



# Pachyonychia Congenita Project

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

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## **Voice of the Patient: Report from the Pachyonychia Congenita (PC) Externally-led Patient-Focused Drug Development (EL-PFDD) Meeting**

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This report has been composed by the patient advocacy group and reflects PC Project's account of the perspectives of those who participated. The document has not been revised and/or modified in any way after the report version date listed above. The submitters have permission to submit the external resource and that linking from the FDA website will not violate the propriety rights of others. For any questions related to this resource please contact PC Project at [info@pachyonychia.org](mailto:info@pachyonychia.org).

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## Introduction

On April 6, 2018, Pachyonychia Congenita Project (PC Project) and Debra of America held a joint public meeting to hear perspectives from patients with Pachyonychia Congenita (PC) and Epidermolysis Bullosa (EB), caregivers, and other patient representatives regarding the symptoms of PC and EB that matter most to patients, and to hear current approaches to treating the diseases. This Voice of the Patient Report will focus on Pachyonychia Congenita, which was the focus of the morning session. PC Project conducted the meeting as part of the FDA's Externally-led Patient-Focused Drug Development initiative (EL-PFDD). Although not organized by the FDA, this meeting was attended by FDA officials who were able to hear from patients with PC via panel presentations, facilitated discussions and public comments.

## Overview of Pachyonychia Congenita

Pachyonychia Congenita (PC) is a rare genetic skin disorder that primarily affects the skin and nails. The predominant distinguishing features are a triad of severe plantar pain, palmoplantar keratoderma (PPK) with underlying blisters and variable hypertrophic nail dystrophy.<sup>1</sup> Oral leukokeratosis, extensive (and often painful) cysts of various types, and follicular hyperkeratosis are often present. Natal teeth are sometimes present. The first signs of PC, typically thickened nails and/or oral leukokeratosis (and in some cases natal teeth), appear from birth to early childhood. Plantar blisters and/or calluses usually begin when a child begins to walk, and the pain is usually constant by age 10.<sup>2</sup> For the majority of patients, plantar pain is the most debilitating feature of PC and has a significant impact on a patient's quality of life.<sup>3</sup> By adulthood, many rely on canes, crutches or wheelchairs to aid their mobility and to avoid increased plantar pain caused by walking. For some, cysts are the dominant feature, characterized by milia in infancy and childhood, and extensive, often painful, body cysts develop at puberty and continue throughout adulthood.

PC is inherited as an autosomal dominant trait, although approximately 30-40% of cases are due to new spontaneous mutations without previous family history (data from the International Pachyonychia Congenita Research Registry (IPCRR); [www.pachyonychia.org/pc-data/](http://www.pachyonychia.org/pc-data/)). This disease affects both males and females with no reported differences among ethnicities. PC is estimated to occur from 5,000 to 10,000 cases worldwide.

The underlying genetic cause of PC is a mutation in one of five keratin genes, *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* or *KRT17* which encode the keratins K6a, K6b, K6c, K16 and K17 respectively.<sup>4</sup> These keratins are normally expressed only in palmoplantar skin, the nail bed, pilosebaceous unit and oral mucosa, body sites specifically involved in PC. Historically, PC was classified into two types, PC-1 and PC-2, based on phenotypic features but now with more than 100 distinct mutations identified allowing genotype/phenotype correlation, PC has been re-classified on a molecular basis corresponding to the gene involved: PK-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17.<sup>1,3</sup> Some mutations are recurrent, i.e. identified in many families; others are 'family specific'.

At the present time, there is no effective or approved treatment for PC. As discussed during the meeting, patients manage their symptoms in a variety of ways, either at home or with professional care. Plantar keratoderma can be managed by paring, trimming, grinding, or filing. Thickened nails are addressed by filing, grinding, or clipping. Cysts can be incised and drained or even surgically removed if infected or painful. Pain medication may be necessary for relief of plantar keratoderma.<sup>5</sup>

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2. Shah S, Boen M, Kenner-Bell B, Schwartz ME, Rademaker A, Paller AS. Pachyonychia congenita in pediatric patients: natural history, features, and impact. *JAMA Dermatol.* 2014;150:146-153.
3. McLean WH, Hansen CD, Eliason MJ, Smith FJ. The phenotypic and molecular genetic features of pachyonychia congenita. *J Invest Dermatol.* 2011;131:1015-7.
4. Wilson NJ, O’Toole EA, Milstone LM, Hansen CD, Shepherd AA, Al-Asadi E, Schwartz ME, McLean WH, Sprecher E, Smith FJ. The molecular genetic analysis of the expanding pachyonychia congenita case collection. *Br J Dermatol.* 2014;171:343-355.
5. Goldberg I, Fruchter D, Meilick A, Schwartz ME, Sprecher E. Best treatment practices for pachyonychia congenita. *J Eur Acad Dermatol Venereol.* 2014;28:279-285.

## Meeting Overview

This meeting provided an opportunity for PC patients, caregivers and other patient representatives to voice their experiences and perspectives on living with PC and to provide input for FDA’s benefit-risk analysis of potential new therapies for PC. Janice Schwartz, Chair of PC Project gave the welcoming introduction, and was then followed by Dr Julie Beitz, the Director of the Office of Drug Evaluation III in CDER at FDA, who set the stage for “why we are here today, what we can expect to learn, and why these learnings are so important”, (see Appendix 2)



Dr. Julie Beitz



Dr. Anna Bruckner

At the start of the meeting Dr Anna Bruckner, (M.D., Associate Professor of Dermatology and Pediatrics at the University of Colorado School of Medicine, and Director of Pediatric Dermatology at Children’s Health Hospital Colorado, Denver) gave a brief overview on the clinical features of PC (see Appendix 2)

The meeting was divided into two sessions and focused on two key topics:

- (1) **Living with PC** – the disease symptoms and daily impact of PC
- (2) **Current and future treatments for PC** – current approaches available to patients and potential future treatments.

For topic 1, five patients and/or caregivers each gave five minutes testimonies to initiate the discussion. In addition a five minute video with clips from patients across the world answering the question “What is the worst thing about PC?” was viewed. For topic 2, six patients each gave five minutes of their experiences to start the discussion. Following each panel, there was a facilitated discussion with patients and caregivers in the live audience (Appendix 1 for discussion questions and Appendix 2 for panelists). The discussion was led by James Valentine, JD, MHS, an Associate at the law firm Hyman, Phelps & McNamara, Washington, DC. Participants in the live audience and over the web were invited to answer polling questions (Appendix 3) to provide insight on the discussion topics.

Dr Jill Lindstrom, the Deputy Director of the Division of Dermatology and Dental Drug Products at FDA, closed the Pachyonychia Congenita EL-PFDD session with a highlighted summary of the meeting and concluded with, “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.”

Eighty PC patients, caregivers, and other patient representatives participated in the meeting in person. The live webcast had 670 views from twenty-five countries. An impressive number of FDA officials attended the meeting – 24 in person, 18 via the webcast.

After the meeting, PC Project conducted an online patient survey to supplement the live poll results and to allow patients not in attendance to write their experiences of living with and managing PC. The poll was open until 20<sup>th</sup> April to PC patients and caregivers. Over 200 responses were received.

A copy of the program, meeting transcription, patient responses and video from the meeting are available at [pachyonychia.org/externally-led-patient-focused-drug-development-meeting-el-pfdd-with-fda/](http://pachyonychia.org/externally-led-patient-focused-drug-development-meeting-el-pfdd-with-fda/)

## Report overview and key themes

This report summarizes the input provided by participants and panelists at the Externally-led Patient-Focused Drug Development initiative with the FDA. It also includes comments from the online survey carried out after the meeting (see Appendix 3).

Key themes that emerged throughout the meeting and from the survey:

- The most consistent theme was that of pain, particularly plantar pain associated with calluses and underlying blisters.
- The impact of plantar pain (and calluses) affects many aspects of patients' daily lives, including limited mobility, sleep deprivation, professional activities, emotional well-being and participation in social activities. Careful planning and management of daily activities is required to control the pain.
- Patients discussed the need for more effective pain medication – many spoke of regular use of various painkillers available to reduce and mask the pain but of their reluctance to be on them long term.
- Patients described mobility issues, such as having to evaluate every step, crawling when the pain was too great to walk, the dependence on mobility devices, and relying on others for transportation.
- Patients require time for regular care and management of their PC symptoms, either by themselves or with the aid of a professional. Care includes trimming calluses and nails, dealing with cysts (draining/excising etc.) and treating nail infections – the latter two of which may require a doctor or hospital visit.
- As well as the physical pain of PC, the mental and emotional pain of PC also impacts patients' quality of life.
- The challenges faced by children when growing up include bullying, limited participation in/exclusion from sports activities, mobility issues around school/college campus, and limited career choices.
- There are no approved therapies for treatment of PC. Patients are limited to a certain number of steps in a day, and existing methods of increasing those steps are negligible.

### Topic 1: Living with Pachyonychia Congenita (PC)

The first discussion topic focused on patients' experiences of "Living with PC" – the disease symptoms and the daily impact of PC.

Each of the five patients and/or caregivers (see Appendix 2) gave five minutes of testimony to describe their specific symptoms and the personal impact of PC on their lives to initiate the discussion.

- A man in his fifties with a spontaneous mutation of PC-K16 used the analogy of a bank account to describe the careful planning required for daily activities due to limited mobility - how the plantar pain of PC controls his life: "This one (bank account) isn't one

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."

- The mother of an eight-year-old daughter with a spontaneous mutation of *KRT6A* described the onset and progression of her daughter's condition from birth. From trouble feeding and painful nail infections, to the development of painful blisters and calluses on her feet that limit her activities and cause her pain. She highlighted the impact that PC has on family life in determining activities that her daughter can participate in. Also, she worries her daughter "won't be able to choose her ideal career because she won't be able to stand or walk long enough."
- A 32-year-old female with PC-K17, who is also a mother of 3 boys with PC, described the painful cysts that developed at puberty and continue in adulthood, in addition to the painful calluses.
- A 49-year-old male with a familial mutation in *KRT16* shared how the pain of PC can affect you mentally as well as physically – "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."
- A 23-year-old female with a familial *KRT16* mutation talked about the physical and emotional pain of PC.
- This video link (<https://youtu.be/zbuuv363FhM>) contains brief comments from 9 PC patients who all emphasize the worst thing about PC is the pain, "the pain just consumes you constantly."



