly's on her way. Is there anyone else who has not been able to participate in the poll?

Our audience today, both here in the room and online, half of the participants are PC patients that are not also caregivers; a third of our participants are caregivers and not patients; and then the remainder are both patients and caregivers, probably a very unique perspective both living with the condition and caring for someone.

The next question is:

Where do you or the person you are here for reside?

I'd like to get a sense of the regional makeup here, both in the room and online, so:

- A. East Coast
- B. West Coast
- C. Mountain West
- D. Central area
- E. Outside of the U.S.

I know it's early out on the West Coast. I imagine that's going to pick up perhaps in an hour or so. I'll give you a few more seconds to participate in this.

It looks like the majority of our participants are from the Central area. I think that's actually somewhat unusual for a meeting on the East Coast not to be outnumbered by East Coasters, so congratulations, guys. Then we have our East Coast representation, and we actually have some participation from outside the U.S. It looks like we're not, at least yet, represented by the Mountain West or the West Coast.

Holly, can you check to see if their responses are going through? Interesting. So, it looks like some of our responses are not showing up on the screen. Hopefully, they're being logged so at least we'll be able to reference them. Sorry about that.

Can I get a showing of hands of our Mountain West people in the room? So, we have Mountain West, and what about West Coast? We do have representation in the room. That's great.

Our third polling question:

What is your age or the age of the person you care for?

If you are a patient that is also a caregiver, please respond for yourself for this question. Your options are:

- A. 0-2 years old
- B. 3-12 years old
- C. 13-18 years old
- D. 18-25 years old
- E. 26-45 years old
- F. 45-65 years old
- G. Older than 65

I will be reading out the results since we're having some kind of displaying issues for the Power Point slide. We have representation actually across all of the age groups.

3% for 0-2
16% for 3-12 years
8% for 13-18
10% for 18-25
1/3 for 25-45
1/4 for 45-65
10% for older than 65

Our next polling question:

In which PC gene is your specific mutation found?

- A. K6a
- B. K6b
- C. K6c
- D. K16
- E. K17

Responses:

40% for K6a
6% for K6b
2% for K6c
1/3 for K16
1/5 for K17

So those of you with K6b and K6c, there's not many of you, but hopefully you'll be brave and share some of your experiences, too, since you're in the minority today.

Our next question, please. This question is:

Do you have:

- A. A spontaneous mutation where no other family member has had PC
- B. An inherited mutation where others in your family have PC

In this case, we actually have a match. More than half of you have an inherited mutation, and a little bit less than have of you have a spontaneous mutation.

That concludes our demographic polling. If our panelists, Panel One, will join us on stage, we're now going to move into our discussion of Topic 1, which is really focused on the burdens and symptoms of living with PC. Starting with our panel, moving into another set of polling questions and our audience discussion, we really want to hear from you what are the most burdensome aspects of your disease, and what are the impacts of those aspects and symptoms of your disease on your daily life? We're interested in knowing how that changes day to day, over the years, and what really worries you about having PC.

Our first panel is made up of a great selection of individuals who I know have worked really hard in preparation for today. We have Jack Padovano, Christine Block, Nicole Lee[44:42], James Rittle [44:43], Tara Atae [44:45], and then as our fill-in for our sixth panelist, we've actually brought together a compilation of several voices of PC members, members of the PC community, to try to help get a broader representation from the community and their experiences with PC.

So, with that, I will turn it over to Jack.

JACK PADOVANO: Good morning. My name is Jack Padovano. I'm 56, and I live in Phoenix, Arizona, and my genetic mutation is on keratin gene 16. That is my foot and my arch nemesis [pointing]. My PC shows up with thick callouses on over 50% of the bottom of both feet, cracks and occasional blisters along the middle and sides of most callouses, and thickened nails on 100% of my fingers and toes.

Like most people, I have a bank account—not the kind that you're probably thinking about. This one isn't filled with money, but instead it's filled with a number of steps that I can physically walk each day before tremendous pain sets in for me. And just like a checking account filled with money, I spend it very wisely, or try my best. Each withdrawal or step that I take is mentally recorded and physically felt right down to my bones. Overnight, while I sleep, the bank account is refilled before I wake up. The amount of the refill varies. If I overdraw from the account the day before by walking too much, I have fewer steps in the account. If I got a good night's rest and monitored my walking the previous day, the account is on full. On my best day, I can walk down a long city block without thinking once about the pain. On my worst, I simply refuse to walk, period. Unfortunately, there are very few best days. If I'm lucky, I get one a month. Most days I think about the pain with each and every step, including standing in place.

PC hurts, both physically and emotionally. PC pain for me feels like someone is sticking pins and needles in the bottom of my feet constantly. It's a deep ache that cuts all the way to the bone. I treat the pain with hot water soaks, cold water soaks, elevating my feet, rubbing creams, massage, Vaseline baths, Advil, and a lot of bitching, mostly under my breath. I treat my PC by paring down the callouses once a week, trying to navigate those pesky blood vessels and nerve endings that cut and inflame and bleed in the process. Nothing really works. The pain is constant and often makes me grouchy, sometimes to the point of lashing out to people I love, work with, and sometimes even total strangers. I think it even contributes to my struggle with depression.

PC makes my fingernails ugly, so ugly, that growing up other kids made fun of me. PC makes me walk weird, something we PCers actually call the PC walk. But kids being kids, they didn't see any humor or have any compassion for my walk. I was just different, and that made me a target for bullying. The really mean kids took to stomping on my feet, so hard I would fall to the ground and writhe in pain. As those with PC in this room can attest, the last thing we PCers need is more trauma to our feet.

PC also significantly impacted my parents. After my diagnosis at three-years-old—this is the 1960s—my parents had a name for my condition, but that's all they had; no treatment, no answer why, or especially, no cure. In fact, they were told the condition would most likely worsen to the point where I could never walk again. And my mom, she was certain it was her fault. She would often say, "Maybe if I smoked less, ate differently, didn't take aspirin," etc., etc. Today, we know none of that matters. I'm a spontaneous case, meaning that I won that lottery.

As an adult the bullying has stopped, but it's replaced by questions, mostly thoughtful and kind, but sometimes not. Questions I really don't like to answer because the

answers are never simple one-word answers. Recently, I learned that the average person walks 10,000 steps per day. It's about five miles. I'm envious. That's a big bank account. For me, I'm lucky to get a quarter-mile in or 250 steps, before the pain sets in. So, while my account may not be as rich as yours, I treasure every step that I take.

Future forward, I worry that my condition will worsen as I get older. I know my pain has gotten progressively worse every year, particularly in the last 20 years or so. I can see it in my walk and feel it in my bones. So, my wish is simple: I want to stand and walk without excruciating pain. I hope and pray that's not too much to ask. Thank you for listening.

CHRISTINE BLOCK: Good morning. My name is Christine Block. I'm from Wasau, Wisconsin. My husband and I have two daughters: Erin, who's ten, and Allison is eight. I also have my doctorate in physical therapy. I'm here today as a parent of a PC patient. Allison has PC. Allison was diagnosed with PC when she was two months old and was genetically confirmed with K6a by the time she was six months old. Allison's PC was caused by a spontaneous mutation, so no one else in our family has PC. We had never heard of PC before she was diagnosed. I immediately started researching PC and connected with PC Project. I quickly learned that PC is ultra-rare, painful, and there are no effective treatments.

Allison's symptoms from PC started as an infant with leukokeratosis, a white film of keratin on her tongue, and First Bite Syndrome, which caused pain with eating. She would cry the first few minutes of nursing, especially in the middle of the night. Fortunately, she outgrew that by about six months old. Allison also has follicular hyperkeratosis, small bumps or plugs of keratin that form around her hair follicles, on her knees, underwear line, elbows and other areas of friction. At times they catch on things and become sore. All of Allison's fingernails and toenails are thick. We have to file down her nails regularly. She also has had some nail infections. They usually occur after she has bumped or bruised the nail, and result in a swollen, red, throbbing finger. We have to ice it, try to relieve the pressure, or drain it, and at times she has needed antibiotics. All of these symptoms have caused problems, but the foot pain, blisters and callouses are the worst. Allison started developing some small blisters and callouses on her feet when she started walking. When Allison was a toddler, she would get a callous or a blister and it would get better and go away. Now she always has some callouses on her feet. We help her regularly trim and shave down the callouses. As she has gotten older, heavier and more active, the callouses and blisters have gotten worse.

One of the first times Allison asked about her PC was one morning driving to daycare. Allison was three-and-a-half, and she looked at her sister and asked why her feet were different from Erin's. With tears in my eyes, I explained that she had PC, and God makes all of us different and special. Allison has had kids stare and ask her questions about her feet and her nails. She simply says that's the way she was born. So far, she hasn't had much teasing, but I fear it will come as she gets older. Each year when school starts I talk to Allison's teachers and I educate them about PC. I make sure they understand that Allison is living with daily foot pain, and they need to let her sit down if

she asks. Currently, Allison is in second grade. She is a tough kid and she doesn't want to miss out, so she will push through the pain. But by the end of the day, it's getting the best of her. I often see her limping as she walks home less than a block after getting off the bus. Some days are worse than others, but the pain is always there.

I'm sure, as she gets into middle school and high school, she will have to crutches or a wheelchair to make it through the day. Allison played soccer during the summer for a couple of years. After a soccer game she would limp to the car. At home she would cry because of the foot pain, and just standing in the bathroom at night to brush her teeth was extremely painful. The time running and the heat of the summer made her foot pain worse. Last summer she did not play because we decided as a family the pain is not worth it. We live in Wisconsin, and the summers can be hot and humid. Heat and humidity cause more sweat and moisture, which leads to more blisters. Winters are a little better, but she still has daily foot pain.

Allison's PC diagnosis has also affected our family life. When we plan family activities we have to think about how far we have to walk, how long Allison will have to be on her feet. Last summer we went to Bryce Canyon National Park, and Allison couldn't walk up a couple of short trails because of her foot pain. My husband carried her piggyback to see a couple of sights. This winter we went snow tubing. It was a busy day, and after standing in line to ride up and tube down the hill a few times, Allison had to be carried to the car because her feet hurt. Allison only has so much time on her feet or steps each day.

As a mother, it breaks my heart to see my child suffer. I see her condition slowly getting worse. I worry about how she will get around in high school and college. Her feet already limit sports she can do comfortably. I am concerned that she won't be able to choose her ideal career because she won't be able to stand or walk long enough.

Finding treatments for the foot pain caused by PC will improve Allison's quality of life and open many doors for her future, as for all PC patients. Thank you.

NICOLE: Hello, my name is Nicole, and I'm 32-years-old. In 2011, I was diagnosed with PC K17. I'm so honored to come here today and share my experience on having lived with PC. This day is truly a dream come true to be able to be involved in something bigger than myself. I believe that today represents a breakthrough for so many people who are affected by PC. For me and my three boys, PC has affected our skin, nails, teeth, feet and hair. It was like it had many other faces to it. It didn't only single out one thing, but it has caused a domino effect of many painful symptoms and abnormalities to most areas of our bodies.

Every day it is a fight for us. Every day I find myself fighting the good fight of faith. I have to be determined in my heart not to let the pain and symptoms kill my joy. I have to be determined to not let this condition turn me into a recluse and make me pass upon opportunities to enjoy life, because just like any sickness or disease, PC has the potential to destroy its victims mentally, emotionally and physically. It is a fight every day

to stay hopeful that better days are right around the corner, and I believe that today is a marker to that better day.

Even before I knew these symptoms belonged to a condition that had a name to it, I would look at myself in the mirror at times and imagine that I didn't feel the hideous scars and bumps that this condition tried to leave on my body. I would look at my children when they were in pain from being on their feet for more than 30 minutes and imagine them running and standing and doing all the things that they enjoy doing that this condition has tried to stop them from doing. I would make collages of beautiful feet, nails and skin from my own pictures of myself and my three boys in my mind to help me to stay encouraged, to keep on living, to not be depressed, and to look forward to that day when I would see myself and my three boys completely healed, and hope.

The condition has caused so much bruising to my body over the years, from flare-ups to boils that will leave behind dark marks on my skin. Some of the cysts that were usually under the skin would become inflamed and would turn into huge, painful boils that had to be lanced; and even after they were lanced they would always take a while to heal because they were so deep and big. When they did finally heal they left an indentation in my skin. I could literally, at times, push my finger into my skin and feel the deepness of where the boil had been, not to mention that after being lanced or having the sac removed, it would sometimes return and be even bigger than it was before. I would get these, hard painful knots under the skin. Sometimes my skin oozed to the point where it would leak through a shirt or wherever the open wound would happen to be. I wouldn't even allow my husband to rub lotion on my back because there was one particular time that when he did, one of the wounds started to ooze right down my back and it had created a very embarrassing situation for me. This was one of the reasons I tried to stay completely covered up at all times, no matter if it was hot or cold outside.

