Pachyonychia Congenita: A Research Agenda Leading to New Therapeutic Approaches

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Pachyonychia congenita (PC) is a dominantly inherited genetic disorder of cornification. PC stands out among other genodermatoses because despite its rarity, it has been the focus of a very large number of pioneering translational research efforts over the past 2 decades, mostly driven by a patient support organization, the Pachyonychia Congenita Project. These efforts have laid the ground for innovative strategies that may broadly impact approaches to the management of other inherited cutaneous and noncutaneous diseases. This article outlines current avenues of research in PC, expected outcomes, and potential hurdles.

Keywords: Drug repurposing, Genodermatosis, Keratoderma, Nails, Pachyonychia congenita

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INTRODUCTION

Pachyonychia congenita (PC) is a rare, autosomal dominant skin disorder that is caused by heterozygous variants in keratin (*K*)6*A*, *6B*, *6C*, *16*, or *17* genes. Clinical signs include palmoplantar calluses causing plantar pain, nail dystrophy, mucosal involvement, and follicular cysts of various types (Leachman et al, 2005; Smith et al, 2006). PC reportedly affects between 5000 and 10,000 people worldwide (see https://rarediseases.org/rare-diseases/pachyonychia-congenita/), but common misdiagnosis of milder phenotypes creates practical challenges for determining its true prevalence.

Currently, there is no routinely available cure or treatment that specifically targets PC. Among many barriers that stand between patients with PC and effective treatments are (i) a lack of coordinated efforts to address persistent challenges that are also relevant to many other rare disorders, (ii) the restricted number of relevant grant funding opportunities, (iii) the small number of affected individuals, (iv) the scarcity of tissue samples, (v) limitations of current animal models, and (vi) lack of validated clinical outcomes in clinical trials, which in combination hinder the design and implementation of randomized trials.

To begin addressing these challenges, the Pachyonychia Congenita Project (ie, PC Project), an international nonprofit advocacy organization, established a PC patient registry in 2004. The International Pachyonychia Congenita Research Registry (IPCRR) currently includes data on over 1100 genetically confirmed patients with PC from 56 countries. The IPCRR has begun to fulfill its promise of facilitating the systematic collection of clinical data, information dissemination among people affected by PC, and clinical trial enrollment (Goldberg et al, 2014; Samuelov et al, 2020; see www.pachyonychia.org). This important achievement has been coupled with advances in developing a better understanding of the multifaceted pathogenesis of PC, increasing the potential to contribute to the design and implementation of robust clinical trials to test new treatments. Lessons learned through previous and

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Abbreviations: BTx, botulinum toxin; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; IPCRR, International Pachyonychia Congenita Research Registry; K, keratin; PC, pachyonychia congenita; PGA-AD, Patient Global Assessment of Activities Difficulty; PPK, palmoplantar keratoderma; PROMIS, Patient Reported Outcomes Measurement Information System; siRNA, small inhibitory RNA

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Table 1. Key Research Priority Areas

Goals of PC Research Agenda
To provide a unified voice from leaders in PC research and clinical care that articulates high-priority PC research topics needing immediate attention
To facilitate PC-focused collaboration as well as exchange of data, material, and ideas among investigators with diverse backgrounds
To facilitate communication of PC research priorities to policymakers and research sponsors
To align research priority areas with patient-driven desirable outcomes
The 6 Identified High-Priority Areas for PC Research
Organizing PC research–related resources
Investigating major clinical manifestations (painful PPK, nail dystrophy, and cysts)
Focusing on better harnessing the power of omics studies
Optimizing new laboratory models, devices, and other emerging technologies
Promoting molecular therapies and drug repurposing in PC
Developing novel regular and technology-based outcome measures

Abbreviations: PC, pachyonychia congenita; PPK, palmoplantar keratoderma.

ongoing trials focused on PC may benefit patients affected by other disorders of keratinization.

PC Project and other PC stakeholders recognize that until the current obstacles to PC research progress are addressed, patients and the clinicians who care for them will not have access to effective therapeutic solutions. To begin addressing these issues, the PC Project convened a panel of PC experts in investigative and clinical dermatology to produce a PC Research Agenda. The development and dissemination of a PC Research Agenda have several goals (Table 1).