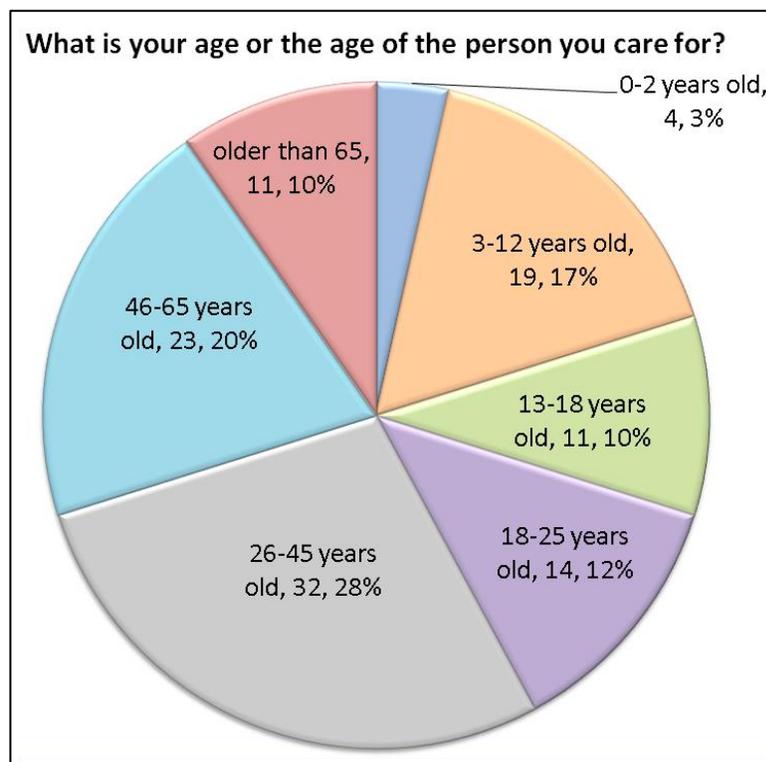
Panel 1: Living with Pachyonychia Congenita

In their testimonies, the panelists described their experiences and the burden of living with PC from childhood through to adulthood. The results from the polling questions and the facilitated group discussion indicated that the experiences of the everyday PC patient were reflected in the panelists' comments.

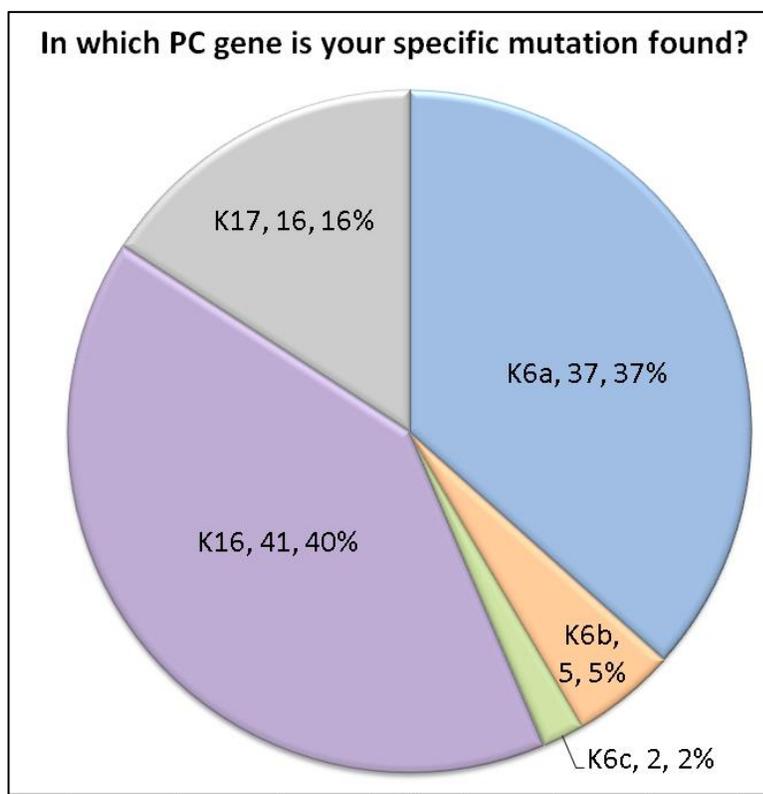
## Perspectives on the Most Significant Symptoms

(All results for the in-person or online survey during the livestream can be found in Appendix 3; some are presented below).

The participants in the in-person or online survey during the livestream of the EL-PFDD meeting (Appendix 3, PC Demographics, Q1) were comprised of 50% (58 of 117) PC patients, 29% (34 of 117) caregivers and 21% (25 of 117) both a patient and a caregiver. As shown below, the largest demographics were in the 26-45 years old age group (28%, 32 of 114) and the 46-65 years old age group (20%, 23 of 114) (Appendix 3, PC Demographics, Q3).



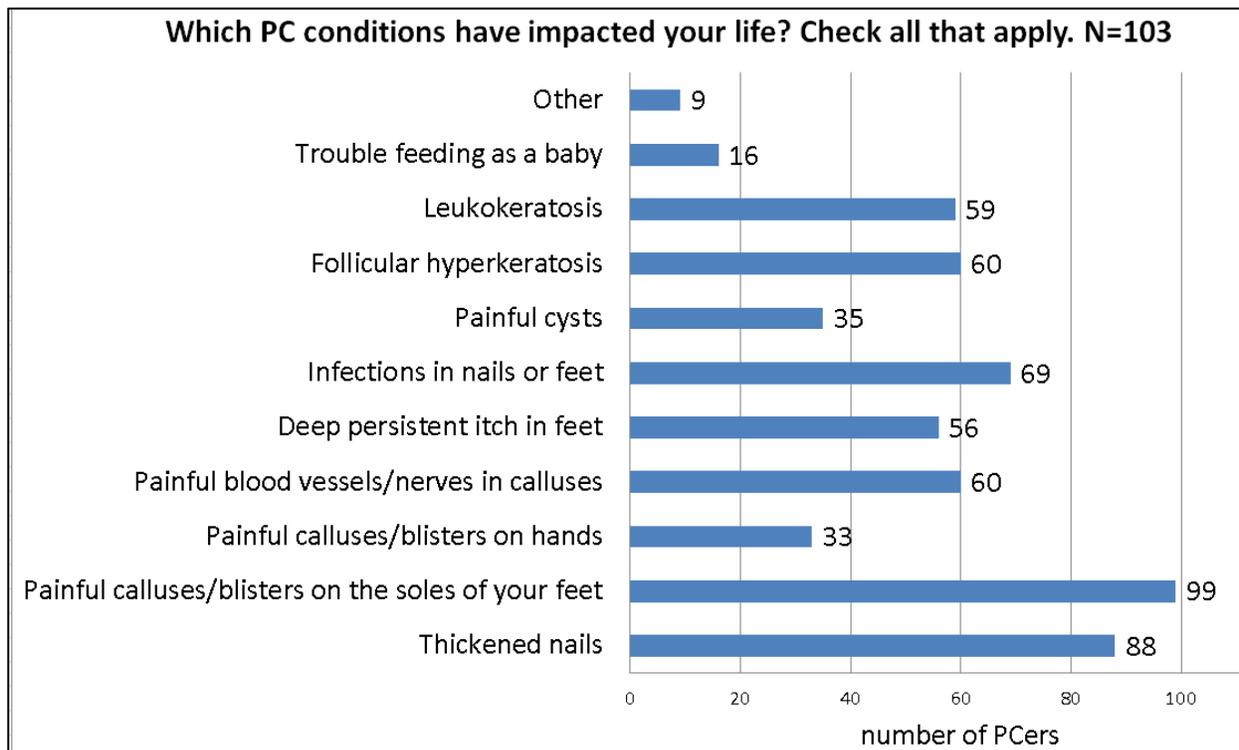
Of the 101 livestream respondents that participated in the in-person or online survey (Appendix 3, PC Demographics, Q4), 40% have a mutation in *KRT16*, 37% in *KRT6A*, 16% in *KRT17*, 5% in *KRT6B* and 2% in *KRT6C*.



There were 61% (67 of 109) with a familial mutation and 39% (42 of 109) with a spontaneous mutation (Appendix 3, PC Demographics, Q5).

The majority of respondents characterized their PC disease severity as “severe” (44% 46 of 105) or “moderate” (40%, 42 of 105) (Appendix 3, Living with PC, Q1). Of the various PC conditions (see chart below) nearly all participants (96%, 99 of 103) reported painful calluses and blisters on the soles of their feet as having the greatest impact on their life (Appendix 3, Living with PC, Q2), with 91% (94 of 103) reporting some level of pain with every step walked (Appendix 3, Living with PC, Q3).

Other features that have a strong impact on the life of PC patients include thickened nails (affecting 85%, 88 of 103) and nail infections (67%, 69 of 103), (Appendix 3, Living with PC, Q2). Oral leukokeratosis, follicular hyperkeratosis, deep persistent itch in the feet and painful blood vessels/nerves in calluses were each reported as conditions that have had an impact on more than half of the participants in the in-person or online survey during the livestream. (Appendix 3, Living with PC, Q2),



Patients gave further insight as to how each of the various features of PC impact a patients' life.

#### **Painful calluses/blisters on soles of your feet**

Painful calluses/blisters on soles of your feet are a major issue for the majority of PC patients as shown in results from the polling questions (above) and as stated by a PC-K16 patient:

“My PC shows up with thick calluses on over 50% of the bottom of both feet, cracks and occasional blisters along the middle and sides of most calluses.”

#### **Thickened nails**

Thickened nails, from all nails being affected, as in a PC-K16 patient who said “thickened nails on 100% of my fingers and toes” to only some nails being affected, can make it harder to perform some daily activities. The visual aspect can also cause embarrassment to patients and result in children being teased or bullied.

#### **Infections in nails or feet**

The mother of an 8-year-old girl with PC-K6a described, “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.”

#### **Painful blood vessels/nerves in calluses**

Previously not realized to be a major factor in PC, the results of the polling showed that a significant number of patients (58%) have these blood vessels.

### **Follicular hyperkeratosis**

The issues associated with follicular hyperkeratosis are common in childhood. As the mother of an 8-year-old girl with PC-K6a describes, she, "...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."

### **Leukokeratosis**

A patient with PC-K6a states: "I actually don't ever remember not having 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." Leukokeratosis can often be misdiagnosed or mistreated, leading to many hours in doctors' offices only to receive an ineffective treatment. For example, one participant commented that she was sent to an oral surgeon because her doctor was concerned by oral leukokeratosis. Even young PC infants with oral leukokeratosis are often misdiagnosed as thrush (Candidiasis).

### **Trouble feeding as a baby**

In some cases, particularly those with PC-K6a, there are painful feeding problems as babies. Often simple feeding solutions, such as a softer nipple with a larger hole on a feeding bottle, resolve the issue, thereby preventing complications and allowing the baby to thrive. The mother of an 8-year-old girl with PC-K6a described how her daughter'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."

### **Deep persistent itch in feet**

Something not widely reported in the literature is that many patients have a deep persistent itch in their feet. A patient with PC-K6a described, "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." And a PC-K16 patient said "I have the problem with the itching... 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."

### **Painful cysts**

Several patients discussed the problems associated with painful cysts. For many of those with PC-K17, cysts are the most painful and problematic symptom of their PC. A patient with PC-K17 said "The condition has caused so much bruising to my body over the years, from flare-ups to boils that will leave behind 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...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."

### **Painful calluses/blisters on hands**

Some patients get calluses on their hands which can be aggravated by daily activities, particularly repetitive ones – "I mean, even like writing or using your hands, even working in the garage on something. By night time, after doing a lot of hand involved wrenching or whatever, your hands really suffer much like your feet would, and you pay for it."