Summertime would always be the most difficult time with this condition, because I would get some of the most painful boils. It was almost as if the heat was causing the blood to boil and causing the boil to be so severe. When I was younger and living with this condition, right at puberty age I would get one at a time, but in adulthood I noticed that they came more often. Sometimes there were five to seven at a time. The pain from those boils could be so excruciating that when I would expand the flare-up, it would make me so miserable and feeling like I just wanted to stay in one place and not move at all. Sometimes I would get them in the pelvic area until I couldn't even walk, or if they were on my backside, I couldn't sit down. There were times when my husband would come home from work to see me crawling behind our three-year-old or crawling from the floor up on the counter to prepare dinner. I've had to watch my 10-year-old son have to ice his feet at their basketball game and stay off his feet for a week or so because this condition had brought on severe pain from the pressure he was putting on the callouses that had covered the soles of his feet. He has even hit strides with his two younger brothers in my 3-in-1 stroller. We have had to push our three boys in the stroller way beyond the stroller age to try and save their feet, and we just got rid of that stroller two-and-a-half years ago because with them growing and, of course, weight increasing, the stroller could not hold them anymore.

Things like hover boards, electric scooters and bikes, or even pushing them in shopping carts have had to become our walking companions during times where walking is painful. And for me, I've had to accommodate this condition over the years by staying at home, since being on my feet has created problems for me with existing callouses that were there and the threat of new ones possibly forming if I was required to stand. So, I opened my own transcription business where I could work from home and still contribute to our financial obligations.

It's truly been our unshakeable faith in the word of God and the knowledge of Jesus Christ and all that he's accomplished for us that has kept us imagining and dreaming to see a complete and total breakthrough where PC is concerned, not only in our lives, but in the lives of so many other people. I really consider this day a major breakthrough and an open door, getting us one step closer to seeing my dream being manifested. Thank you so much again.

JAMES RITTLE: Good morning. Ladies and gentlemen, it's an honor to be here in front of you today. My name is James Rittle. I'm from the Chicago area, and later this year will be my 50th birthday. My PC is hereditary. My father was a fraternal twin, spontaneous K16 L-132P. He had a hard time growing up in the '40s and '50s in the coal mining areas of Pennsylvania. I know now he suffered from depression. I've been aware since I was nine he suffered from alcoholism, and he was very verbally and mentally abusive. I would imagine if he was here today, he could speak to you about pain, both physical and mental, and both due to PC.

Part of our story I want you to understand today that PC doesn't just affect us, but it forms us, and it encompasses us. It affects the people around us by how we control it, or it controls us, and that can change daily and hourly due to pain. I've cried—I mean really cried—three times in my life because of PC, and I want to share those with you today.

First, as a young boy playing outside all day, I was sitting on the floor in my room at night examining my newly developed day's blisters on my feet to see which ones I could pop. This was not a pleasant evening ritual. However, I did this regularly as I grew taller and heavier because more blisters and callouses were constantly developing. Probably to your horror, sterile is not a word I care about even today. When I need to relieve the pressure of a blister, especially under a nail, anything sharp will do. The blisters would dry overnight, I would peel the dead skin away in the morning, and have a normal pink skin area, but pretty much guaranteeing to have another blister in the same spot that night. So, I was popping blisters when down the hallway when I heard my mother and sister arguing, but all I could make out was my sister saying, "His feet really stink, and I'm sick of it." Now, as a young boy, in addition to dealing with blisters, infections that I thought were cloudy blisters, developing callouses, red sore spots and pain, I had something else to worry about. I closed my bedroom door, crawled over to my bed, went under the covers, and I cried while wishing that a car accident could somehow chop off my feet, and I would be okay with that.

Second, as a young teenager, due to my PC, I became introverted. I wasn't into playing sports because I was not able to run more than a couple of minutes without sitting down due to pain. With a somewhat less than an ideal home life due to PC, I was not a good student and I did not do well in school. After high school my options were limited, and I got a job working outside where I had to wear, of all things, steel-toed boots. Before long, after a bad weather day of soaking cold rain, being on my feet all day, I managed to make it very slowly to my car, where it hurt to press the gas pedal. After crawling up the stairs to my apartment, I got inside the door and collapsed, in pain, and I broke down. I struggled for a very long time to take off my shoes, and I cried myself to sleep, just inside the door, fully dressed, on the floor.

The third time I was a new father when my wife called me into my daughter's bedroom. She was just about nine months old and starting to crawl, and I had been watching her very closely, as you can imagine. My wife had just finished giving her a bath and was cutting her nails. She asked me to look at her little toes and said, "What is that?" I knew immediately with one look that it was PC. I turned to my wife and said, "That's it. She has the callouses." I walked down the hall to our bedroom, closed the door behind me, and collapsed, crying the hardest I've ever cried, because I know what it means to have PC, painful callouses, and I do not wish that on anyone, let alone my child. I understand my father a little more today.

As a final note, I'd like to add that I could not be prouder that now a 16-year-old, she sits here in the audience. I have and will continue in any way and every way I can, like being here today with all of you, not just hoping for a better tomorrow, but doing something about it. I will push her to not be controlled by her PC, physically, mentally or emotionally, but most of all, to not suffer the pain that I have suffered. However, I'm sure that through living, she will have her own stories of struggles and endurance, and she will have stories about pain. Forget running and hiking. Walking and standing are difficult at best because there's no life with PC that doesn't include pain.

Ladies and gentlemen, I will push you like my daughter, while continuing to give you all the help I can. I will be uncompromising, like my PC. I want a cure. It exists in the universe. We just have to find it. Thank you for your time.

TARA [1:07:18]. Hi, my name is Tara [1:07:17]. I'm 23-years-old, and I was diagnosed with PC at the age of two. Living with PC is not easy. It affects you on an emotional and physical level.

I would like to start out by talking about the physical pain and then get more into the emotional pain. The emotional pain is what I believe is the worst part of the disease and affects you most. I would like everyone to bear with me for a second and close your eyes. Imagine yourself barefoot with no shoes, no socks, just your bare feet and nothing else. Now, imagine yourself stepping on a bed of misshapen, sharp, hard rocks. Stand there for a second as gravity does its job and pushes your feet deeper and deeper into the rocks. Now, you may open your eyes. I bet that made you feel a little bit

uncomfortable. Well, that's how I feel every day. My pain fluctuates in intensity, meaning sometimes it's bearable, and sometimes I'm at the point where I can't even stand. But I'm one of the lucky ones. My PC was genetic, not spontaneous like the others. My father has PC, and I'm lucky because I grew up learning how to manage the pain that comes with PC, but the one pain none of us seem how to know how to relief is a never-ending itch. Having a father who has PC is great and all, but it's also hard to have him understand the things I have to go through as a girl.

As a female, I grew up feeling a bit of pressure to be perfect. When I was younger I did not care much about what people thought about my PC until I started being bullied in elementary school for how I looked. This is what led me to feel self-conscious about my PC, and I tried my best to hide it. I honestly cannot remember the last time that I left the house without socks on or went ten minutes without nail polish on. Whenever people ask me why I walk weird, I say it's because of a sports injury that never healed, even though I've never played sports. I stuck with this lie for years. It took me seven years to come out and tell my best friend the truth. I felt like I needed to lie to my friends because I did not want them to treat me differently. I did not want them to see me as someone who is broken, and I did not want them to ask me if I was okay or if I needed a break. I know my limits and I know when the time comes, I'll push through the pain to do what I want to do.

A few years ago, my family and I went on a trip to Italy. We did a lot of sightseeing, which required a lot of walking. Now, the one place I really wanted to see on this trip was the Vatican. We got a tour of the Vatican Museum, which was great, and it was fine up until halfway through, when the pain started. I was at the point of dying from pain and my family kept telling me, "If you're in pain, let's go," but I kept saying, "No, I really want to see this museum." When we finally finished our tour, I was about to collapse. My sister gave me a piggyback ride to the taxi stand, where we got back to the hotel and I fell, crying from the pain.

One of my biggest fears with PC is passing it down to my child and having them go through the things that I had to go through. I hope one day there's a cure, so no one has to experience going through this. Thank you.

VIDEO VOICE: The worst thing about PC is the pain, and unlike a lot of other conditions, the pain is always there, but it's a pain that a lot of people can't see, so it's pretty hard to get across for them to understand how much it can affect you. A cure for PC would go a long way to help the pain. That's the main thing.

VIDEO VOICE: For me as a PC patient, pain is one of the things I deal with on a daily basis, and managing the pain is one of the most important parts. I can manage pain to the point where it's not as painful as it would be if I didn't have the tools available that prevent the pain. That would make a much better day in life for me.

VIDEO VOICE: I am PC, and I get callouses and blisters on my feet. It usually hurts when I'm running around a lot, and when I'm standing still for a really long time. If they

can make a cure for this, I would wish that the cure was to make it go away forever, but if they couldn't make it go away forever, I would just wish that they could make it stop hurting so that I could run around a lot.

VIDEO VOICE: The pain just consumes you constantly. The pain has been so bad to where I would just be crawling around my house for a couple of days, and at that point my feet were in terrible condition. And I just thought, you know, pain—if you could only feel the pain that I'm in. They have no idea what pain is when every step you take is literally—it's just hell, every step you take.

VIDEO VOICE: The worst part about having PC is that unknown pain factor. I get up every single morning and get out of bed. That first step on the ground, I know it's going to be painful, and it is, and I dread it. I lose my balance because the pain is so bad. It's hard to walk. The second thing is the fact that I'm so dependent on other people to help me with everything.

VIDEO VOICE: The worst thing about PC is when I grow older, it's going to hurt more, and I won't get to do anything I do now. Yeah.

VIDEO VOICE: They don't understand that when you say—they usually say—somebody will see you and say, "Did you hurt your ankle?" And I say, "No, I just have really bad feet." "Well, what's wrong with them?" "Well, I have these callouses." "Oh, yeah, my Aunt Gert had callouses and, you know, she worked in a factory or whatever. My uncle was a paratrooper. He had callouses." You know. "But these are different callouses. You don't understand different callouses, you know. It feels like you're walking on stones in your shoes. It's a different kind of callous. When you sit down the pain doesn't go away. It changes from more acute to more of a throbbing, burning, you know, so it's pain, just in a different format."

VIDEO VOICE: I would say the worst thing for me about having PC is the pain that comes from just day-to-day activities. The worst part about it for me is just not being able to do the simple tasks that other people can do, such as just like walking to class, or being to help out with, like, moving things. I always have to be really careful about how much I do every day, and sometimes that limits my ability to interact with other people, to participate as much as I want to. And then, even if I do hold myself back, I still have to suffer the repercussions for it. So, I think probably the biggest thing that I would want in treatment for PC to do would be to address the pain.

VIDEO VOICE: The relief and the possible future that my—excuse me—the possible future of my grandnephew having the pain lightened and maybe even cleared up. Maybe his future and his wife and his child would not have the 16K that we have right now. The problem is, no one saw my condition, and no one saw the pain many nights going home, barely able to walk, barely able to walk. It's to find solutions to the pain and perhaps the cure. The first step is to lessen the pain.

JAMES VALENTINE: Join me in thanking our panel for being brave and starting us off today.

[Applause]

Now we're going to transition our discussion of this topic of the burdens and symptoms of living with PC to the broader audience, and we're going to go to our polling questions on Topic 1. So, go ahead and pull out your phones and get on the app again, and we'll go ahead and work through these.

Our first question for you is:

Overall, how would you characterize your PC disease severity or the severity of the person you care for compared to someone without PC?

Your response options are:

- A. Mild, which is while I have symptoms, I am able to, on most days, manage those symptoms and live a healthy, normal life without limitations
- B. Moderate PC has an impact on my everyday life, and on some days limits my ability to function normally due to ambulation challenges, pain or otherwise
- C. Severe. PC is debilitating to my everyday life, and in many cases limits my ability to live a normal life due to ambulation challenges, pain, or otherwise, or
- D. Unbearable. PC at times causes me to withdraw from society. I feel it's difficult to continue on, and occasionally I have suicidal thoughts.

I'm looking to the back corner to let me know. We're good? We're aligned.

It looks like our responses are in, and all of you rate your PC disease severity as severe, meaning that to you.

We're not aligned? I'll do my best to look. It might actually be easier for you to see than me. So, it looks as though the majority of you do rate it as severe, your PC disease severity, but a significant amount of you, just slightly less than you, rate it as moderate. About 10%, unbearable, and less than 10%, mild.

Moving to our second question, which is:

Which PC conditions have impacted your life—and here we're going to ask you to check all that apply? Your options for PC symptoms are:

- A. Thickened nails
- B. Painful callouses and blisters on the soles of your feet
- C. Painful callouses and blisters on your hands
- D. Painful blood vessels or nerves in callouses
- E. Deep, persistent itch in feet

- F. Infections in nails or feet
- G. Painful cysts
- H. Follicular hyperkeratosis, which are little bumps on your waist, legs, arms or elsewhere that cause irritation
- I. Leukokeratosis, which is the white growth on your tongue
- J. Trouble feeding as a baby
- K. Other

You should be able to see all of those options in the app. Please select all that apply. I'll give you another moment to respond to this question.

It looks like the two most common PC conditions are the thickened nails and painful callouses and blisters on the soles of your feet, although for pretty much all of the others, there are a fairly wide distribution of responses, and it looks like there are some others. So, when we get to the audience discussion, for those of you who have experienced things that were not listed on here, please chime in with those, so we can understand what other symptoms of PC you experience.

We're going to move to our third question. This question is:

Do you typically feel some level of pain with every step that you walk, yes or no?

This one is a little easier to respond to; just a binary choice (A) Yes or (B) No.

So, of our PCers here in the room and on the web, it looks like 95% of you do experience pain when standing and walking, and 5% of you do not experience that. For those of you who do not experience pain, it would be interesting to explore why that is. You might perhaps be a caregiver of someone young, or perhaps you only experience other manifestations of PC.

Can we go to our fourth question? Our fourth question is:

How has your PC changed over time or with age?

- A. Has it gotten better
- B. Has it gotten worse
- C. Has it stayed the same

For the vast majority of you, your PC has gotten worse over time. We definitely want to explore how your condition has gotten worse. Then, it looks like we have about 15 % of you where your PC has stayed the same over time, and for some of you, 5%, it's actually gotten better over time.

We go to our fifth question. Our fifth question is:

How do your PC symptoms affect your daily life?

Again, we're going to ask you to select all that apply.

- A. Does it limit your walking
- B. Limit your standing
- C. Limit your ability to work consistently and effectively
- D. Limit the types of jobs you can realistically perform
- E. Partially or completely limits your ability to participate in activities
- F. It causes depression or discouragement
- G. It causes difficulty sleeping
- H. It causes difficulty socializing
- I. It forces you to hide your nails or your bare feet
- J. It forces you to make up stories about why you walk the way you do, why your nails or your feet are the way they are, instead of having to explain your PC.

A lot of different aspects of living with PC in your daily life. Please select all that apply.

It looks like the symptom with the highest response is limiting your walking. After that, it's limiting, either partially or completely, your ability to participate in activities, or your standing. After that, there are still very high responses across the other categories, the lowest of them being causing difficulty with sleeping.

Can we go to our final Topic 1 polling question? This question is:

In living with PC, which situations create the greatest stresses and/or worries in your life?

Again, check all that apply.

- A. Job security and employment issues
- B. Fear of disease worsening
- C. Social issues
- D. Family life issues
- E. Caring for yourself as you grow older
- F. Lack of ability to participate in activities
- G. Living with pain
- H. Embarrassment

Which things worry you or stress you the most in life about living with PC? Select all that apply.

It looks like those things that worry you or stress you the most about living with PC are the lack of the ability to participate in activities and living in pain. After that, the next highest batch of responses are embarrassment, as well as the fear of your disease worsening. Then were still high responses to the other options, with the lowest being family life issues.

Now we move to the part of the program where we're going to ask you in the audience to build on what we've heard from the panel, from what you've shared in your polling responses to help us really further understand what it is like to live with PC, what it is that you experience in your daily life. Let's start with the thing that we heard the most. From what I heard from the panel and from what I saw in your polling responses, we've heard that excruciating pain when standing or walking is the greatest burden for most of you—not all of you, but most of you. It sounds, though, that there's a range of different pain severity that you experience, and that results in different impacts on your daily life.

What I would like to hear from the audience is help me understand how the level of pain that you experience affects your daily life. Help me understand what activities you can or cannot participate in. When you're sharing this, please feel free to share examples like our panelists did in how the pain and the activities that you can or can't do actually manifests in your experiences.

Do we have anyone who wants to break the ice? We've got a hand right here in front. When you start, for those on the webcast and so we can reference this when we're putting together the summary report, please say your name and the PC gene affected.

SARAH DELANTY: Hi. My name is Sarah Delanty, and I have K6a. Many of you are probably wondering why I'm not barefoot today. Last night I wanted to put together some thoughts about my PC, and it's like with my mostly invisible PC.

As I lay down here to write about my life with PC, specifically K6a, something is distracting me. This is a paper cut like throbbing, pinching, cutting glass pain in my lower right foot. Oh, yes, indeed, my PC will not let me forget that it is here. This is what PC is, a constant painful reminder that my body has betrayed my spirit. Just when I think I can relax or rest, my PC reminds me that it's still here. Same with when I want to walk somewhere. I'm considering the distance. I'm counting the steps, at the same time checking in with my PC. Are my shoes too tight, too high, too loose, too new, too old, too soggy? Is my PC spongy, sweaty or not? Is it dry, is it sore, or is it just so-so. Sometimes I think, hey, maybe this is a good day. My feet aren't sore at all, but no shoe is ever a good fit. I try all kinds of shoes, except for those pretty Barbie doll 1950s pumps. So, I strap on my shoes du jour and venture outside for a walk. Minutes later my feet have betrayed me. Nope. They throb a little, then a little more. Then my wonderful shoes turn into instruments of torture. My PC screams, "Sit down. Get these things off. What's the matter with you? You must have forgotten about me." But, oh, no, not forgotten, never forgotten.

I try to reason, and I bargain with my PC. If I can just stand on my feet one more hour to finish this job, I will gladly take another ibuprofen. Who cares if it clouds up my contacts? Who needs their liver anyway? If I can just do my grocery shopping, laundry and errands around town, I will rest. I will give up cooking dinner and playing with my kids. I'll skip walking in the park with my husband. I'll skip walking the dog, or I will keep going all day long despite the fire in my shoes, the next day unable to move. Then, the

sadness and disappointment arrive. They are good friends of my PC, not my favorites. My optimistic spirit lets them go. I do not allow for long visits. When my PC is angry, I try to calm it down. I use ointments, oils, lotions, potions, soft, feathery motions, ibuprofen, lidocaine, CBD, hemp, marijuana, alcohol, and Epsom salts, menthol, wintergreen, tea tree and ice water baths. I've walked around barefoot in the snow, but my PC still stings, especially in the spring. I sand my feet with power tools meant for drilling wood or metal. I cut my own feet with single and double-edge razor blades. My PC is angry. My PC is stubborn. My PC, it seems, is here to stay, but hope I'm not going to let it get the best of me.

I've had dreams of myself without PC. In my dreams I peel off my blisters and callouses to find normal, smooth skin. I'm not crying through wretched pain anymore. I'm fine. I'm finally free. And then I wake up, usually to a crazy burning itch or a jolt of electricity in my feet. Or worse, to my toes curling up underneath my feet, cramping so much so that I have to jump out of bed and firmly place my foot on the ground so that they do not do that. Pain so sharp that I have to shriek out loud. I wake up my husband. The people in my life without PC are mostly patient and kind, but I see the disappointment when I can't join in. It breaks my heart. I can't ski with them. I can't walk more than a few yards, or if I do, I pay the price of not being able to do anything for a day or two afterwards. I worry about those times when I simply cannot move or be active. I do not want heart disease or obesity. I know how important it is to move. My PC, however, is ignorant to that reality. It does not care about broken hearts or disappointments. It wants what it wants. It must tend to its needs. It is relentlessly self-serving. It is a force. I am one with PC, and the PC is one with me.

JAMES VALENTINE: Thank you, Sarah. Thank you for putting together your thoughts and sharing those with us. You covered so many of the topics that we want to talk about today. So, thank you for sharing the physical manifestation and how that evolves throughout the day, and the things that you forgo in your daily life because you have to make those hard choices about what you can do and can't do, and whether you can pay the price and are willing to pay the price the next day, as you said. In our next session, we will definitely want to explore more about all the lotions and potions and everything you try to do to manage your PC. Thank you so much for sharing about all those burdens and impacts on your daily life.

Who else would like to share about how the impacts of standing and walking and the pain associated with that impacts on your daily life?

JAMIE SIMPSON: My name is Jamie Simpson. I have K17. I've dealt daily, since I was 15, with my feet. The cyst is extremely painful as well. It makes the depression come in very heavily because I feel like I'm not worthy enough to be a wife or a mother. It's hard to have intimacy when you're ashamed of the way you look. You feel sick because you hurt so bad. And I would just like to say that I met someone at a meeting, and he had spoke to me and told me he tried to take his life, and I begged him please don't do that again. And he told me he couldn't promise me that. However, I have looked for him for several years, and I have not found him, and my thoughts and prayers go out to him in

hopes that he changed his thought pattern, but every single day it crosses my mind that a bullet wouldn't hurt near as bad as PC. But with my beliefs I do not agree with taking my life. However, now my daughter has it and I watch her lay in bed every day, and it's very, very hard, and it's hard for me because I feel like people doesn't understand. Even my husband sometimes, he doesn't understand because he sees me, but he doesn't feel it.

JAMES VALENTINE: What would be the type of thing that would be an example of where he might not understand? What type of scenario or activity might you not be able to do?

JAMIE SIMPSON: We own a property management company, and a lot of times the help's called in sick. He needs me to come and help. We may have to move furniture, houses. By the end of the day I can't even pick my feet up off the ground. I'm dragging my feet because I can't even bend my knees anymore. I fall a lot due to the instability of the pressure if I step wrong. I've learned now how to fall. You kind of just throw yourself into a roll, instead of falling and trying to catch yourself, because if you try to catch yourself, you're going to break your bones and everything. So, I think I've become a little bit of a stunt person. And you look around for the softest place to drop and roll. So, I just want to let everyone know it is a very serious thing, and it is mentally and physically very challenging. Thank you.

BOB BAKER: Hi. My name is Bob Baker, and I have K6a. I've battled PC into a stalemate, and I'm pretty good right now, but I'm not here to talk about me. I'm here to talk about my son Cameron. Cameron died January 3rd. He had PC. I gave it to him. His callouses on his feet were extremely thick to a point of bruising his bones in his feet and affecting the way the bones grew in his feet, which gave him even more pain on top of the pain of PC. He went away to college, and along with studying, he also blazed a path in trying to find a cure for his own pain. It involved pain clinics, and he received some kind of—nothing to deal with his real pain, but like Lyrica, and Gaba-something. I don't know. He was able to find opioids, which apparently people will sell you, but doctors don't. No one was willing to prescribe them for his pain, so he went out and found his own. The pills don't last, so then he had to go on to find heroin, and he used heroin, and he had an overdose, and he was brought back from that. That was two years ago. And he fought his addiction, but he lost January 3rd. I came and found him in his room. The pain is really, really bad. It's a real pain, but it's not as bad as [1:40:02]. I don't want anyone to go through this again. So, that's why I came down. Thank you.

JAMES VALENTINE: Thank you, Bob. Thank you so much. I can't imagine what you're going through, Bob, so thank you so much for sharing that.

I don't want to ignore this side of the room. I know I had seen a hand earlier. Would other people like to share about the pain they experience and its impact?

JASON: Hi, my name is Jason. I have K6a. My mom has K6a and so does my sister. Unfortunately, my son has it, too. The question was, how do we deal with the pain. I get

up every day, and I know like Jack said, that it's a limited amount of steps, so I drive to work. I try to let my feet air out. I wear no socks, no shoes. I get to work. I have to be on my feet, but I try to use as much breaks as I can without abusing it because I still have to do my job. I drive home the same way, my shoes and socks off. That way my feet can air out, get a little rest, because I know when I get home the little guy is going to want to play. Luckily right now he does not have any symptoms, but I know they're coming. We know they're coming. It's one of those things that no matter what we do or try, the pain—you can take ice, you can take Advil, but the pain is still going to be there. I guess I'm a knucklehead. I just try to soldier through, put my head down and do what I do, but it's not fun. It's not easy, and like everyone said, it's mentally challenging. It's depressing at times because you can't do things, you can't go anywhere. I refuse to miss out on family activities. We were walking around yesterday. I did it. I'm paying the price now. We're going to go walk again because I refuse to miss out. It's hard and it's difficult at times, and it's not an easy thing to live with.

JAMES VALENTINE: I think what you just said is really important. You talk about soldiering through, and I think that's something that we hear a lot with PC patients. When you are doing activities the pain is always there, and so tell me about, at least for you, how do you decide when to soldier through versus when to take a break, and does it depend on the day and even throughout the day?