### **Overall impact of Pachonychia Congenita on daily life**

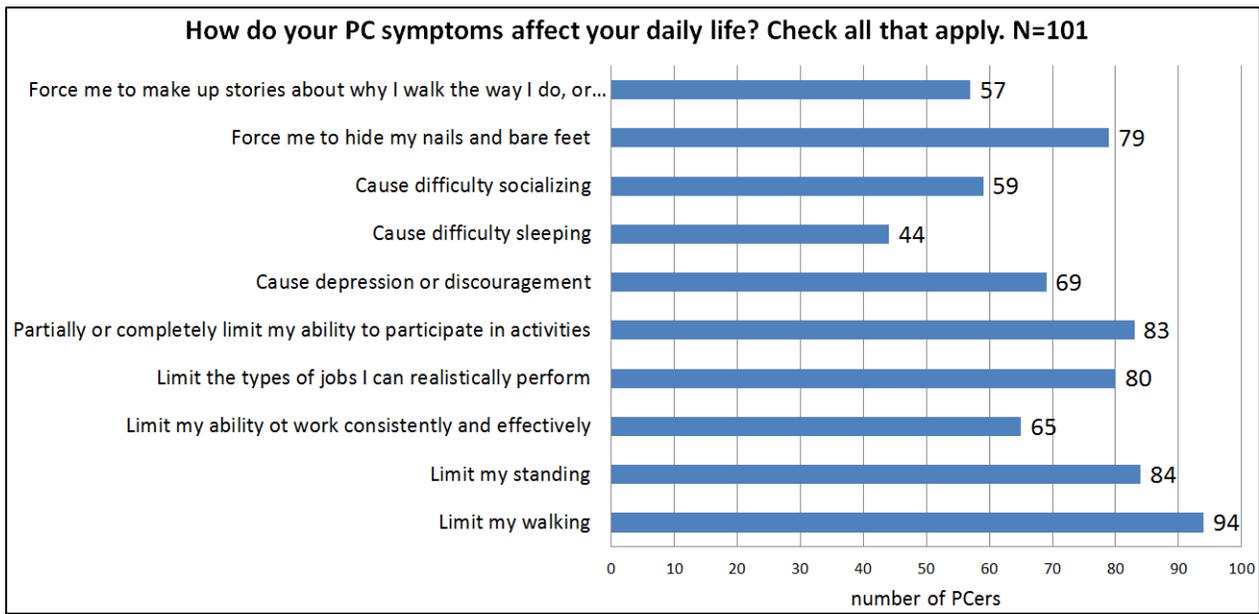
The majority of respondents, 80% (82 of 103) reported their PC had gotten worse with age, a very small number 7%, (7 of 103) had some improvement with age and 13% (14 of 103) reported it had stayed the same (Appendix 3, Living with PC, Q4).

A couple of patients who reported improvement of PC with age described their understanding/reasoning for this. A gentleman with PC-K6a said "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."

However, most patients agree their condition has worsened over time. Some of the greatest frustrations patients face is slowly watching their ability to do the activities they love decline. A College student with PC-K6a shared: "Having PC is hard for me. Back in elementary school, I used to be able to run around with other kids at recess, and I could play on sports teams. Now that I am in college, I can't even make it to a single class on foot. I have to take my bike with me everywhere I go, and if there's nowhere to put a bike at my destination, it's just 'too bad for me'. Every time I make a friend, I have to explain why I'm able to bike and walk around the

house, but I can't join their intermural sports team or go hiking. I guess it would just be kind of nice to actually participate in activities again instead of just watching from the side lines."

PC symptoms affect many aspects of daily life (see below). Most significantly, they limit walking and standing, and the ability to participate in activities (Appendix 3, Living with PC, Q5).



In the discussion session patients described how their PC symptoms affect their daily life and some of their personal strategies for dealing with this.

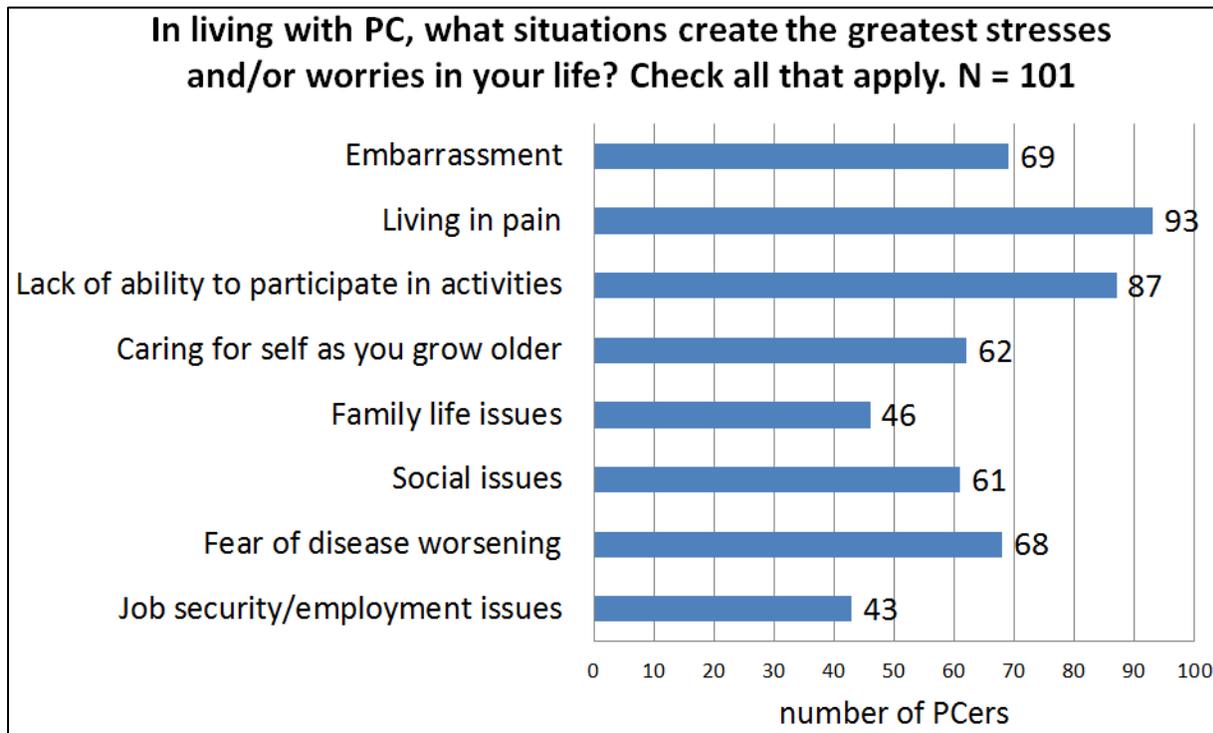
A lady with PC-K16 said "PC affects my life in so many ways; it's difficult to spend a few minutes explaining that impact. Beginning the moment I wake up, I reach for my Memory Foam slippers before I can roll out of bed to make it across the carpeted floor to the bathroom." another PC-K16 patient said "Forget running and hiking. Walking and standing are difficult at best because there's no life with PC that doesn't include pain." and another with PC-K16 said "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." A patient with PC-K17 said "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."

A patient with PC-K6a said "I definitely take advantage of the breaks, my lunches. I sit down, you know. Anytime I have a chance, I sit."

Another participant discussed the impact of PC on his daily life and how management has been key for him. "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 the 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. I've had very good success in managing my PC."

Consequently, living with PC leads to many additional stresses and/or worries for patients or their family's life as shown below (Appendix 3, Living with PC, Q6).



Of those that participated in the in-person or online survey during the livestream "living in pain" was the situation that created the greatest stress to PC patients (see graph above, (Appendix 3, Living with PC, Q6). The knock-on effect of this constant pain (in terms of not being able to participate in activities, embarrassment, family life issues, job security etc.) was very apparent in the audience discussion session, as described in some of the comments below.

As one patient said "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 able 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."

Another quoted, "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 another described the daily pain factor "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."

"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 like walking on glass, quite literally."

"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."

One PC-K6a patient shared the heart-breaking story of his young adult son: "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 3<sup>rd</sup>. I came and found him in his room."

For some, particularly those with mutations in *KRT17*, painful cysts are the hardest symptom to deal with, due to pain and emotional effects. "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." Another PC-K17 patient said "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. 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."



Drs. Beitz, Marcus, and Lindstrom

Misunderstanding in medical community about various symptoms/aspects of PC can cause stress for patients. One patient described the confusion over PC cysts: “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.”

Some PC patients have social issues – some may suffer from bullying as discussed by a female PC-K16 patient: “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.” It is important for parents of children to work with teachers and school staff so that they are well informed about PC and the ability/limitations of a child with PC. The mother of an 8-year-old with PC-K6a described how “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.”

PC affects everyone in the family. “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.”

Some patients feel embarrassed about their condition and find it hard to discuss, even with close family and friends. A lady in her 20’s with PC-K16 said “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.” Some hate feeling like invalids and asking for help.

Career choices and job opportunities may be limited for PC patients as they have to consider the amount of walking/time on feet required for the job, transportation options to the workplace, time allowed off if needed etc. From a PC-K16 mother of a son with PC-K16, “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?” The mother of a young child with PC said, “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.” A 51-year-old female spoke about how “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.”

The fear of passing PC on to future children causes concern and worry to some patients “It’s really hard passing it on to one of your kids, too, and seeing them suffer through.” A young adult with PC-K16 explained “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.”

## Topic 2: Patient Perspectives on Treatments for Pachyonychia Congenita

The second discussion topic focussed on current and future treatments for PC. Six PC patients (Appendix 2) each gave five minutes of testimony to describe their treatment/care of PC to initiate the discussion.