JASON: It definitely depends on the day. Obviously, the mornings start out great, right, and the day goes—I know my limits, what I can and can't do. So, I go to work. I try to do it, try to be smart with maybe my steps and my energy that I use, right? I'm trying—like, okay, don't do this, don't do this, and as the day goes on, I definitely take advantage of the breaks, my lunches. I sit down, you know. Anytime I have a chance I sit, you know. Sitting in traffic is terrible. It's also a relief because I'm off the feet, and the same thing when I get home. I try to put some fresh socks on and maybe change to a different pair of shoes to let the older ones—because our feet sweat so much that it feels like for me, personally, that my feet are just soaked in sweat. I try to switch, and at that point it's on the feet again. Like I said, mentally, everyone pushes through, and you just have to know your limits. By the end of the night I'll tell my wife, I'll say, "Hey, look, I'm done if you need anything else," because once I take my shoes off, that's it. It's like the pressure—your shoes are holding the pressure in, but once you release that pressure, you are done. That is it. I'll tell her—I'll say, "Look, if you need me, tell me now. If not, I'm taking my shoes off," and I'm on the couch until it's bedtime. I try to make a list, this is what I have to do. I do the things I need to do, and then, at that point, the day is over for me.

JAMES VALENTINE: Thank you.

DR. LEACHMAN: Hi. My name is Sancy Leachman, Dr. Leachman. I'm not a PC patient, but I just felt compelled, James, to bring up something in the data that I saw that I think is inaccurate. There is something really funny, and I just don't want the FDA to be left with a misimpression that only 17% of the people in this room have a feet problem, because I think there was some kind of a problem that was supposed to be checked,

“All that apply,” and it wasn’t checked “All that apply,” and it got distributed across to a total of 100. I would encourage you to actually ask how many PC patients in this room don’t have foot pain or don’t consider that a problem, just a raise of hands to kind of get a better, more accurate, valid answer for the FDA. I don’t want to leave them here with a misimpression on that point.

JAMES VALENTINE: The counts were the more important number there. The percentage was distributed amongst the number of responses, not the numbers of individuals.

TERRY GOOD: I may be the oldest PCer here. I’m 74-years-old. So, I’ve managed PC for a long, long time, and I just wanted to share with everyone that they key word is “manage” for me. Pain is there. Everything that’s been described here, I’ve experienced, but it’s a matter of planning for me, something as simple as going shopping. I think about that ahead of time, and I think about where am I going to park to minimize the number of steps I may have to use to get to that shop or this shop. Heavily involved in—I’m a big sports fan, and my wife and I and other friends, we travel to football games, but I always plan ahead about how many steps am I going to burn today. Another quick observation is there’s a slight irony involved in all of this, and it is that the body is actually—when the body callouses—normal people callous. We just do it a lot, quicker and a lot more severely. But the body is trying to tell you something when it forms a callous. It’s trying to protect that tissue with the callousing. My father was a professional baseball player. He was a pitcher, and one of the things that was very important to him was, he actually wanted to form a callous on certain of his fingers on his pitching hand in order to protect it from blistering, because a blister would put him out of business. So, a nice callous was a good thing. Not for PCers, of course. So, management has been the key for me, and I want to make sure that all PCers understand that nobody knows PC like a PCer. We know it, okay? One of my doctors complimented me some years ago, about 30 years ago. She said, “You don’t really need to spend a whole lot more time asking me what you should do. You’re the person that knows it best. You can manage this, and you should manage this.” So, I’ve spent my entire life managing it. I talked to a young couple last evening about—and I gave them a calling card because we need to talk to each other and share our experiences and our successes. I’ve had very good success in managing my PC. I’m one of the few up there that said it’s gotten better. The reason it’s gotten better is not because it has genetically gotten better or medically gotten better. It’s because I manage it. And so if I don’t use those steps during the day, my feet are less traumatized, and that is worth gold.

JAMES VALENTINE: Thank you for sharing your strategies, as well as letting us know how things have gotten better for you.

We’re going to take a comment, but just one thought before you comment so other people can be prepared. We talked a lot about the pain and walking and standing. I do want to make sure that we hear from those of you whose most significant or maybe one of your most significant symptoms or burdens of PC is something other than the pain on your feet. I know we had some responses that kind of indicated that. If we have anyone

in the room with that experience or something else, whether that be something different than pain. We heard on the panel, itching. We also heard about cysts over the body, so I want to make sure we get the full representative PC community here today. Go ahead, Tod.

TODD WISEN: I'm Todd Wisen. I'm type 1, like James, K16 and the L132P mutation. I'm second of three generations of PC. I don't know that it was mentioned here so far, but if you have it, you have a 50% chance of passing it on to your kids. Two of my siblings do not have it; one of them does. One of my three birth kids has it. It's very painful. I don't want to be on pain meds. I take them as very seldom as possible. I do take a lot of Advil for the inflammation part of it. I'm on gabapentin or Neurontin for the pain piece of it as a maintenance type drug, if you will. A lot of the drugs that I've heard other people taking are really made for other diseases and so forth. With the gabapentin or Neurontin, it kind of puts me in a cloud, so to speak. I don't really like that feeling either, but in order to do my day-to-day activities—and you really have to prioritize what you're going to do, and there's a lot of things on your list that will never get done. A lot of PCers are overachievers. It's very evident from all the careers and stuff people pursued. But I want to lose the focus on pain so much as more towards the cure and meds directed at specifically PC to try and help with the pain management. Maintaining your feet and fingernails is a huge piece of it. I don't know if you can see, but I am right-handed. I have PC a lot more on my right hand than my left hand. I have about 90% coverage on my feet. So, yeah, the pain piece is really hard. It's really hard passing it on to one of your kids, too, and seeing them suffer through. I know when I went to elementary school, the physical fitness thing was huge, and everyone had to run the mile, me included. And I can remember going home that day and really, really suffering for like a week afterwards. Nowadays you can get a doctor's note and stuff and hopefully get out of that if you have the condition and so forth.

JAMES VALENTINE: Todd, I have a question for you. We haven't heard a lot about impacts of PC on the hands. We've heard a lot about impacts on the feet, and since you mentioned you do have callouses on your hands, has that impacted you in your life at all?

TODD WISEN: Yeah, I mean, even like writing or using your hands, even working in the garage on something. By nighttime, after doing a lot of hand involved wrenching or whatever, your hands really suffer much like your feet would, and you pay for it. You kind of have to pick and choose what you do. I have knee pads. I'll crawl around the house at night and try to save my feet for the next day. You learn to adapt and do things quite a bit differently. I'll sit or kneel to do things that most people would maybe stand to do. Standing in line at the airport, walking, taking your shoes off and walking through the scanners and stuff is horrible. It's walking on glass, quite literally. That's about all I have. I'm a public servant like you folks at the FDA. I do IT for the State of Minnesota, so it's great that you're all here today and listening to our stories and learning a little more about how we deal with PC on a day-to-day basis.

JAMES VALENTINE: Do we have any takers that want to talk about symptoms beyond the foot pain?

BETH MARTZ: Hi. My name is Beth Martz. I have K17. It's been in my family for about a billion years, since the dawn of time, so we've been dealing with this for a long time. One of our symptoms—our bigger issues are the cysts. So, I just want to explain a little bit about those. They're everywhere. I have them in the skin on my toes and my scalp. What happens is they can just be dormant, or they become inflamed and erupt into boils, and can cause extensive scarring. Excuse me. I don't know why I feel nervous. Look at a friendly face. So, they can cause extensive scarring, and, like, when you hit puberty, I think my chest looked almost like it was burned in a fire, kind of very extreme scarring. Probably a lot of you can relate to that. Also, just other misunderstandings in the medical community. I made it all the way to a breast surgeon who thought I had a breast tumor, but it was just a big cyst, so that's a lot of time and a lot of money sort of wasted on a false diagnosis.

JAMES VALENTINE: When you do have the cysts, or the periods of time where you had more cysts, how does that impact your daily life?

BETH MARTZ: It can be completely debilitating. It depends on the location. I've missed a lot of work, usually without explanation. It limits mobility. It just depends on the location, but it is extremely painful and it's rarely just one. It's usually a couple at a time.

JAMES VALENTINE: Thank you, Beth. Anyone else on symptoms outside of foot pain? Hand involvement, cysts, something different besides the pain itself, such as the itch?

DIANE BUTLER: I'm Diane Butler, and I have K16. I go to doctors that don't have any idea what I'm dealing with. I've wasted money. Like one time I went to the dentist, and my tongue was all white. Oh, you have to go to the oral surgeon right away, get right in. But by the time I get to the oral surgeon, have the appointment, blah, blah, blah, it's gone. So, I spent \$350 on nothing, and I don't know when it's going to be there. I go and he, like, checks my tongue, and I feel like I'm a guinea pig, which is fine, because I would like to find something for my kids and grandkids. It is funny when they don't have any idea. Like Mayo Clinic has no idea at all, but sometimes I don't even know what it is. It's just painful. I'll get sores in there, in my mouth, besides all the foot things, and all that. It's bad enough that your feet hurt, but now you have these sores in your mouth as well.

JAMES VALENTINE: How long do those usually last when they do come?

DIANE BUTLER: I don't know, sometimes a week or two. Like, right now I have a sore in there. I don't know what's normal because—maybe people don't get that, but we do. So, that's our normal.

ROXIE: Roxie, and I have K6a. I actually want to join in on that with the mouth. I actually don't ever remember not have whitening of the tongue, so a lot of times the sides of the interior of my mouth are like scallops because I'm chewing on them inadvertently; especially in the middle of the night, it gets worse. That affects how I talk sometimes or I don't talk because it's thick, and it's hard to eat sometimes, too. You're chewing and you're, like, oh, I'm not chewing food, and that is painful because you're chewing on your tongue or you slice off some. The other thing is I do have nail issues, and I can actually feel my nails growing sometimes. In the middle of the night they're throbbing, all my nails, and I try to elevate my arms or my hands. I wear nail polish, so I can see a millimeter of growth sometimes or more, just within a day or two. You use your hands a lot. Think about when you put on nail polish. You literally have to wait and let them dry, so you can't do anything like button a shirt or pull up your pants or open a door or anything like that. That's how it feels, but it's with pain. Sometimes it goes away and sometimes it can wake me up, or I have to go home from work. Luckily, I do a lot of drawing with a computer pen, so I don't have to type or do anything that involves using my fingernails. But those two pains are a reality each day for myself.

JAMES VALENTINE: That's all the time we have for Topic 1 discussion. That being said, we have another discussion coming up: purchase to treating, including strategies for managing, different products you might take to treat it, and purchase to foot care, and, of course, all of those are related to the symptoms and burdens you're trying to treat. So, if you didn't have a chance to talk this first session, please chime in at the next session. We'd love to hear from you. We're going to take a ten-minute break, and then we're going to come back for Topic 2.

[Break]

TOPIC 2

JAMES VALENTINE: For Topic 2, we're going to explore current and future treatments for PC, so we're going to build on our earlier discussion of all of the symptoms and burdens on your daily life, and we are going to explore how you try to manage that, whether that's medical treatments, self-care, or even just lifestyle modifications. We're going to ask you questions about what you're currently doing, how well it's working, what are the downsides of those things and then, ultimately, what are the gaps and what is it that you would like to see from a future treatment.

To kick off our conversation about this important topic, we have another all-star panel for you. We have Andrew Butler, Julianne Bennett, Roseann McGrath, Austin Penardo, Riley Diffenbach, and Janice Schwartz. Andrew, kick it off.

ANDREW BUTLER: My name is Andrew Butler. I am 40-years-old. I have a K16 gene mutation and, honestly, I'm a miserable human being. I am a father of three and, thank God, only one of my children, my eight-year-old Braden, has PC. My entire life revolves around my feet. Absolutely everything, from the socks I wear to trying to find shoes that won't kill me, to finding a parking spot on a family outing. Then I have to decide if I will

go inside or just wait in the car because I'm in too much pain. Even my profession revolves around my feet. I started my own trucking company in 2005 so I could get off my feet and try to make a living. The biggest thing I deal with every day is ridiculous, overwhelming, debilitating pain. Just the thought of walking in a mall or going shopping causes me stress. Yard work, mowing the lawn, hell no. I'll let the lawn die before I'll walk on the grass. This pushes my responsibilities onto my wife and my family. To make it perfectly clear, I am always in pain and I'm always miserable. The two most important things I do to treat my condition are foot maintenance, which is the shaving and trimming of the callouses, and taking several prescription medications. I need to shave off my callouses every two to three weeks, where I can literally remove up to half of a pound of callous. I soak my feet before, an hour in hot, soapy water to soften them up, and then use an old '60s style double-edge razor blade shaver to cut off the callouses. This is very effective and mandatory for me, but can cause cuts and nicks, and severely increase the pain the day afterwards. My history with pain medication has changed throughout the years. In my teens I took large amounts of Advil, up to 20 tablets per day. When I learned about Alleve, I took three to six tablets every day. All through my 20s and up until 2010, I used narcotic pain killers, anything left over from my family and friends, who knew nothing about my condition other than I hurt constantly. Friends could see the way I walked and acted that I was suffering. I lived in fear of being caught with prescriptions that were not mine. It was not until 2010 that I was finally diagnosed with PC. Shortly after, I met a great pain management doctor who, because of the vast information on the PC Project website, understood the amount of pain I was in. This was the first time in my life I had a doctor sincerely try to understand what I was going through. He prescribed me 15 mg of Meloxicam and 50 mg of Tramadol every single day. I take them before I'd even get out of bed and can't imagine living without them. He also prescribed me 120 10 mg tablets of oxycodone per month to use as needed. I'm ashamed about this at times because of all the bad things in the news and about prescription drug use and the stigma that comes with it. I feel the treatment that I use is the best I can do for now, although there is nothing that can be done to stop or slow the progression of my disease. The treatment I'm using helps me to do the most with the cards that I have been dealt. I think of oxycodone as my ace up my sleeve. I only use it when I really need to use my feet for a lot of walking, especially for playing with my kids. A huge downside of using oxycodone is that because it masks the pain, I can pay dearly with even more intense pain later in the day and the next day once all the pain medication wears off. Another downside to the oxycodone is I have to choose between being in excruciating pain but completely present, or due to oxycodone's side effects, feel doopey and not totally present. Memory loss is also a real issue. There are entire conversations I can't recall. Another problem I have with my medication is in my professional life. I own a small trucking company with five trucks, and I'm also a driver. I have to choose between working with lots of pain or using my medicine while operating a commercial vehicle. Neither of these choices are acceptable. When the pain gets bad enough, I risk losing my license and possibly my business if I take my medicine. This is a struggle that I deal with every day.

As for my eight-year-old son, Braden, with PC, I lay awake at night worrying about him. How many more good years will he get? How long until my son will be miserable like

me? What will I do for him? Pain medications? Oxycodone? I pray to God there's a better answer. There has to be. I just cannot accept all the pain and pain killers for his future.

I know there are currently no treatments and no cure for my condition. All I can do is cope with the symptoms. I can't imagine sleeping, hiking with my own kids, or even doing any normal, everyday activity without wondering can I do it? Can I make it? How far do I have to go? I really wish there were other forms of pain management that didn't require me to take pain killers but would give me the same or better relief.

Thank you very much for taking the time to listen to me today.

JULIE BENNETT: My name is Julie Bennett. I was diagnosed at age 27 as PC K16, but my family can trace our PC back at least six generations. For my entire life I've watched as my great-grandmother, grandmother, mother and now my son, each of whom struggle to live as normal a life as possible, while dealing with chronic, intense pain every single step of the way. PC affects my life in so many ways, it's difficult to spend a few minutes explaining that impact. Beginning the moment I wake up, I reach for my Memory Foam slippers before I can roll out of bed to make it across the carpeted floor to the bathroom. I'm fortunate because my shower floor is smooth, and my pain level still allows me to take a daily shower. My mom can't tolerate the pain of standing for even a few seconds, so she must bathe and never shower. Every morning as soon as I'm awake, I start my day by taking two Excedrin or two to three ibuprofens to try to get ahead of the pain that will inevitably be part of my day. I typically take three to four doses of Excedrin in a day, but on long days like today, I alternate between Excedrin and ibuprofen all day long to manage the pain. Evenings at home are spent with my shoes off, slippers on, and feet elevated to try to recover from what most people would consider a very minimal number of steps each day. On a weekly basis I spend 15-30 minutes of my morning using a surgical scalpel and a number of other tools on my softened callouses. I try to keep them trimmed to just the right density. If they're too thin, they'll bleed. If they're too thick, it still feels like walking on rocks. Regardless of how diligent I am with trimming the callouses that cover most of my foot, the pain with every single step persists. My closet is filled with dozens of shoes. I don't have a shoe fetish. My shoes are not fashionable. Each and every pair of my shoes is carefully selected with the hope that they might be comfortable enough to take the steps required in a given day. Something as simple as buying a new pair of athletic shoes or slippers can take a month of shopping, purchasing, trying, returning. It's a rare day when I find a pair of shoes that seems comfortable enough to tolerate wearing all day. Very few of the dozens of shoes I buy are actually tolerable all day. Packing for even a brief trip like today, when I'm in D.C. for 24 hours, required four pairs of shoes and a pair of slippers, because I'm never quite sure which pair of shoes might work today. Regardless of the comfort of my ugly shoes, too many steps mean that I will not be able to walk at the end of the day, or I may pay the price for several days to come. Business networking and social events are particularly painful, both psychologically and physically. Standing to talk to people, often on a hard floor surface for an hour or more, will inevitably result in

tremendous pain, then a sleepless night, as my feet throb with pain and jab, punishing me for mistreating them. Sometimes Advil PM works. Other times it simply doesn't. I have a wonderful husband and coworkers that are acutely aware of my pain. They drop me at the entrance, fetch me food and drink, move conversations to softer carpeted areas, pull up a bar stool, bring me the car. I hate feeling like an invalid. Every step I take has to be accommodated.

One of my three children inherited PC. Tate's a high school senior this year. Nearly every decision to participate in activities or make life choices is driven by his PC foot pain. During Tate's senior trip to the Smoky Mountains this spring, we came up with a reason for me to pick him up on the day of the all-day hike. That way he wouldn't have to hike and experience debilitating pain the rest of the week, nor would he be humiliated for needing to stay behind from the group and be questioned and treated differently. As we visit college campuses, our decision can't be based only on the ranking or academics of an institution. Instead, we must evaluate the steps required to get to the shower in the dorm, to get to class, and we must evaluate access to different modes of transportation. Is it possible to drive and park near class? On this campus would a bike, a scooter, a skateboard even be allowed? For six generations my family has based our lives on the steps required to try to minimize the intense pain. I lead a fulfilling life. I have a wonderful family, a rewarding career, extensive international travel. I do not let PC pain stop me. I manage the pain with routine care and lots of Excedrin and ibuprofen, but I cannot live what most people call a normal life.

Additionally, I know as I age my pain will continue to increase. My mom now trims her callouses every day or two, and she can rarely find a pair of shoes or slippers that are tolerable. I cared for my grandmother's PC as she was aging, and I watched her pain progress. I know that she could no longer walk outside of her home without the use of a wheelchair because the pain was just too great.

I hope a treatment will come that may enable me to work for a full day without debilitating pain that affects me for days to come. An increasing number of steps or hours standing that I could tolerate would be a tremendous accomplishment. I hope that someday my son will be able to enjoy an all-day hike. At a minimum, I hope he will be able to walk from his dorm or apartment across his college campus without concern for how many steps it takes. Maybe someday my son and I will be able to dance at his wedding without unbearable pain. I hope my future grandchildren will have a treatment that enables them to live their life without minimizing their steps and being limited in the activities they can enjoy. That would be a true miracle and one the scientists and the FDA in this room might be able to make a reality.

Thank you for allowing me to share my story.

ROSEANNE MCGRATH: God morning. My name is Roseanne McGrath. It is truly an honor and a privilege to speak to you today. Although I don't think I'm going to say anything that you probably already haven't heard, but I reside with my incredible husband in the suburbs of Philadelphia. I'm a spontaneous K6a mutation. The PC

presented at birth. I was actually diagnosed in Philadelphia shortly after I was born. The fact that I'm spontaneous is really a paradox because as you heard, I think from Terry, every blessed thing we do, we have to mind map and preplan, so I can minimize my every step, minimize the pain, hide my limp, as you heard from Jack earlier. We've coined it the PC walk, or as I call it, the Walk of Shame.

The best way I can describe living life with PC is like a fuel tank that is always on "E" for empty, praying not for another mile because we can certainly cannot walk a mile, but praying I can make just a few more steps each day, because the debilitating pain doesn't have you running on empty; it's got you struggling to barely get by on fumes. You've already heard, PC is very simple. It's all about pain. You must be thinking, can skin really cause this much pain? Yes, because is our largest organ. Appearance and care is so important, but it's the excruciating, debilitating, chronic pain that rules our existence. We need relief from this pain. I try to appear normal, but the truth be told, as you probably heard for Andy, cranky and suffering from sheer, utter exhaustion. Every minute of every day, while awake or asleep—and try to sleep and the mattress and the merest touch of the sheets are just torture. Since the age of four I have had a physician use a scalpel to debride my hands and feet—my hands are affected just as well as my feet—every other week. As I got older and in my 20s, the weeping blisters changed into smaller callouses where, actually, as you heard from others, the blood vessels present through our nerves and through our cracks and fissures. I use a dremel drill every other day on my nails so they can appear normal, but the nerves grow up through the nails, so that's very painful. I have a special blade that I use to excise the cysts that grow on my back and groin, and scar our bodies, as you've heard from before. I actually look like I have a railroad going through my groin and backside areas. If I don't debride my hands and feet regularly, I simply can't exist. As I think you heard from Jamie, our balance is off. I have fallen four times and broken bones in each of my feet. I've been diagnosed with osteoporosis. What is further gut-wrenching that you've already heard is the emotional torture of being shunned and made fun of and bullied while growing up, which I can now say makes us actually stronger, more caring, more sensitive, but I wasn't thinking that at the time I attempted to end my life as a teenager. Although blessed because PC is not life-threatening, as a 51-year-old adult, I actually pray to the dear, sweet Lord that He would take me over someone else sooner than later, because then I could fulfill my dream of being an angel, without PC on my wings where I could fly. I wouldn't have to sit, stand, crawl, use my cane, use my wheelchair. I'd also be remiss not to mention the torture I went through deciding whether I should have my own children or not. I have no regrets. I decided not to, but it leaves a void. The good Lord blessed me with two beautiful stepdaughters and now a beautiful grandson.

So, I just want to paint an animation for you, an angel on one shoulder and a devil on the other. That depicts inner turmoil, emotional turmoil. On the one shoulder is, I think what everybody may call me, effervescent, angelic Roseanne, always happy, a successful Human Resources professional for 30 years. I always tap PC a condition I have. It's part of my life. I won't let it define me. It's all about perspective. I have the most incredible parents that have always kept me focused and always told me it's not what you can't do, it's your mission to focus on what you can't do, because can't means

won't. Growing up I've always said, "No pain, no gain. Mind over matter. God gives you lemons, make lemonade." But embarrassingly, it's the demonic side, where I have to put vodka in my lemonade to survive. I eat Advil like candy every four hours. I take Lyrica. I take opioid pain medication, and this is only to be a productive, functional human being of society.

The angelic Roseanne always says that the glass is half full, there's far worse things in life, but my glass is full of alcohol and I'm screaming enough is enough. God only knows what my liver and kidneys look like. As a seasoned HR professional, I'm described as a tough cookie with a heart of gold, but the truth be told, I'm a crumbling cookie. I had to recently retire from a position I loved and held for 23 years. My motto is fake it until you make it. I couldn't make it anymore. I try to not allow PC to interfere or limit me, but to motivate me. I try to keep a positive attitude and persevere, because people really are my passion, but the pain of pachyonychia congenita rules my life. It makes me pissy, pissed off, sharp tongued. I know there's no cure in my lifetime, but an effective treatment would be an answer to my prayers, and not that prayer for death.

You've asked earlier about risks. I'll take all the risk in the world. What level of activity would be meaningful? What would be meaningful is to not have to pretend I'm normal, but to actually be normal; to not live in constant, agonizing, physical, mental and emotional torture 24/7; to not live every moment awake or asleep in excruciating agony while trying to be a productive member of society; to be able to do the things that the average person takes for granted, like standing in the shower, walking on a beach, going in the ocean; to not feel like such a burden to those I love and who love me; to no longer have to use a cane or a wheelchair; to not have to crawl; to be able to sleep; to not take pain medication and drink. And simply stated, just to have a better quality of life.

So, I thank you, the FDA, for working with all of those who are researching to find effective treatments, relief and a cure that will not only help me, but those that are suffering from other debilitating conditions.