- A 40-year-old male who, like his eight-year-old son, has PC-K16. He spoke about how “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 calluses, and taking several prescription medications.” He went on to describe the different medications he has tried over the years to alleviate the pain.
- A female with a familial *KRT16* mutation that can be traced back at least six generations, spoke about her routine to care for her PC and the pain medication required to allow her to carry out daily activities and perform her job. “Every morning as soon as I’m awake, I start my day by taking two Excedrin or two to three ibuprofen 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.”
- A 51-year-old female with a spontaneous mutation in *KRT6A* described the pain and subsequent lack of sleep resulting in “utter exhaustion.” How she eats “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.”
- A 21-year-old male with a *KRT6A* mutation discussed how having his thickened nails removed had been beneficial to him in eliminating the pain in his fingers and nails and in giving him confidence with hands now looking “somewhat normal.” He spoke about



Panel 2: Treatments for Pachyonychia Congenita

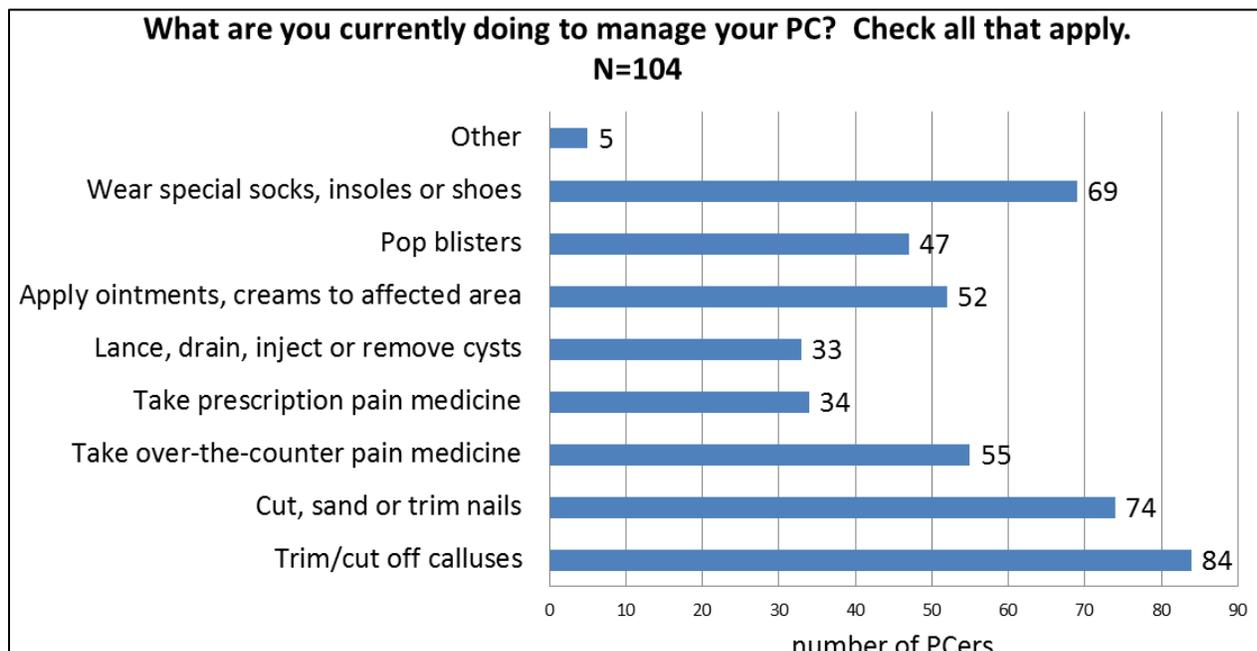
caring for his feet by cutting the calluses down and by taking non-prescription pain killers.

- An 18-year-old female with a spontaneous mutation in *KRT6A* said “Everything I do to manage my PC has to do with treating the pain in my feet... 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.”
- A 49-year old female with a spontaneous mutation in *KRT6A* who has two boys in their 20’s, also with PC. She described, “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.” She concluded by speaking about how her quest for an effective treatment has led to her involvement in many studies including a Phase 1b study for topical Rapamycin and an FDA approved Phase 1b clinical trial for siRNA.

Polling questions for the second topic covered several different aspects of managing PC and future treatments

### Perspectives on current treatments

As shown in the chart below, livestream participants in the in-person or online survey indicated the most common strategies in managing PC are to trim/cut off calluses, cut, sand or trim nails and wear special socks, insoles or shoes. Over-the-counter pain medicine, creams/ointments are also used and a lesser number take prescription pain medicine. Blisters are popped, and cysts are lanced, drained or removed (Appendix 3, Managing PC and future treatments, Q1).



Following the polling questions, ways patients manage their PC were discussed in more detail with the audience.

### **Trim/cut off calluses**

PC patients trim/pare calluses regularly, either by themselves or with assistance from a podiatrist. A variety of tools/methods are used based on personal preference, as observed in the comments from some patients below.

A PC-K6a patient said “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.” One with PC-K16 said “I need to shave off my calluses every two to three weeks, where I can literally remove up to half a pound of callus. 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 calluses. This is very effective and mandatory for me, but can cause cuts and nicks, and severely increase the pain the day afterwards.

Several patients mentioned painful blood vessels/nerves in the calluses and the difficulty in avoiding them when trimming calluses. “I also shave my calluses 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” said one PC K6a patient, while another patient with PC-K16 explained “I treat my PC by paring down the calluses 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.”

A PC-K6c patient described how, “If you coat the calluses in a really fine Super Glue or Crazy Glue and then sand it down, it takes all those little, tiny pieces of the callus 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” while a PC-K16 patient said “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.”

From a PC-K6a patient, “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 on, 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 surfaces with thick socks really work well for me.”

### **Cut, sand or trim nails**

PC patients regularly cut/trim/sand their nails using a variety of tools including clippers, Dremel drills, etc. One PC patient with a *KRT6A* mutation said, “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.”

## **Pain medications**

Many patients spoke about the constant pain, the lack of effective pain medications to control the pain, and their reluctance to take pain medication long term.

Another PC-K6a patient said, "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." Comments from another PC-K6a patient included, "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.

For pain medication, a patient with PC-K16 said, "I used to use ibuprofen until the doctors said I can't take that anymore, so now I'm on gabapentin, meloxicam, and Tramadol. 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." Another PC-K16 stated, "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," Other comments from PC-K16 patients included, "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.", "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 Aleve, 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." Another with PC-K16 said, "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."

A PC-K17 patient said, "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."



### **Painful cysts**

For many patients, especially those with PC-K17, management and care of their cysts is a large part of their regular management routine for PC.

A mother of a PC-K17 young girl said, “Her cysts and her follicular hyperkeratosis... 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.” A PC-K6a patient said, “I have a special blade that I use to excise the cysts that grow on my back and groin.”

### **Pop blisters**

Patients mentioned how blisters that develop under the calluses may need to be drained by popping them, as a PC-K6a patient described: “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.”

### **Wear special socks/shoes**

Patients may have special insoles or orthotic shoes to help reduce the pressure on their feet. Wicking socks can also be of benefit if excessive sweating is a problem.

A lady with PC-K6c said, “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.” Another PC-K6a patient said, “I try to put some fresh socks on and maybe change to a different pair of shoes—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."

One PC-K16 patient described her shoe needs, "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... 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.

More than half of respondents (62%, 63 of 102), in the in-person or online survey during the livestream were very unsatisfied with the treatments available today for PC, as they do little to help overcome the everyday burden that PC presents. 35% (36 of 102) were unsatisfied, only very few (3%, 30 of 102) were satisfied and nobody highly satisfied (Appendix 3, Managing PC and future treatments, Q2).

### **Mobility assistance devices**

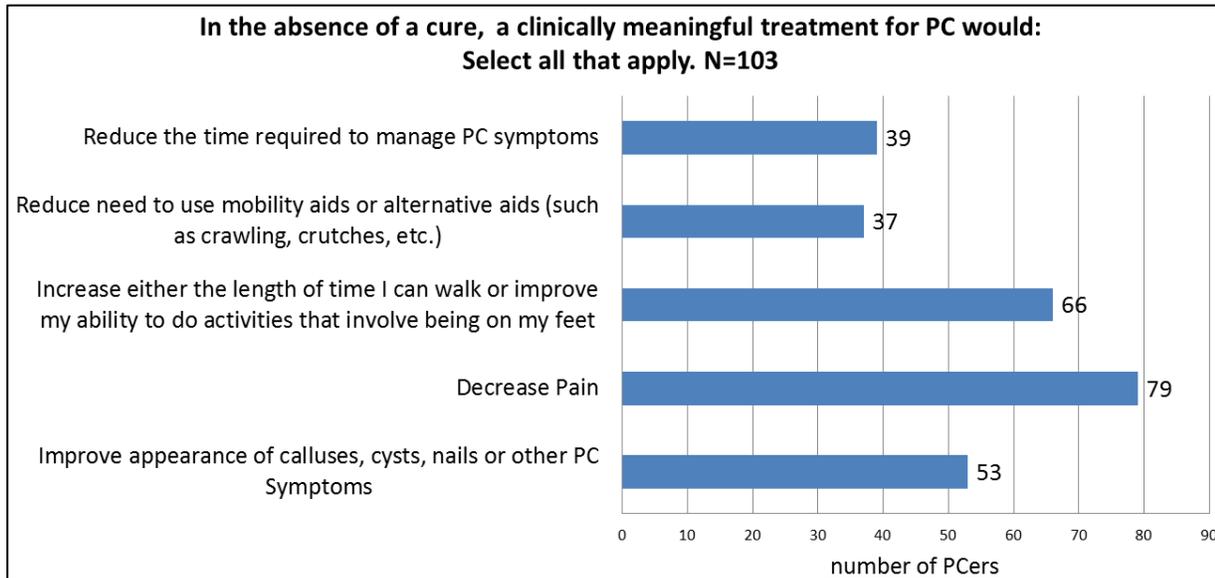
The majority of participants (85%, 86 of 101), in the in-person or online survey during the livestream) reported using a mobility assistance device (e.g. wheelchair, cane, scooter, walker) or employed alternative form of mobility (e.g. bikes, strollers, crawling, holding onto walls or rails, piggy-backing, holding onto another person, etc.).

Comments regarding the use of mobility assistance devices included those from a female with PC-K6a "On any given day, I rotate between walking with crutches, using a wheelchair, or crawling to avoid putting pressure on my feet," and from an 18 year old female with PC-K6a: "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."

### **Perspectives on ideal treatments for Pachyonychia Congenita**

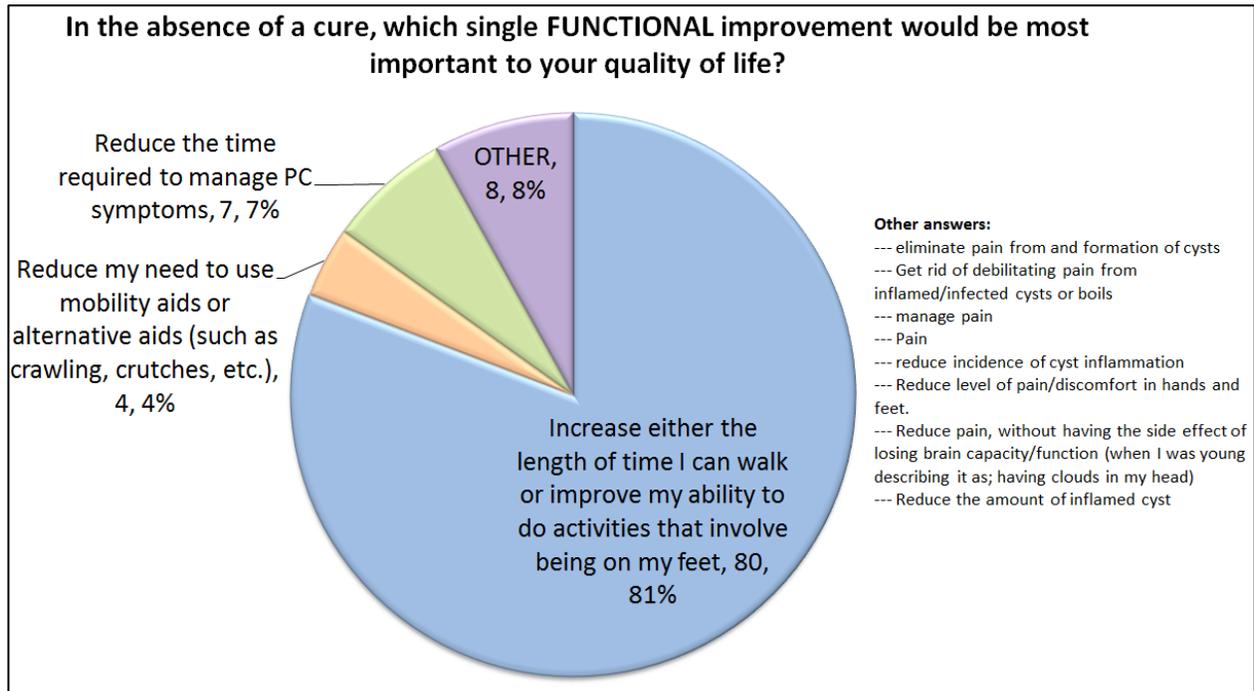
The second part of this session involved questions looking at what patients want from future treatments, what would be of most benefit etc. in the absence of a cure.