AUSTIN PINARDO: Good morning. My name is Austin Pinardo, and I'm a 21-year-old senior here at Marshall University. I start my graduate program in physical therapy in May. Originally, I'm from Shady Springs, West Virginia, but while I'm at school at Marshall, I live in Huntington, West Virginia, while attending Marshall University. But I am a diagnosed K6a patient who's been struggling with PC since I was nine months old. My symptoms I experience are the thickened, blistering and callouses on my feet, follicular hyperkeratosis, and leukokeratosis. My doctor I've been going to since I was 18-months-old, from Duke, has always tried to find more medicines for me to try, just to see if my condition would lessen. Mainly, the only area of my disorder my physician usually focuses on is the blistering and callouses, and the pain that is cause by them on my feet. I will admit that in my entire life I've never had a medicine that lessened the pain. Since I was younger, I have always been on some form of lotion medication that I would put on my feet daily. On the other end, I do try to stay away from pain medication as much as possible. I am prescribed hydrocodone to cope with the everyday pain, but I

only take them when I am in the absolute worst pain, either after I dare to do a sporting event or if I have a long day of walks at the mall. I try to take non-prescription pain killers. My normal week consists of taking a few Alleve here and there, in total throughout the week, but the amount varies depending on the activity level for that week.

As I grew older, my medications went more experimental, and I started taking pills or using lotions that were meant for other disorders. One example of that was when I prescribed Lovastatin. Statins are used for managing one's cholesterol, although the other effects of the drugs had a possibility of helping out dry my feet. This had the possibility of reducing the blisters or reducing the callouses by drying them out, but I had no luck on reducing my pain, or the blistering or callouses. But my doctor focused still mainly on drying out my feet, but the only bad thing about drying the feet out is the pain stays on the callouses and then you are added pain with your skin cracking and breaking open.

As of today, I'm currently not taking any specific medication for my disease. The only care I do for my feet is by cutting the callouses down about every week. I have to make sure to cut them down evenly, or they become uneven and the pain ends up increasing. The blisters grow back pretty quickly, so if you do not keep up with maintaining them, they can end up becoming worse. I haven't been on medication recently because my doctor is still researching possible treatments that we have not tried yet. Everything we try, I have a moment of relief, hoping for a good outcome, but in the end we're back to square one and my pain has not changed. The only form of treatment that I currently partake in is soaking my feet in hot water and Domeboro. It does not do anything other than relax my feet when they're in severe pain, but I still do it just for that little bit of time that I have without as much pain. I do not know the real reasoning as to why Domeboro seems to help, but I believe soaking my feet in general tends to reduce the swelling I have. No treatment has shown to stop the progression of my disease, although some people while have improvement by using certain medication. Sometimes I believe that the disease adapts to the medicines that relieve some of the symptoms, but in the end, I admit that my mind just hopes for too much improvement.

I do want to point out that because of the thickened nails I suffer from, I did have my fingernails removed during my transition from elementary school to middle school. Not that many people have done this, but I highly recommended it. The problems my nails used to cause me were tremendous. Without them I feel so much more confident in public, and my hands look somewhat normal. Before the surgery my nails would be in pain and I could not completely touch my fingers together. They seemed to just get in the way of almost everything I did. The only problem I had from getting them removed was while I was still in recovery. The problem was when I first started middle school, it was a rough time for me since I started my first day with both hands still bandaged up like boxing gloves. One kid took this to heart and would never let it go that there was something wrong with me. He was a bully to most of the kids at the school, but that year he decided to take a big interest in me. My hands were still recovering, and my bandages were cut down to smaller ones at this point, but the kid decided that he

wanted to see if I was in pain. He chose to hit my hands every chance he got, not lonely causing me loads of pain, but in the end causing my grafts to be messed up, and some of the nails grew back.

If I was to go back and get to do it over again, I would still have the surgery done because my life has changed tremendously since my nails were removed. Although I cannot pick up a dime off the ground because of my lack of nails, I think the more important aspects outweigh the bad of not having what I used to have.

To choose between the many symptoms I have, I believe I wouldn't be the only one who wishes for only the pain to stop. By now, I've accepted that a cure may not be found during my life, but in my opinion, I have learned to live with my disorder. The only aspect that I cannot fully live with is the pain that I endure daily. If I had to choose for one symptom to be treated, I would choose to eliminate or lessen the pain that I have. The visual aspects of my disorders do not matter to me anymore. I just want to be able to run or to play sports or exercise. Simply being able to walk around my school and enjoy the campus more would make my life a lot more enjoyable. I used to play sports when I was younger, even though my mom would carry a medical kit with her to manage my blisters as they got worse. If I could even walk enough to stay in shape and lose weight, I think that would be a victory. If there's anything that can be done about my pain, I want it to be done.

Thank you for listening, and I hope that one day we can have a cure, but until then I will live on, one step at a time.

RILEY: Hello. My name is Riley. I'm 18-years-old and I'm a senior in high school. I am a spontaneous mutation of PC K6a. Everything I do to manage my PC has to do with treating the pain in my feet. One thing I do is try to keep my feet in the balance between wet and dry. I leave my socks and my shoes on a lot to keep my feet from drying out. If my feet get too dry, they hurt more. The callouses get hard like rocks and they hurt super badly. They will crack, and they will bleed. The worst is when they have to stick to my socks. I'll have to put them in water, socks and all, in order to peel them off. So, I try to keep my feet not too dry. I regularly soak my feet in plain water. Soaking helps. It feels good and is very soothing. It also helps it not to itch. The itch is so bad, I'll scratch them until they bleed. I just can't seem to get the itch no matter how hard I scratch. To get the itch I'll have to rub my socks against my foot. It will rub my skin off because I don't have good nails for itching. I'll have to use my sock, the floor or even a backscratcher. I never take my socks off. It's more comfortable to have my socks and my shoes on. Still, it's a hard balance when my feet are wet and blistered. They hurt when they are dry, and they hurt when they are wet. It's a lose-lose situation. The worst thing about PC are the blisters and callouses. For every symptom I have, the pain and itching is from the blisters and callouses. I have to pop the blisters all the time. Sometimes I just squeeze the blisters with my fingers and they will pop, or I use needles. My mom used to cut my callouses down with razor blades until I was about nine or ten. She used to cut so close to the skin, they would bleed. I used to have to put Band-Aids on my feet every single day on every single one of my callouses, but at some

point, they changed from solid callouses to blisters, where I can't even touch them. My callouses don't grow up. They just stay flat. I used to be able to walk without shoes, but once my feet changed, I couldn't do that anymore. I was on the high school swim team my freshman, sophomore and junior year. Then they just hurt too bad to do it anymore. Walking around the pool was sore, but also the water went against my callouses, so that hurt, too. Last year I started taking Tramadol. I take pain medicine each morning in order to go to school. The medicine takes the edge off. It also takes the throbbing and the sharp pain away. The hurt doesn't go away, but I can stand up more.

I am very social. I like to be out and about. The medicine makes me very tired, but the pain also makes me tired, so it's hard to tell which one makes me the most tired. I use the medicine to help me get through school without crutches or a wheelchair, but I do use my wheelchair every time I go to the mall, grocery store, concerts, or on vacation. My family needs me to go on vacation with them, so we can use my wheelchair, and I'm their line cutter. None of these things—the medicine, the soaking—really stop the pain or how my callouses grow. The only thing that helps stop the pain is to limit my walking. Staying off my feet is the only thing I can do. I made my school schedule so all my classes are close together. I don't eat in the lunchroom because it's so far away. I'll bring my own lunch and eat in the library because it's closer to where my classes are. I also have a handicap placard for my car and I use it at school every day. In junior high I walked a lot. I just can't do that anymore. The pain in my feet hurts my whole entire body. When I stand up or walk too long, I feel like I'm going to pass out. I can only walk for about two minutes before my body starts to shut down. My legs will go all red and purple, and I will have to sit down. I'll even throw up sometimes because of the pain.

Another way I manage my PC is by crawling. When I come home from school at the end of the day, I usually park my car in the driveway, crawl from my car to my house because my feet hurt so badly. Inside my home I'll crawl 24/7. The only bad thing about crawling is it bruises my knees. I got to the point where my knees hurt so bad, I couldn't even bend them. If there was no cure for PC, I would at least want a treatment that would give me less pain. Everything starts with pain. I can't walk without my shoes because of the pain. I wouldn't crawl if I didn't have the pain. I would like a treatment that would let me walk a lot longer, like I wish I could take my dog on a walk. I'd love to be able to walk at the mall or go to a concert. I'd love to walk on the beach without dying. I'd love to be able to have a typical teenage job and do what most people do my age. The most simple things to other people are the hardest thing in the world for me.

Since I'm always in a good mood, people call me Smiley Riley. There's no point in being a negative person because I have a disease that is so rare. My dad will always say, "You're going to win the lottery." For me, if there's a good treatment out there that would make it so I don't have as much pain that I could stand or walk, that would be like winning the lottery.

JANICE SCHWARTZ: I'm Jan, again. I'm 49-years-old and I have a spontaneous mutation of the K6a gene. Two of my four children have PC. Those two boys are now ages 23 and 21. For me and for my boys, the worst part of PC is the debilitating pain

from the callouses on the bottoms of my feet. Because there are currently no effective treatments for PC, I simply try to manage the pain each day. I take ibuprofen several times a week, especially when I have activities that I don't want to be blinded by pain for, like going to the store or maybe to one of my children's school functions or sports event for one of my kids, my kids who don't have PC. However, over-the-counter ibuprofen simply dulls the pain for a short while. The trauma from having socks and shoes on too long, or from standing on my feet still occurs, and I pay for those choices later with increased pain. Lately, I have been taking Motrin PM more often at bedtime in order to sleep; otherwise, I'll wake up throughout the night from either pain or itching in my feet, or both. And by the way, last night the Motrin PM did not work. I often apply an ointment with benzocaine on the callouses that have those neurovascular structures growing in them. The benzocaine will somewhat temporarily numb the bloody endings that stick out, so I can put on my socks and so that I can bear the sharp, stinging, pulsating pain, which is pretty much constant whether I'm on my feet or not. On any given day, I rotate between walking with crutches, using a wheelchair, or crawling to avoid putting pressure on my feet, like Riley. I also shave my callouses down as needed, maybe once a week, with a Ped Egg or razor blade, but even that is difficult with those bloody nerve endings sticking out.

Mostly, I manage my pain by managing my activities. I try to choose what activities are most important each day with a limited amount of time I can bear on my feet. And I confess, I manage a lot with the help of others. For example, my good husband does the grocery shopping and the yard work. He runs a lot of errands for me. He probably hears all the time, "Honey, can you do a little favor for me, please?" I think that is probably the most common line of our marriage. Anyway, I used to be embarrassed by using mobility aids or needing help, but now I just try to be gracious and grateful. I try to never take advantage of the people who help me, but I am very thankful for that.

In the quest for an effective treatment, I try to help when needed. For example, I've lost count of the number of skin biopsies I've given over the years, including ones out of my PC callouses, and I will tell you a pop biopsy punch out of the skin is not a problem. It's a simple punch and a few stitches. Not a problem. Out of a callous with PC, it's a different story. I have been involved in numerous studies—too many to name here—so I'll tell you about two.

The first was a Phase 1B study for topical Rapamycin, and the picture you're seeing there is not it. It happened at Stanford, and I applied the treatment on my foot callouses. Along with 14 other patients, I flew to California for my regular appointments. I experienced some relief from my pain, but not a great enough amount to stop walking with crutches. I still have hope for a topical product that would reduce the pain enough to walk on my own for a significant amount of time, and I'm actually thrilled that a company has stepped up to carry this drug, this Rapamycin drug forward and be more effective than it was in the Stanford trial.

I was also the one patient in an FDA-approved Phase 1 clinical trial for siRNA. That particular treatment, for me, showed the most visible improvement I've ever seen in a

callous. I saw the callous at the treated site pull off like Velcro, and a nice spot of beautiful pink skin on a small area. The rest of the foot still had painful callouses where it was not treated. I would have liked to have seen what more of that treatment could do to my entire foot. However, I didn't especially enjoy the manner it was delivered, and that was the last picture that you saw, because the treatment involved injections into my PC callouses in both feet twice a week for 17 weeks. I will tell you the injections were horrific. I needed to mentally and physically gear up for them, and they kept me incapacitated for two days a week. A shot in the foot is not a big deal. A shot in my PC callouses were an indescribably painful experience. I'm still hoping for a more tolerable delivery method for that treatment as well, and really hope that the company that is trying to do this is successful. It was a pretty amazing thing.

This, I've been in two major trials with treatments that show promise, but in very different ways. I remember watching a presentation a number of years ago by one of the scientists that discovered the PC gene. His name is Professor Irwin McLean. He showed a picture of a mountaintop with many pathways to get to the top. He compared the top of that mountain to effective treatments or a cure and pointed out that there were many pathways possible. And I thought about that because of my two experiences. There's a possibility of many pathways that might help our PC, and what would the top of that mountain look like for me? Short of a cure, what I really wish more than anything, is that my two sons with PC could come home to visit without needing to scoot around the kitchen on an office chair with wheels. I wish they could come home to visit without sinking in the door once they got in, with pain to their knees. I wish they could get around their college campuses without fear their bikes will get a flat tire. I'm the mom in mandatory family pictures. I wish we could have a family picture, an outside family picture, without pain. You see the smiles up on that picture. You don't know how bad it was getting across that grass for those boys. Oom! We really are happy, but that was a painful picture. Anyway, I wish they could do all the activities they've ever sat out of because of pain. And the truth is, I would like a treatment that reduces pain and increases mobility for every PC patient. Every single patient in this room right here has a confirmed genetic mutation and they're here because they want to help. These people are my family and I would love a treatment for their pain, for all the other patients that are watching out there, and for all the patients that are not watching out there, as much as I would ever want one for my two boys with PC.

Thank you.

JAMES VALENTINE: Wow! Thank you so much for sharing your very personal stories and your own thoughts and insights to where we might go from here. I think that's an important aspect of the second part of our discussion. We're moving beyond just sharing the present. We're moving into the future and what it is that really would be beneficial for you from future treatments. I think that's really the ultimate goal of what we're working towards.

In that light, we're going to gain move to broaden the discussion to all of you here in the room and on the webcast. This is our third and final set of polling questions, and these are related to managing PC and future treatments.

If we can have our first polling question. This question is:

What are you (or the person you care for) currently doing to manage your PC?

For this question, please check all that apply. Your options are:

- A. Trim or cut off callouses
- B. Cut, sand or trim nails
- C. Take over-the-counter pain medicine
- D. Take prescription pain medicine
- E. Lance, drain, inject or remove cysts
- F. Apply ointments or creams to affected areas
- G. Pop blisters
- H. Wear special socks, insoles or shoes
- I. Other

Again, please check all that apply to you. Now, you may, once this is fixed, have to exit the question and go back in, but we'll let you know when to do so. If everyone can exit out and enter Question 1 again, you should be able to now check all that apply. Can I get a thumbs-up if someone is able to check? Not yet. We have a thumbs-up. Keep trying. You should be able to exit out and go back in. Close the app and reopen it, and that works. Just keep in mind, the percentages that are displaying are the percentages of responses, not the percentage of people, when it's a check all that apply question. If you want to see the relative, wait, we can look at the bars and ignore the percentages since that's the percent of responses, not the percentage of people.

Of what everyone does to currently manage their PC, it seems that the most common strategies are to trim and cut off callouses, cut, sand and trim nails, and wearing special socks, insoles or shoes. It does look like we have a number of people who also take over-the-counter pain medicine, apply ointments, pop blisters. A lesser amount take prescription pain medicine or need to lance, drain, inject or remove cysts; and then there are some of you who do something else not listed, so we will definitely explore that in the discussion.

We move to the second question. Our second question is:

How satisfied are you with the current treatments available today for your PC?

The things that you just responded to in the first question, how satisfied are you? Your options are:

- A. Highly satisfied, where current treatments allow you to live a life with no limitations
- B. Satisfied, current treatments allow you to live a life with only a few limitations
- C. Unsatisfied, or even with current treatments you're living a life with many limitations
- D. Very unsatisfied, current treatments are unsatisfactory, do little to help you overcome the everyday disease burden.

Please select that which applies to you. How satisfied are you with what you currently have available to treat your PC?

The majority of you are very unsatisfied with your current treatments. They do very little to help you. Over a third of you, however, are unsatisfied, meaning that you live life with many limitations. Then there are some of you, either in the room or online, that are satisfied with what you currently have, but nobody is highly satisfied.

We move to the third question. This question is:

Have you ever utilized a mobility assistance device, which could include a wheelchair, cane, scooter or walker, or have you employed an alternative form of mobility, such as using bikes, strollers, crawling, holding on to walls or rails, piggybacking, or even holding on to another person, because of your PC?

Your options are:

- A. Yes, at some point during every day
- B. Yes, not every day, but at least once or more during the week
- C. Yes, on some occasions, but not every week
- D. No, you never need a mobility assistance device or need to employ some kind of alternative form of mobility because of your PC

It's looking like a pretty fair spread here. Between a third and a half of you at some point every day, either utilize a mobility assistance device or use some alternative form of mobility. Almost a third of you do so, but only on occasion, not every week. One-fifth of you, almost, are doing this weekly; and then, almost 15% of you never need to do one of these things.

Can we go to our fourth question? Now, we're going to start looking and talking about future treatment and what you might be looking for. This question is:

In the absence of a cure, a clinically meaningful treatment for PC would:

Please check all that would apply.

- A. Improve the appearance of your callouses, cysts, nails or other PC symptoms
- B. Decrease pain

- C. Increase either the length of time that you can walk or improve your ability to do activities that involve being on your feet
- D. Reduce your need for use of mobility aids or alternative aids, such as crawling, like we talked about in the last question
- E. Reduce the time required for you to manage your PC symptoms

This question, again, is in the absence of a cure, what would be meaningful to you in treating your PC? Go ahead now and ex it out and come back into the app and give me a thumbs up if it's working. Should be good to go.

So, in the absence of a cure, what would be a meaningful treatment to you for your PC? Check all that apply. Since this is a check all that apply again, the percentages are the percentages of responses, not percentages of people.

The most selected meaningful treatment benefit for you short of a cure, the highest one is decreasing pain. Next after that is increasing the length of time you can walk or improve your ability to do activities that involve being on your feet. Number three appears to be improving the appearance of the PC symptoms. Then, after that, probably tied in fourth is reducing the need to use mobility aids and reducing the amount of time you need to care for your PC symptoms.

Move on to the fifth question. This question is:

In the absence of a cure, again, which single functional improvement would be most important to your quality of life?

Here you're only going to select one. Do you want to:

- A. Reduce the time required to manage PC symptoms
- B. Increase either the length of time you can walk or improve your ability to do activities that involve being on your feet
- C. Reduce your need to use mobility aids or alternative forms of mobility, such as crawling
- D. Something else, some other kind of functional improvement

We'll give you another moment to respond to which of these, absent a cure, would be the most important to your quality of life.

It looks like the overwhelming majority would like something that increases the length of time they can walk or improve their ability to do activities on their feet. However, there are individuals that would like to see some kind of improvement in the other categories, as well as some that have something else that's not listed. Again, if you've selected one of those, especially "Other," we would definitely like to hear what it is you'd like to see to improve your quality of life when we go to the discussion.

Lastly, if we can go to our sixth and final polling question. The question is:

Which of the following manifestations or symptoms of PC do you wish to see most improved by treatment:

You can select from the following options:

- A. Thickened nails
- B. Painful callouses and blisters on the soles of feet
- C. Painful callouses and blisters on your hands
- D. Painful cysts
- E. Follicular hyperkeratosis, which are the little bumps on your waist, legs and arms or other
- F. Leukokeratosis, which is the white growth on your tongue

Which of those would you wish to see most improved by a treatment?

It looks like the large majority would like to see the painful callouses and blisters on the soles of feet improve by a treatment. After that, over 10% of you that would like to see improvement with the painful cysts. Some of you, a small number, that would most want to see improvement in thickened nails or the painful callouses on your hands. Nobody selected follicular hyperkeratosis or leukokeratosis.

We've made it through the polling. Thank you for bearing with us the technical difficulties. I think it's important because it does give everybody an opportunity to weigh in on the range of things that we're interested in exploring. Now, we're going to explore those in more depth with you. Let's take it back to the first part of Topic 2 discussion questions, which relate to your current approaches to treatment. What I heard from the panel and what I saw in the polling questions is that there are a lot of different things that you in the PC community do to try to manage the symptoms and burdens of PC, ranging from medical treatments, whether that be pain medicines, topical products; whether that be foot care, the paring of callouses, the draining of blisters; using alternative forms of mobility and managing your activities. We even heard about foot soaking. We heard a number of things, but what I want to hear from you in the audience is what really works best for you. It could be combinations of things. It could be a single approach to your treatment, but when you answer that question of what works best for you, I want to know why. What is the benefit that you see when you're telling me this gives you the most benefit because I want to understand what you see in treatment success. It might not be, again, full success. We're not talking about cures here, but short of that cure, what kind of benefit are you getting from your best care?

Would someone like to share with me what works best for you? Just a reminder: Please say your name and what PC gene is affected, when you speak.

JAMIE: My name is Jamie and I have K17. Ibuprofen helps me better than any of the pain medications that are prescribed. However, I take 800 mg five times a day. Also, I smoke a lot of marijuana. I have smoked for 40 years. I don't think I would be here

today if I had not. It just kind of takes my mind away from myself and out to deal with the world. I don't think strongly about things after I smoke. I've smoked so long, I don't get high, but it does help to mentally keep me stabilized to make it through the day. Those are the only two things that I do other than the trimming and the hot bath soaks for cysts. And then, when I have the cysts, I do run a low-grade fever, so the ibuprofen also helps with that. But I have a lot of swelling, water retention, swelling in my joints, aches and pains, a lot of muscle aches and cramping, but I'm sure it's from being like this from all the pain all day that makes my muscles do that. So, that's what I do.

JAMES VALENTINE: In terms of where you started, which was with the ibuprofen and the marijuana to somewhat disconnect, but also to help with pain, it sounds like, have you noticed, as you've figured out what works for you, how do you know that this is your best current treatment regimen?

JAMIE: I don't know that that's the best, but that's the only way I've known to deal with it. I just found out in 2014 what it was, so I've dealt my whole life self-treating myself. However, my daughter also has it, and she is one of the opioid people that she just thinks she can't live without the opioids, and it really concerns me because I don't want it to go further, but you never know what's on someone else's mind.

JAMES VALENTINE: Sure. It sounds like it's what you need to help you get through the day.

JAMIE: Yes, yes.

JAMES VALENTINE: Thank you. Let's see if we have a comment on the left side.

JACK BUTLER: My name is Jack Butler. I got the K16 gene. I guess for pain management for me, I do shave my feet. For the itching, I soak them in bleach when I shower. For pain medications I used to use ibuprofen until the doctors said I can't take that anymore, so now I'm on gabapentin, meloxicam, and Tramadol. That seems to work the best for me.

JAMES VALENTINE: Did you notice a change in your pain when you started these new products?

JACK BUTLER: Yeah. It seems to help. Gabapentin helps it not hurt as much right away in the morning, kind of knocks the edge off everything throughout the whole day. The meloxicam is a lot better because I take it once a day instead of multiple times throughout the day.

JAMES VALENTINE: Have you noticed any changes in what you are able to do in a given day because of the pain relief?

JACK BUTLER: Yeah, I can do more with it than I could with just the ibuprofen, and it seems I can take a lot less.

JAMES VALENTINE: Thank you, Jack. We have Terry.

TERRY GOOD: I'm Terry Good, K6a, and after all my years of experience with K6a, it comes down to how I treat my feet on a daily basis and daily activities. I've learned that hard, firm surfaces that I put the soles of my feet onto, are best for me because it minimizes the shearing action that occurs on your feet, particularly the sides of your feet, when you walk, if I can minimize the shearing by having a hard landing pad for my feet. Now, on the feet themselves, I like thick hunter's socks, really thick socks. These are like that. Hard surface with thick socks really work well for me.

JAMES VALENTINE: And the thick socks, is that for cushioning or is that to keep your feet dry? The use of the thick hunter's socks, is that so you have some cushioning? Is that to try to help with the moisture?

TERRY GOOD: And wide shoes, so there's not a whole lot of tightness on the sides of the feet.

JAMES VALENTINE: Great. Thank you, Terry.

I just want to make sure the people on the web can hear, too.

We're hearing a range of different strategies. Are there other strategies that you in the room have tried that haven't been talked about?

RICHARD STEADMAN: Public speaking is my nightmare, so I apologize. When, especially the callouses on my heel get dry and split, I've begun to use superglue to coat the entire callous. I tried Gorilla Glue and it promptly glued my sock to my foot because it wasn't quite dry, so that took about an hour to get off, at the end of the day. If you coat the callouses in a really fine Super Glue or Crazy Glue and then sand it down, it takes all those little, tiny pieces of the callous and prevents them from hooking in the socks when you pull your socks off, and just kind of gives it a little bit of a protective coating. It's worked for me, along with all the other things that I've heard here today. Yeah, the Gorilla Glue guy who glued his sock to his foot. Richard Steadman K6c.

JAMES VALENTINE: We'll hear from Sarah and we'll take any other additional strategies, but then I want you to also start thinking about—we'll move to future treatments, and I'll have some questions about that. We'll go Sarah and then we'll go over here.