When asked about the most meaningful treatments for PC in absence of a cure, as shown in the chart below, participants in the in-person or online survey during the livestream, chose a therapeutic to decrease the pain and increase mobility as the most significant clinically meaningful treatments for PC (Appendix 3, Managing PC and future treatments, Q4).



Decreasing pain and increasing mobility was reiterated many times during the discussion sessions. A 21-year-old male with PC-K6a said, '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.' Another patient said, 'Probably the biggest thing that I would want in treatment for PC to do would be to address the pain.' and another, 'It's to find solutions to the pain and perhaps the cure. The first step is to lessen the pain.' The mother of 8-year-old girl with PC-K6a said, '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.'

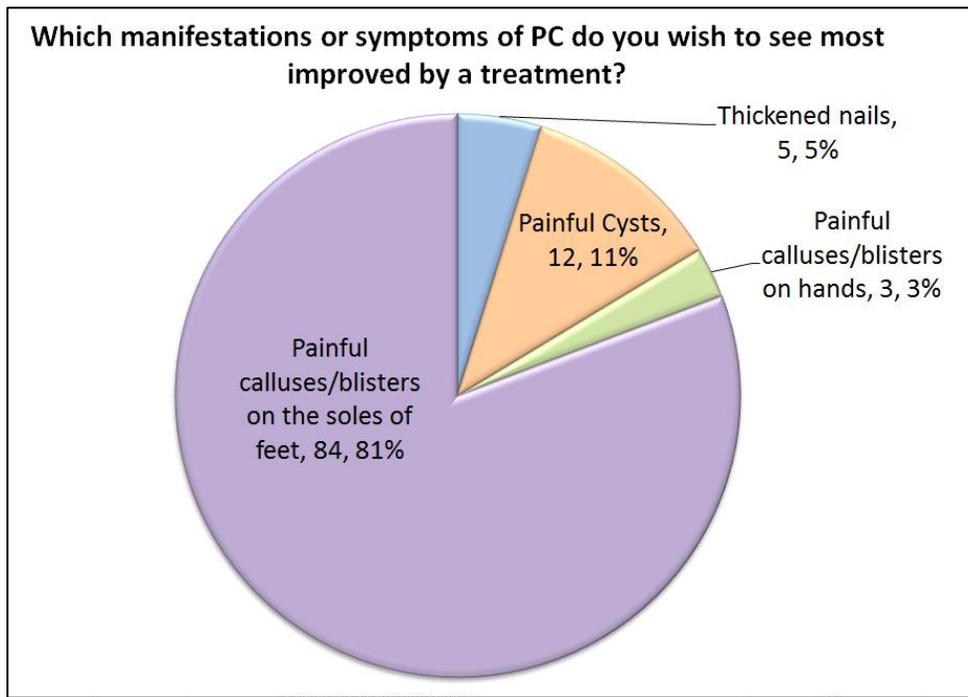
In answer to the question ‘In the absence of a cure, which single functional improvement would be the most important to your quality of life?’ (Appendix 3, Managing PC and future treatments, Q5), the majority of participants (81%, 80 of 99) reported something that increases the length of time they can walk or that improves their ability to do activities that involve being on their feet as the most important single functional improvement they would like from a treatment, as shown in the chart below.



A PC-K6a patient commented, “I would like a treatment that reduces pain and increases mobility for every PC patient.”

Earlier in the meeting, a lady with PC-K6a spoke about the level of activity that 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.”

When questioned about the manifestations or symptoms of PC, the large majority of respondents (81%, 84 of 104) would like to see the painful calluses/blisters on the soles of their feet improve with a treatment (see below and Appendix 3, Managing PC and future treatments, Q6).



For one patient with PC-K6a, “What I would like the most is for my feet to be totally numb. If the blisters are still there, if the calluses 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.”

11% (12 of 104) would like to see an improvement in painful cysts, the majority of whom are individuals with PC-K17 for which cysts are typically the most problematic manifestation. A patient with PC-K17 said, “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.” The mother of 3-year-old with PC-K17, “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 callusing or pain on her feet, but the skin problems are at very much risk of infection. They are painful for her.”

## PC Session Summary



Dr. Jill Lindstrom summed up the meeting by stating, “One theme that I heard strongly was that of pain, and the pain that you feel - 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 calluses, 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.

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)."

## Summary of Comments Submitted to PC Project

Approximately 200 PC patients participated in a post-meeting survey which included free-response questions. Pain in some form was mentioned 660 times in topic 1 and 385 times in topic 2. Below are links to all of the comments that were submitted.

TOPIC 1 comments:

[www.pachyonychia.org/wp-content/uploads/2018/03/Appendix1Topic1AfterMeetingComments.pdf](http://www.pachyonychia.org/wp-content/uploads/2018/03/Appendix1Topic1AfterMeetingComments.pdf)

TOPIC 2 comments:

[www.pachyonychia.org/wp-content/uploads/2018/03/Appendix1Topic2AfterMeetingComments.pdf](http://www.pachyonychia.org/wp-content/uploads/2018/03/Appendix1Topic2AfterMeetingComments.pdf)

## Conclusion & Acknowledgments

This Externally-led-Patient Focused Drug Development meeting on Pachyonychia Congenita provided representatives from the FDA, the medical and scientific community, and industry the opportunity to learn directly from those who experience the pain and suffering from Pachyonychia Congenita and the debilitating effect it has on their lives.

PC Project gives special thanks to the 42 FDA officials who attended in person and remotely. Without their support, this meeting would not have been possible. PC Project also appreciates the members of the International Pachyonychia Congenita Consortium who attended the meeting in person – Drs. Anna Bruckner (who gave the PC clinical overview), C. David Hansen, Roger Kaspar, Sancy Leachman, and Joyce Teng – and all who attended via the web broadcast.

PC Project recognizes the service of the PC patient panelists and audience members (those in person and those who participated remotely) for selflessly giving their time and vulnerably sharing their experiences about living with PC. Many patients, ironically, live in shame and embarrassment for having a disease they cannot help. Yet, these patients generously let in the rest of the world for this meeting in order to tell their stories of depression, discouragement and pain.

Finally, PC Project hopes this meeting not only assists the FDA in evaluating the risks and benefits of new drugs, but also demonstrates the urgent need for drug developers and industry to move forward with effective treatments for PC. The ultimate goal is relief and increased mobility for PC Patients who suffer in pain every day of their lives.



James Valentine, Moderator

Appendix 1: Meeting Agenda and Discussion Questions  
 Meeting Agenda Friday, April 6, 2018

7:00 am	<b>BREAKFAST</b>
8:30 am	<b>OPENING REMARKS</b> Janice Schwartz, Chair, Pachyonychia Congenita Board of Trustees
8:35 am	<b>WELCOME REMARKS</b> Julie Beitz, M.D., Director, Office of Drug Evaluation III, Division of Dermatology and Dental Products
8:50 am	<b>INTRODUCTION AND MEETING OVERVIEW</b> James Valentine, J.D., M.H.S., Hyman, Phelps & McNamara, P.C., Meeting Moderator
8:55 am	<b>PC CLINICAL OVERVIEW</b> Anna Bruckner, M.D., University of Colorado—Denver
9:05 am	<b>PC DEMOGRAPHIC LIVE POLLING</b>
9:15 am	<b>TOPIC 1: LIVING WITH PC</b> <ul style="list-style-type: none"> <li>• PC Panel discussion: Jack Padovano, Christine Block, Nykole Lee, James Rittle, Tara Atae, PC Video</li> <li>• Living with PC live polling</li> <li>• Moderated audience discussion</li> </ul>
10:35 am	<b>BREAK</b>
10:45 am	<b>TOPIC 2: CURRENT &amp; FUTURE TREATMENTS</b> <ul style="list-style-type: none"> <li>• PC Panel discussion: Andrew Butler, Julianne Bennett, Roseann McGrath, Austin Pinardo, Rylee Defenbaugh, Janice Schwartz</li> <li>• Managing PC live polling</li> <li>• Moderated audience discussion</li> </ul>
11:55 am	<b>PC SESSION SUMMARY</b> Jill Lindstrom, M.D., Director, Division of Dermatology and Dental Products
12:10 pm	<b>LUNCH</b>

## Discussion Questions and Comments

### TOPIC 1: LIVING WITH PC - DAILY IMPACT DISCUSSION

1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?
2. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
3. How has your condition and its symptoms changed over time? Do your symptoms come and go? If so, do you know of anything that makes your symptoms better? Worse?
4. What worries you most about your condition?
5. How has your condition affected your mood (for example; depression, apathy, patience/tolerance for frustration)?

#### Topic 1: Comments from PC patients during meeting

**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.

**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.

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 3<sup>rd</sup>. 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 3<sup>rd</sup>. 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.

**JASON ROCHA:** 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.

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.

**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.

**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.

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.

**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.

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.

**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.

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.

**ROXI LO:** Roxi, 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.

### Topic 1: Comments from PC Patients after meeting

An after meeting survey was made available for 30 days for anyone who wanted to share their comments to be included in the voice of the patient. The open-ended questions went along with the discussion questions from the meeting. The questions asked are as follows:

- Of all the symptoms that you experience because of your PC, which 1-3 symptoms have the most significant impact on your life?
- Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?
- How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?



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.

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.

**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.

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.

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

**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.

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

**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.

**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.

**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.

**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.

Yes [daily maintenance]. 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.

**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.

**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.

**JASON ROCHA:** 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.

**JIM RITTLE:** 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, which could possibly reduce the pain and the amount of treatment.

**SELENA MERRIMAN:** My name is Selena Merriman and I'm here representing my daughter, Naomi Merriman. 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.