SARAH DELANTY: I'm Sarah, K6a. Desperate times call for desperate measures sometimes with our PC, and I found myself stuck in the airport at San Jose in California. And I found BioFreeze, which was a gel. It's topical. It got me through that day at the airport. It literally instantly cooled my feet down and it was just a nice, tingling sensation so that I could walk. The other thing I found was this adhesive, and it's for something that you can put on—I haven't tried it yet; I'm waiting for summer—but it's something

that you can put on the bottom of your feet when you're at the pool. It's a little foam and it may be helpful. I'm on Facebook, Sarah Delanty. I'm in the PC group there, so if you want more info on it, just let me know and I'll shoot you the link. Thank you.

JAMES VALENTINE: Thank you, Sarah. All right. We'll take these two comments.

MARY HOWARD: Mary Howard. I have K16. One of the things that has helped my feet feel better is getting older. It's about the only thing that's nice about getting older. Going through menopause, they seem to have been better than when I was younger. And also, I've lost weight. I've changed my eating habits. I stopped sugar. I don't eat anything that's fried. That made a big difference also. The one foot I still have a lot of the fissures in it, and I use moleskin on that to hold it together, so I can walk okay. The other foot, I have the problem with the itching, so when I the stuff off at night, it itches so bad, I actually rub it on the side of the metal trim on my bed, and I rub it to the point where it itches so bad that I make it hurt even more. Then it still itches. I can't get to it, to the point where I have tears in my eyes, but it's still itching. But getting old helped.

JAMES VALENTINE: Getting old helped. Maybe that's good news for everybody in the room. Some hope for the future. Did I have a hand over here?

DIANE SPINDELL: Hi. My name is Diane Spindell, and I have the K6c gene. I try to stay as active as I can, and the only way I can do that is by wearing certain sneakers. They have to be running sneakers. Even when I walk or do house chores, I have to wear the running sneakers. And I just have found, ironically, that I can't go barefooted, but at the beach, on the sand, I can. I don't know, maybe my condition is different from everybody else in this room, but I found that I can walk a long distance, pain-free, on the sand at the beach, and I can play beach volleyball on the sand, barefooted, at the beach. So, I don't know what the deal is with that. In any case, I use the razor also to shave down my callouses and a needle to pop the blisters, but I have to have maintenance of my feet daily in order to be active.

JAMES VALENTINE: In other words, the daily maintenance.

DIANE SPINDELL: Yes.

JAMES VALENTINE: That's more frequent than maybe we've heard from others. Is it just keeping up with it?

DIANE SPINDELL: Yeah, even like taking foot baths. I usually soak them in cold water, cold, icy water. When I say daily, maybe every other day or every couple of days, but if I do that, I can be active to a certain degree. But if I'm in the sand I can go for a very long time, pain-free.

JAMES VALENTINE: Wow! I'm glad that you discovered that. That's great. So now, with our last couple of minutes, I just want to turn to the future. Smiley Riley mentioned that everything starts with the pain, but we've heard a lot—Jan and others—talk about

you manage your pain and you manage your activities. We heard in the first session from Jason that you are powering through and doing activities despite the pain. It sounds like living with PC is quite complex. There's this pain that's always there, whether you're doing activities or not. There's clearly, it sounds like, an impact on the activities that you can do, and lots of things that you have to not do because of your PC pain. It's a complicated disease, and so this is going to be a hard question to answer, but I think maybe the polling questions gave you some ideas. Really, I want to know what specifically would you look for that you don't get from your current treatment options from the next therapy that you would use? Again, not a cure, but if there was one thing that you could get, let me know what that is and tell me why, because going back to Smiley Riley, everything starts with the pain. For example, if you want some relief from pain, tell me why that is. What is the benefit that that would provide. If it's something else, for example, one of the examples was less amount of time needed to care for yourself. Let me know why it is that you're choosing that. But we'll take a few different responses to just get a feel for the room. Anybody want to weigh in on what they would look for specifically from a future treatment short of a cure?

DIANE BUTLER: My name is Diane Butler, and I have K16. Of course, we can't get a cure, but I would like less pain. I would like to walk on the grass or go to the airport, like even coming to the airport you have to take off your shoes. That was horrible. So, I would just like to do, like, normal stuff, like not wear shoes every single second that I'm awake.

JAMES VALENTINE: Thank you. We'll go to Holly, then Jason.

HOLLY JONES: Hi. Holly Jones, K6a. What I would like the most is for my feet to be totally numb. If the blisters are still there, if the callouses are still there, I can live with that because I've lived with it for 68 years. But if I could just have something to numb them, not necessarily numb my head with a drug that's going to do that, but maybe a topical just to numb the pain so that I wouldn't feel it. I can still have the condition, but I could cope a little bit better.

JAMES VALENTINE: Thank you. That's great. Jason.

JASON: Hi, my name is Jason K6a. For me, it would be—my feet sweat tremendously, and then it makes a callous soft, and then that's what really hurts. So, I think for me, if I could figure out a way to keep my feet dry and keep the callouses hard, then the pain wouldn't be as tremendous because right now they get soft, and once they're soft, it's all over for me. Right now, my feet are sweating, and I'm just sitting here. So, something to help with the sweating, and that would be probably a cure for me. Thank you.

JAMES VALENTINE: Thank you. That's great. Jim.

JIM: One of the things that Julie passed on earlier when she said she was laying down and she could almost feel her nails growing, Jen and I had talked about it years ago when we said how fast the nails grow. I'm hearing today about everybody daily trimming

their callouses and popping blisters. Possibly, I'm thinking if there's a way to slow the expression down. If you could slow it down so it doesn't manifest as fast, that could possibly reduce the pain and the amount of treatment.

JAMES VALENTINE: One more thought. Right here.

SELENA [[3:27:10]: My name is Selena [3:27:10] and I'm here representing my daughter, Naomi [3:27:13]. She's three and has a K17 variation. I would like to have some sort of treatment to improve her cysts and her follicular hyperkeratosis. It may be because of her age she doesn't have a lot of problems with callousing or pain on her feet, but the skin problems are at very much risk of infection. They are painful for her. As the hyperkeratosis gets worse, she doesn't like to be touched. She doesn't like for her clothes to touch them. We sometimes have to put bleach in her bath water to fight infection, and there are probably 50 different lotions and creams that we have tried to just improve the cysts and the bumps. Some of them she doesn't tolerate well at all. Some of them maybe help some. We're using one made by Vaseline right now and it's improved it by making them less red and softer, so that makes it less painful, but there's definitely not anything that fixes this problem. That's my biggest concern for her right now.

JAMES VALENTINE: I know I said last one, but there's a voice that we haven't heard today, and he's raised his hand. We'll give you the last word.

JUSTIN Rokisky: Hi, my name is Justin Rokisky, and I have K17. A treatment that I would hope for the future is one that would reduce the likelihood of inflamed cysts, and there are times that I've had several of these in just the most inconvenient locations on your body that you are forced to accommodate how you sit, how you sleep, how you lay down, how you walk. So, it's not only do we have to cope with the addition of the callousing on your feet when you're walking with those as well, but then you have to think about how you're sitting there or how you're sleeping. And I think what's most frustrating about that is you never know where the next inflammation will be, so you're constantly forced to be accommodating, like just on the daily of how you're doing anything. So, I think that's something that would reduce the likelihood that they're going to become inflamed. Also, when they do become inflamed, as she mentioned before, there's a risk of infection, which I've had myself, too. I've had MRSA as a result of the cysts, and so that literally crippled me to the point of where I was crawling on the floor with that infection. So, I think it's really important to target inflammation so that we can prevent that whole, like, progression to infections like that.

JAMES VALENTINE: Thank you very much. I think I was right to say that PC is complex, and just from the range of things that we heard that you all would want from a future treatment I think reflects that. So, this concludes the patient engagement portion of our program. As we move to our summary remarks, then lunch, before we do that, I just want to thank you all for your openness in allowing me to ask you very personal and hard questions. It's been a very great honor to get to work with PC Project, with the panelists, and now you today, the audience. So, thank you for doing that and being so

open and trusting, and I know I think we're going to hear very shortly that what you had to say was exactly what we needed to hear to really understand PC and experiences that you have in your daily life. Thank you for giving me that opportunity.

And now, I'd like to introduce our FDA official who's giving our summary remarks for the PC session, is Dr. Jill Lindstrom. Dr. Lindstrom is the Deputy Director of the Division of Dermatology and Dental Drug Products at FDA, and she's a Board-certified dermatologist. In this role at FDA she works with companies and researchers that are navigating the development of safe and effective products for conditions like PC; and ultimately, Dr. Lindstrom helps determine if the benefits of these new drugs outweigh the risks and can be FDA approved. Prior to joining FDA in 2002, she served eight years in the Army and six years in private practice in Washington, D.C. She's a graduate of Northwestern University, Feinberg School of Medicine, and completed her internship and dermatology residency at Walter Reed Army Medical Center. Jill?

DR. LINDSTROM: Thank you. It's my privilege and challenge to summarize this impactful, and I think profound morning session. Before I attempt to do so, I'd like to thank a few organizations and individuals. I want to thank the PC Project for bringing together this session. I want to thank James for his expert moderation, and I want to thank him and Frank [3:32:24] for their preparation with PC Project to bring this session together. And I'd like to thank Dr. Beitz for setting the regulatory framework, bringing forward that we at FDA have a legislative mandate to hear and incorporate the patient voice. I want to thank Dr. Bruckner for laying an excellent clinical foundation for today's discussion. But most of all, I want to thank the patients and the caregivers, each of you on the panel session and in the audience, and also on the web, although we didn't hear from them directly. I want to thank you. I want to deeply thank you for coming here today, for giving so generously of your time, for your courage, your transparency, your dignity, as you shared your stories, for your courage and your dignity as you confronted your disease and lived your lives in the face of the challenges that your diagnoses have presented to you.

What you've said today has been impactful and profound, and I think it's going to be extraordinarily useful to me and my colleagues at FDA, but also to academicians and to pharmaceutical companies and others who, whether they participated today here or on the web, or will read the Voice of the Patient report that will come out from it, I think that they will find much to mine from that. So, thank you very much.

In attempting to summarize this morning's session, I want to acknowledge that I cannot do justice to that, to the eloquence and breadth of your comments, but I want to attempt to highlight a few themes that I heard. And in my inadequacy in summarizing the session, I want you to take comfort in that there will be a report that will come out that will doubtless do a better job than I am able to do today.

But one theme that I heard strongly was that of pain, and the pain that you feel—I wrote down and now I can't find it—but I believe it was 95 % of you experience pain with every step; 94% rated your pain as moderate, severe or unbearable. That is profound to me.

There is not only the primary pain that you experience from the callouses, but then there's the secondary pain from the limitation in your lives that results from that pain; the limitation in your activities; the depression; the bullying that people described experiencing or observing their children experience.

In my role as a physician, scientist, regulator, I often work from a certain scientific or position of intellectual detachment as I'm engaging with data, numbers. But you have not afforded me that luxury today, beginning with the first person on the morning panel, Mr. Padovano, who spoke of a bank account, a limited bank account of steps. I couldn't be detached anymore, suddenly. It was real flesh, not just numbers; a limitation of steps; a limited bank account. And then the remaining panelists who spoke either of their children or of their future children. I'm not ashamed to say you moved me to tears. I wept at your stories. They were profound. Thank you very much for sharing them. I want you to know that while you described that your pain is often invisible pain, it was not invisible today. I am sure I don't fully understand it, but I heard it and I felt it, and I know that my colleagues did as well. And I think, again, it will be impactful to us.

As I listened to the second session and the therapies that people tried and are trying and are using, a theme, something that I did not hear much of, was effective pharmaceutical approaches—yes, pain medication, but not direct therapeutic approaches, some in development. And I think the challenge for myself, my clinician colleagues, my colleagues in the pharmaceutical industry, is to change that trajectory. An outcome, I think, of today's session is that we now have information from you that can help us with creative approaches to end points as scientists and pharmaceutical companies seek to develop agents to treat pachyonychia congenita.

So, in summary, I heard from courageous and dignified individuals suffering from pachyonychia congenita, that this very serious condition causes pain and limitation, immobility and other impacts on your lives. And again, I want to thank you for sharing with us your voice, your experience, and doing so in such a courageous and dignified manner.

JAMES VALENTINE: Thank you so much, Dr. Lindstrom. I think that is going to take us a long way in our journey, PC Project's journey, of trying to summarize this session, and thank you for those very insightful and thoughtful remarks.

Thank you, all. We have now concluded the full PC session, and we have lunch next door. We invite you back to participate in the EB session in the afternoon and look forward to seeing you after the lunch break. Thank you.