**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.

## Topic 2: Comments from PC patients after meeting

An after meeting survey was made available for 30 days for anyone who wanted to share their comments to be included in the voice of the patient. The open-ended questions went along with the discussion questions from the meeting. The questions asked are as follows:

- What are you currently doing to help treat your condition or its symptoms?
- What specific symptoms do your treatments address?
- How has your treatment regimen changed over time, and why?
- How well does your current treatment regimen treat the most significant symptoms of your disease?
- How well do these treatments stop or slow the progression of your disease?
- How well do these therapies improve your ability to do specific activities that are important to you in your daily life?
- How well have these treatments worked for you as your condition has changed over time? What are the most significant downsides to your current treatments, and how do they affect your daily life?



## Appendix 2: Patient Panel Participants and FDA Presenters

### Patient Panel, Topic 1

- Jack Padovano
- Christine Block
- Nykole Lee
- James Rittle
- Tara Atae
- PCers video: What is the worst thing about PC?

**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 overdrew 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.

**NYKOLE LEE:** Hello, my name is Nykole, 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 50<sup>th</sup> 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 ATAEE:** 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.

**PC VIDEO: What is the worst thing about PC?**

**PC Patient VOICE 1:** 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.

**PC Patient VOICE 2:** 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.

**PC Patient VOICE 3:** 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.

**PC Patient VOICE 4:** 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.

**PC Patient VOICE 5:** 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.

**PC Patient VOICE 6:** 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.

**PC Patient VOICE 7:** 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."

**PC Patient VOICE 8:** 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.

**PC Patient VOICE 9:** 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.

## Patient Panel, Topic 2

- Andrew Butler
- Julianne Bennett
- Roseann McGrath
- Austin Pinardo
- Rylee Defenbaugh
- Janice Schwartz

**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.

**JULIANNE 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 Pinaro, 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.

**RYLEE DEFENBAUGH:** Hello. My name is Rylee. 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.

## FDA Presenters

- Julie Beitz, M.D., Director, Office of Drug Evaluation III, Division of Dermatology and Dental Products
- Kendall Marcus, M.D., Director, Division of Dermatology and Dental Products
- Jill Lindstrom, M.D., Deputy Director, Division of Dermatology and Dental Products

**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 congenital 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.

**DR. JILL 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.

**DR. KENDALL MARCUS:** Dr. Marcus gave the EB session summary presentation.

### Clinical Overview Presenter

- Anna Bruckner, M.D., Associate Professor of Dermatology & Pediatrics at the University of Colorado School of Medicine, and Director of Pediatric Dermatology at Children's Health Hospital Colorado

**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.

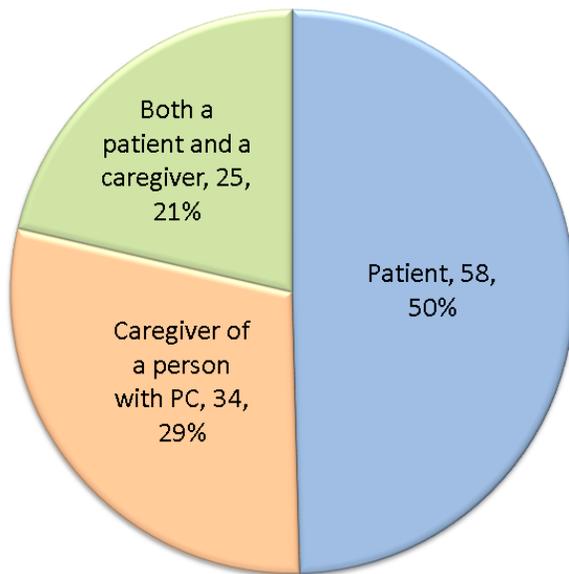
I'd like to conclude by pointing out that there are no approved therapies for PC, and you are honestly going to be hearing more about treatment in the upcoming sessions. Patients will rely on nonspecific modalities in order to help them manage their callous, in order to manage their nails, and also to 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.

### Appendix 3: Meeting Polling Questions and Responses

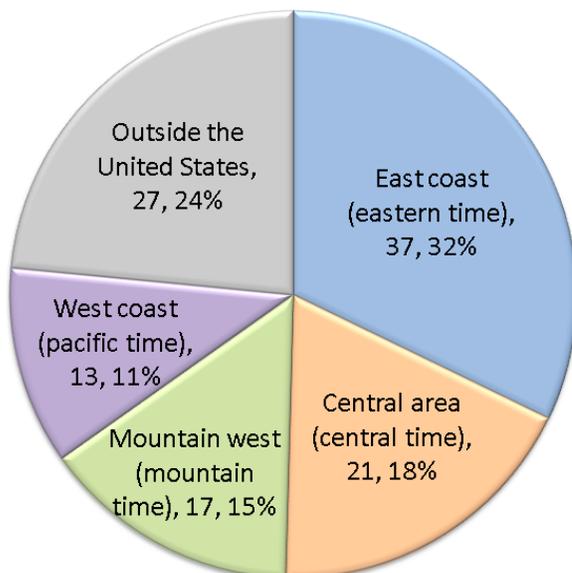
The following questions were posed to in-person and web meeting participants at various points throughout the April 6, 2018, PC Externally-led Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results presented here represent both in-person participants, those who participated online during the livestream of the EL-PFDD meeting.

#### PC Demographics:

1. Are you a patient or a caregiver?
  - a. Patient
  - b. Caregiver of a person with PC
  - c. Both a patient and a caregiver

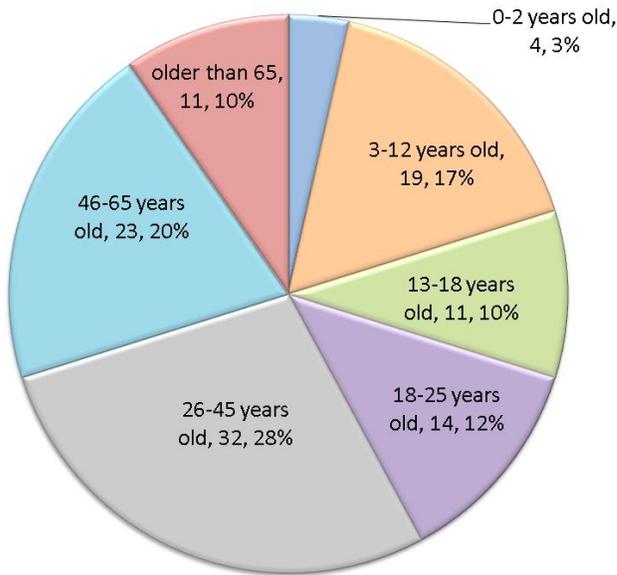


2. Where do you or the person you care for reside?
  - a. East coast (eastern time)
  - b. West coast (pacific time)
  - c. Mountain west (mountain time)
  - d. Central area (central time)
  - e. Outside the United States



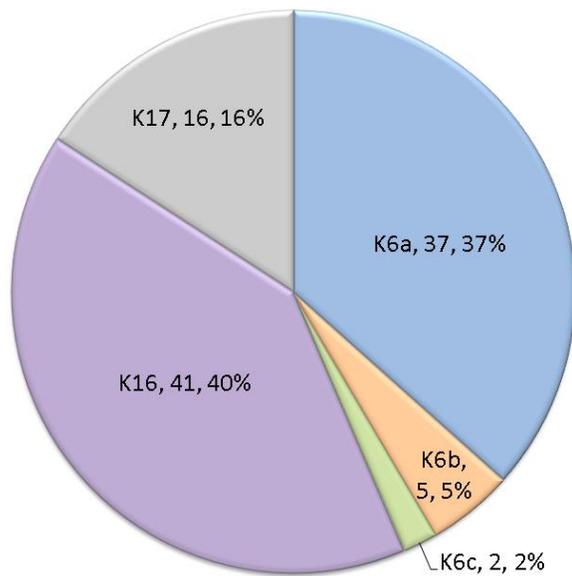
3. What is your age or the age of the person you care for?

- 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

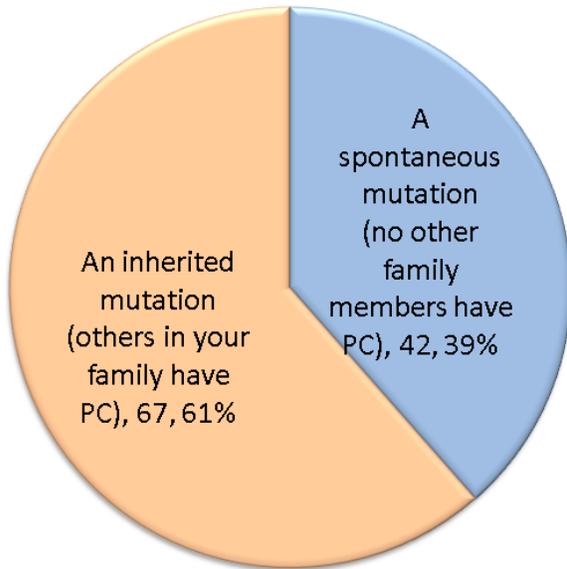


4. In which PC gene is your specific mutation found?

- a. K6a
- b. K6b
- c. K6c
- d. K16
- e. K17

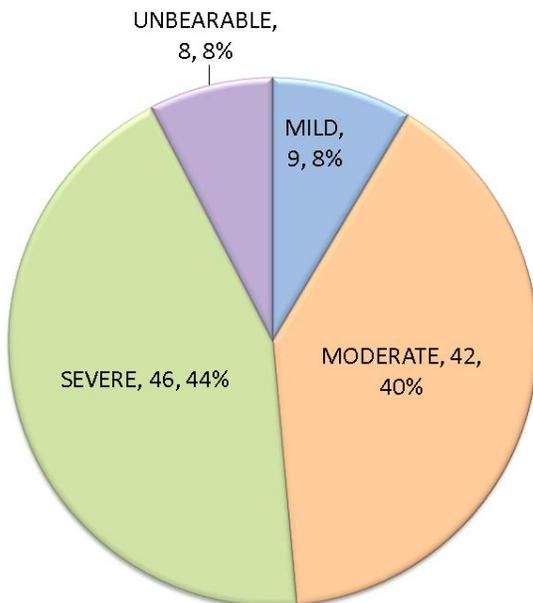


5. Do you have:
- a. A spontaneous mutation (no other family members have PC)
  - b. An inherited mutation (others in your family have PC)



Living with PC:

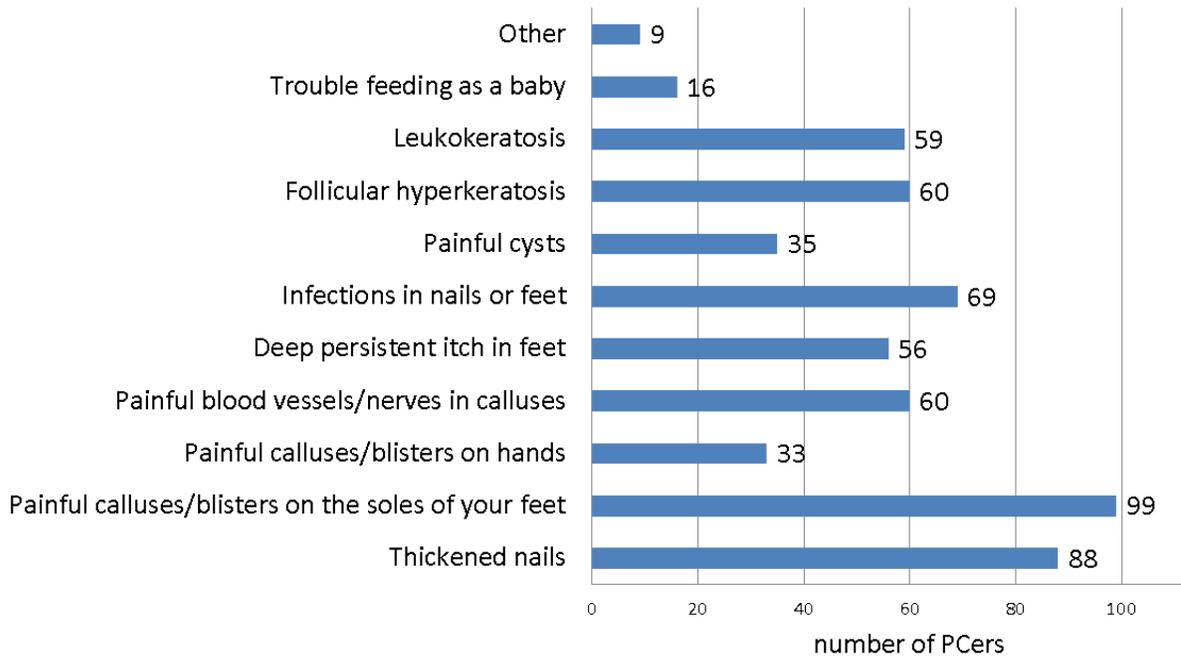
1. Overall, how would you characterize your PC disease severity or the severity of the person you care for compared to someone without PC?
- a. **Mild** (While I have symptoms, I am able to, on most days, manage those symptoms and live a healthy, normal life without limitations)
  - b. **Moderate** (PC has an impact on my everyday life, and on some days limits my ability to function normally due to ambulation challenges, pain, etc.)
  - c. **Severe** (PC is debilitating to my everyday life, and in many cases limits my abilities to live a normal life due to ambulation challenges, pain, etc.)
  - d. **Unbearable** (PC at times causes me to withdraw from society; I feel it is difficult to continue on and occasionally I have suicidal thoughts)



2. Which PC conditions have impacted your life? Check all that apply.

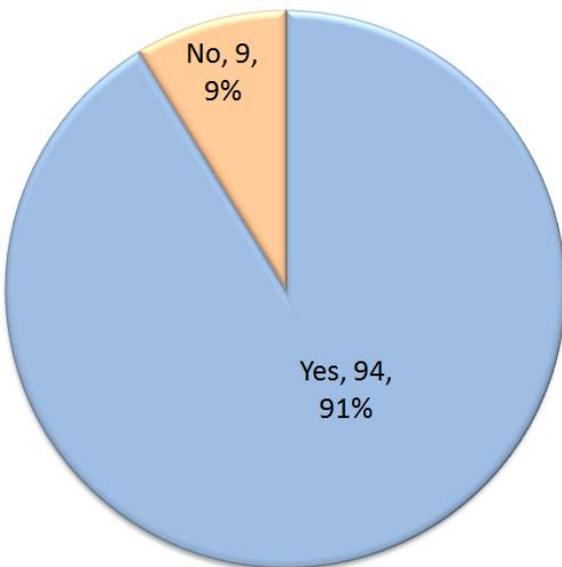
- a. Thickened nails
- b. Painful calluses/blisters on the soles of your feet
- c. Painful calluses/blisters on hands
- d. Painful blood vessels/nerves in calluses
- e. Deep persistent itch in feet
- f. Infections in nails or feet
- g. Painful cysts
- h. Follicular hyperkeratosis (little bumps on waist, legs, arms, etc. that cause irritation)
- i. Leukokeratosis (white growth on tongue)
- j. Trouble feeding as a baby
- k. Other

**Which PC conditions have impacted your life? Check all that apply. N=103**



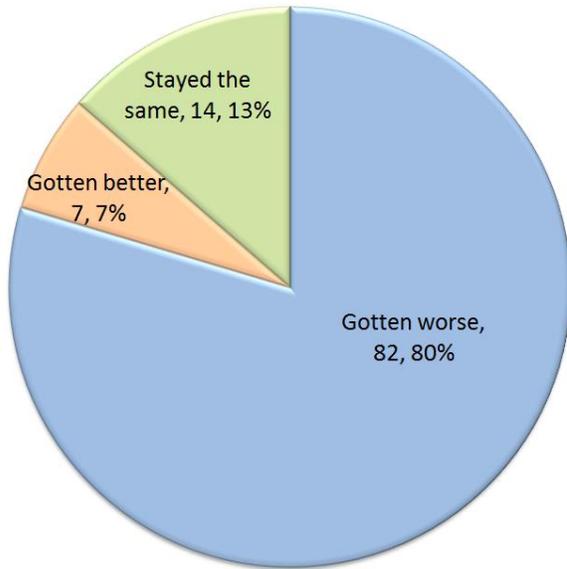
3. Do you typically feel some level of pain with every step that you walk?

- a. Yes
- b. No



4. How has your PC changed over time/with age?

- a. Gotten better
- b. Gotten worse
- c. Stayed the same



5. How do your PC symptoms affect your daily life? They (check all that apply):

- a. Limit my walking
- b. Limit my standing
- c. Limit my ability to work consistently and effectively
- d. Limit the types of jobs I can realistically perform
- e. Partially or completely limit my ability to participate in activities
- f. Cause depression or discouragement
- g. Cause difficulty sleeping
- h. Cause difficulty socializing
- i. Force me to hide my nails and bare feet.
- j. Force me to make up stories about why I walk the way I do, or why my nails and feet look the way they do, to avoid having to explain PC.

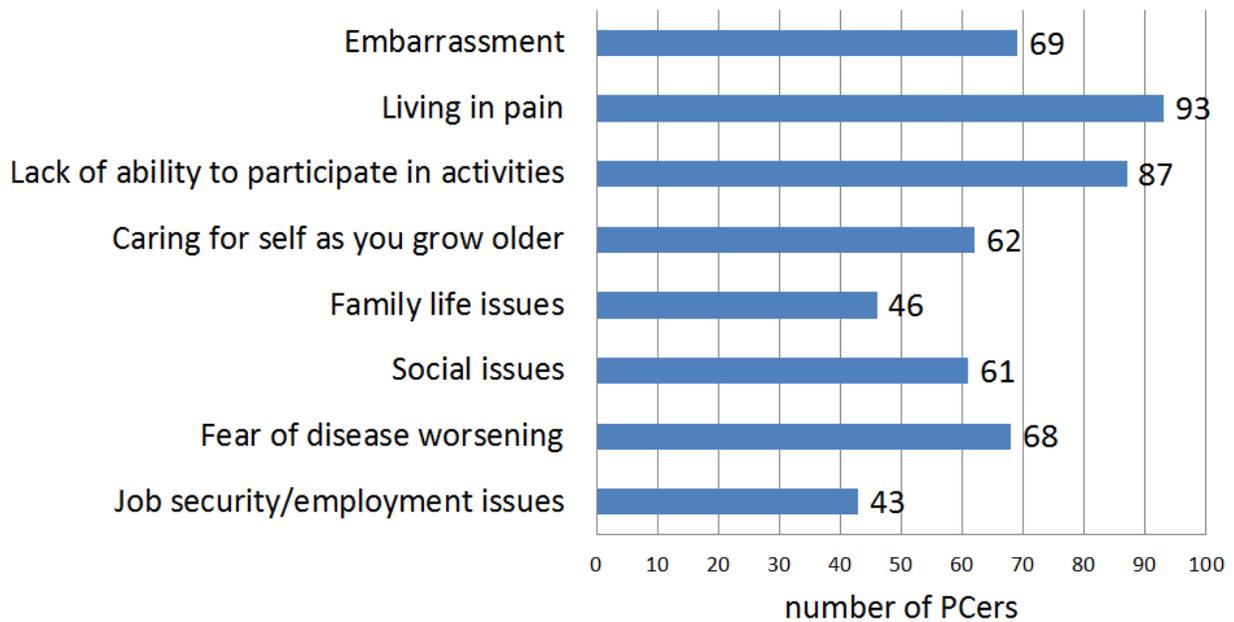
**How do your PC symptoms affect your daily life? Check all that apply. N=101**



6. In living with PC, what situations create the greatest stresses and/or worries in your life?  
Check all that apply.

- a. Job security/employment issues
- b. Fear of disease worsening
- c. Social issues
- d. Family life issues
- e. Caring for self as you grow older
- f. Lack of ability to participate in activities
- g. Living in pain
- h. Embarrassment

**In living with PC, what situations create the greatest stresses and/or worries in your life? Check all that apply. N = 101**



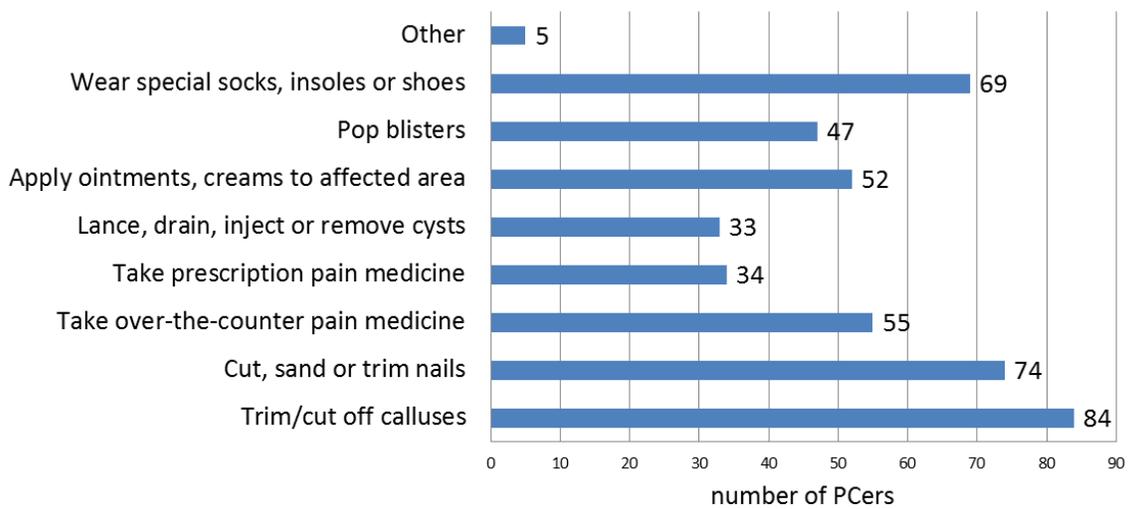
Managing PC and future treatments:

1. What are you (or the person you care for) currently doing to manage your PC? (check all that apply)

- a. Trim/cut off calluses
- 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, creams to affected areas
- g. Pop blisters
- h. Wear special socks, insoles or shoes
- i. Other

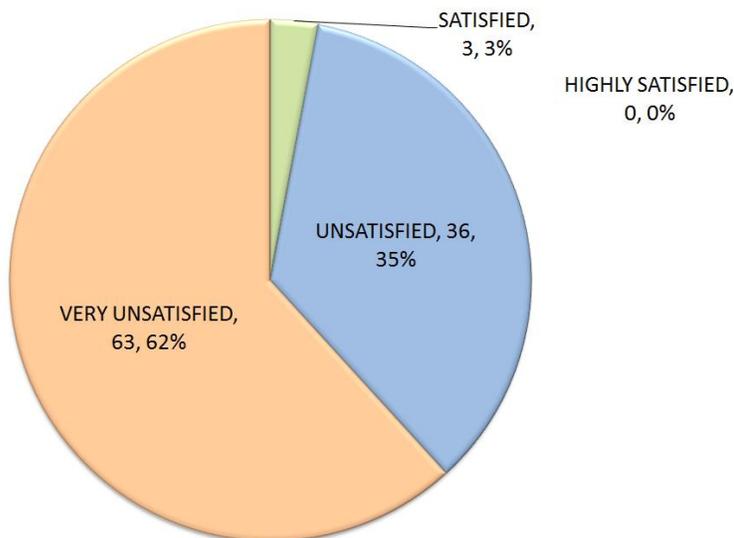
What are you currently doing to manage your PC? Check all that apply.

N=104

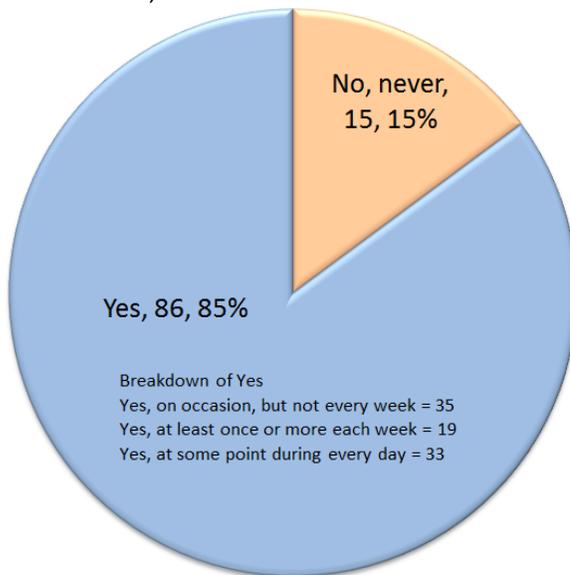


2. How satisfied are you with the treatments available today for your PC?

- a. **Highly satisfied:** Current treatments allow me to live a life with no limitations
- b. **Satisfied:** Current treatments allow me to live a life with only a few limitations
- c. **Unsatisfied:** Even with current treatments, I am living a life with many limitations
- d. **Very Unsatisfied:** Current treatments are unsatisfactory, and do little to help overcome the everyday disease burden

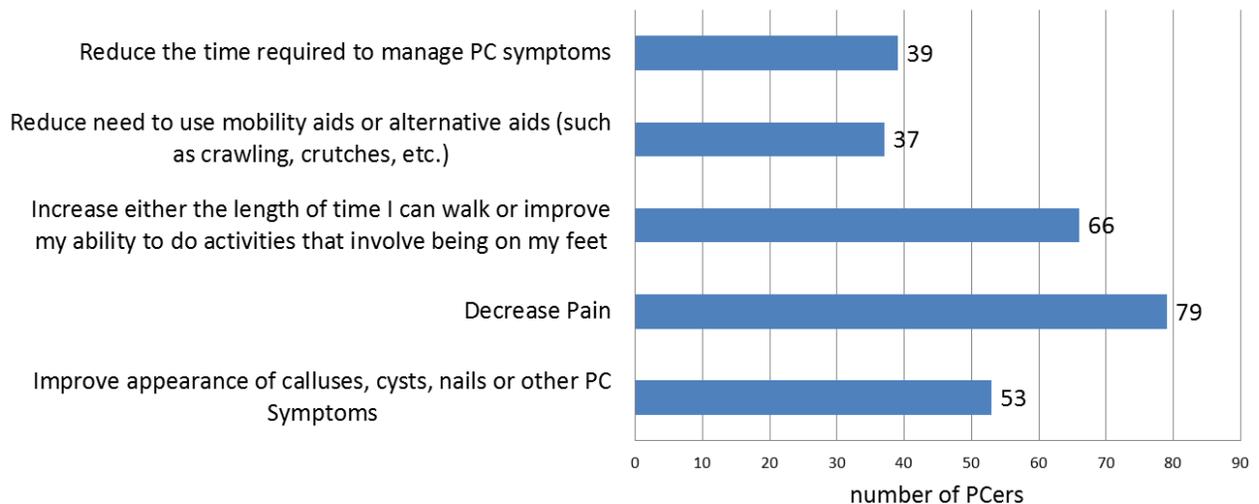


3. Have you ever utilized a mobility assistance device (e.g., wheelchair, cane, scooter, walker) or employed an alternative form of mobility (e.g. such as bikes, strollers, crawling, holding onto walls or rails, piggy-backing, holding onto another person, etc.) because of your PC?
- Yes, at some point during every day
  - Yes, not every day, but at least once or more during the week
  - Yes, on some occasions, but not every week
  - No, never

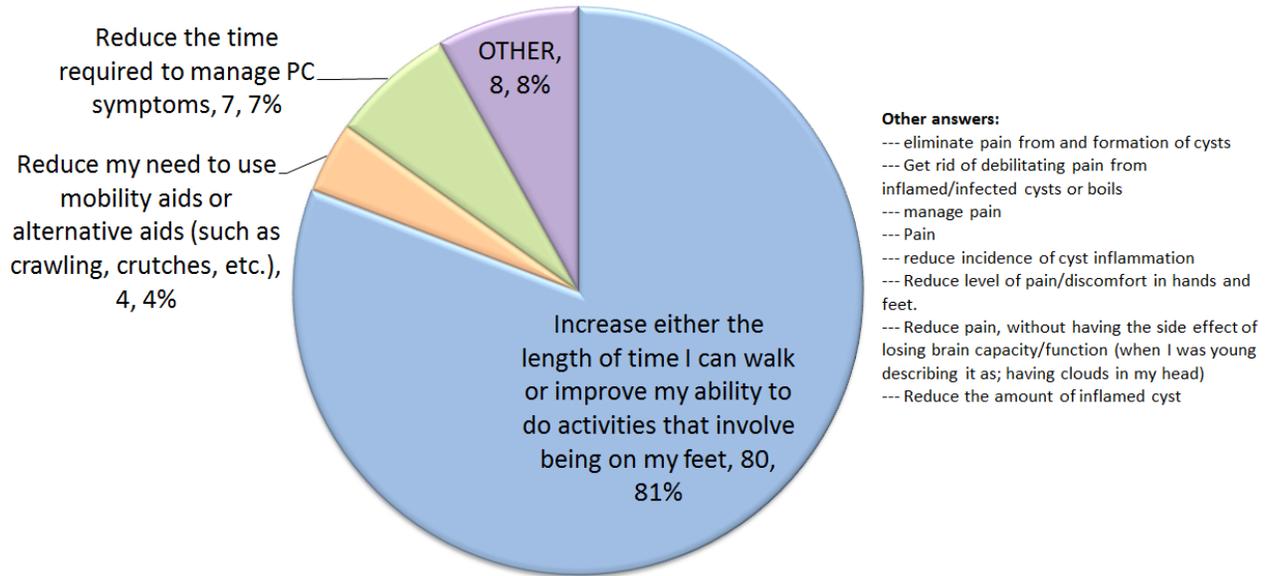


4. In the absence of a cure, a clinically meaningful treatment for PC would: Check all that apply.
- Improve appearance of my calluses, cysts, nails or other PC symptoms
  - Decrease pain
  - Increase either the length of time I can walk or improve my ability to do activities that involve me being on my feet
  - Reduce my need to use mobility aids or alternative aids (such as crawling)
  - Reduce the time required to manage my PC symptoms

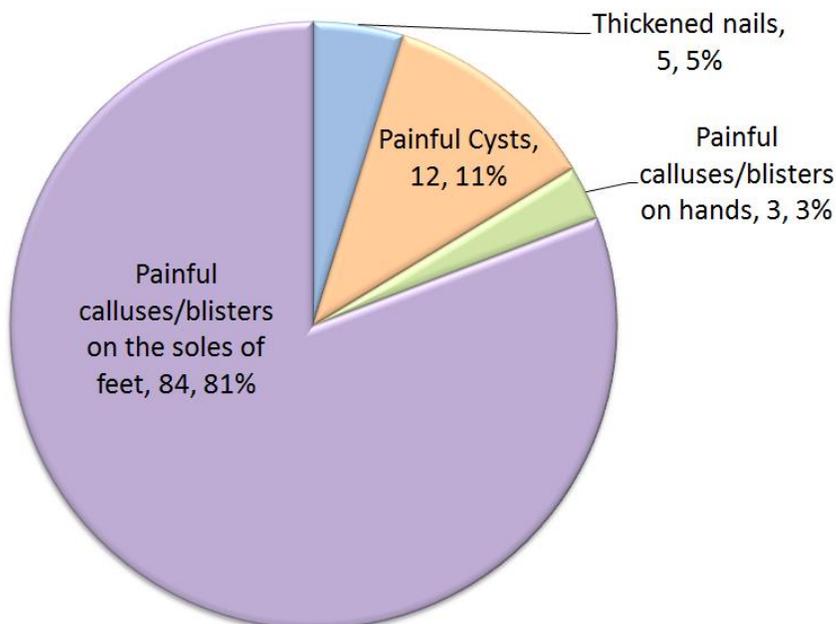
**In the absence of a cure, a clinically meaningful treatment for PC would:  
Select all that apply. N=103**



5. In the absence of a cure, which single **functional** improvement would be most important to your quality of life?
- Reduce the time required to manage my PC symptoms.
  - Increase either the length of time I can walk or improve my ability to do activities that involve me being on my feet
  - Reduce my need to use mobility aids or alternative aids (such as crawling)
  - Other



6. Which of the following **manifestations or symptoms** of PC do you wish to see most improved by a treatment?
- Thickened nails
  - Painful calluses/blisters on the soles of feet
  - Painful calluses/blisters on hands
  - Painful cysts
  - Follicular hyperkeratosis (little bumps on waist, legs, arms, etc.) 0, 0%
  - Leukokeratosis (white growth on tongue) 0, 0%



## Appendix 4: Links to EL-PFDD Archive

A copy of the program, meeting transcription and video from the meeting are available at [pachonychia.org/externally-led-patient-focused-drug-development-meeting-el-pfdd-with-fda/](https://pachonychia.org/externally-led-patient-focused-drug-development-meeting-el-pfdd-with-fda/)