Among PC's many challenges is the reality that it is a rare and complex disorder associated with multiple complications that require timely interventions, continuous follow-up, excellent patient education, and effective communication with various members of the care team. To address these challenges, new lines of research are needed that optimize existing and emerging technologies with the goal of developing an accessible toolbox of molecular therapies and digital aids. These efforts will offer meaningful progress in disease management support to patients, families, and other members of the care team. This review provides an expert opinion of the research areas to be prioritized to accelerate the development of novel therapeutic approaches in PC and probably other disorders of keratinization.

ORGANIZING PC RESEARCH–RELATED RESOURCES

Many groups are investigating PC using a wealth of resources, including clinical and genetic data, a wide range of biological materials obtained from patients with PC, as well as animal and humanized models for PC. Clearly, a centralized structure responsible for organizing and presenting this information in an accessible format could further empower PC research.

PC Project has already developed a single, centralized registry for PC (and some other palmoplantar keratodermas [PPKs]) that includes clinical and genetic diagnostic screening data. In conjunction with this registry, we are considering the establishment of a multicenter biobank. In addition to PC itself, such pooled resources may positively impact patients who suffer from PPK as a result of disease-associated variants in other genes. Indeed, PPKs of other etiologies likely share pathophysiological mechanisms with PC and thus may benefit from similar or even identical therapeutic solutions. Because PC and other PPKs are rare conditions, it is critically important to ensure that collection and use of tissue samples, including palmoplantar skin, from consenting patients are ethical and are performed with robust protocols of tissue collection, storage, and distribution procedures. In addition to small full-thickness skin biopsies, callus and noncallus tape strips and nail clippings from patients with PC may provide invaluable materials for mechanistic studies, diagnosis, and patient stratification in the context of clinical trials and monitoring of therapeutic outcomes. Additional biological materials that could be of help include paraffin-embedded and frozen section skin biopsies, sera, and primary or immortalized keratinocyte cell lines. Of note, similar tissues from matched controls are also needed. Experimental models for PC, whether humanized or murine (see below), have been developed by some groups and should be made available to the community of PC researchers.

INVESTIGATING MAJOR CLINICAL MANIFESTATIONS (PAINFUL PPK, NAIL DYSTROPHY, AND CYSTS)

Plantar pain associated with keratoderma of varying magnitude can be the source of major functional incapacitation for patients with PC and is therefore considered the most pressing issue to be therapeutically addressed in this disorder. Nail dystrophy and cysts are additional manifestations that can have a disproportionate impact on QOL among patients with PC (Samuelov et al, 2020). Treatments for these symptoms are inadequate, in part owing to a limited understanding of their underlying pathophysiology.

Plantar pain has been attributed, at least in part, to the formation of subepidermal blisters, fissures, and neurovascular bundles in the plantar skin, although additional mechanisms cannot be excluded. In turn, these features of PC can decrease physical function, with an accompanying impact on QOL and mental health.

One or more dystrophic nails are a characteristic finding in PC, especially in early childhood when plantar keratoderma may not yet be present. Of note, not all patients with PC display dystrophic nails. Hyperplastic nails can cause pain, swelling of periungual folds, and increased risk of injury, all of which can impact ambulation and overall physical function.

Various types of follicular cysts have been reported in PC, reflecting their origin in the hair follicle. Cysts can show secondary infection, inflammation, and scarring and be a source of pain. More recently, a phenotype resembling hidradenitis suppurativa has been reported in patients with PC, especially those carrying *K17* sequence variants (Pavlovsky et al, 2022).

Although developing a validated scoring mechanism for plantar keratoderma severity that can be used in clinical trials will undoubtedly be difficult, research directed at this goal is a top priority. The use of innovative imaging techniques as detailed below may significantly facilitate the assessment of keratoderma response to therapeutic interventions (Goldberg et al, 2013).

Improved delineation and quantification of the PC-associated pain to define and stratify pain phenotypes using both patient-reported symptoms and quantitative sensory testing is imperative to identify appropriate quantitative outcome measures for clinical trials that target each subset (Brill et al, 2018).

FOCUSING ON OMICS STUDIES

Although keratin function has been extensively characterized, to gain broad insights into the pathomechanisms underlying PC, an unbiased hypothesis-free approach is needed. Human tissue/model systems interrogated with relevant tools may shed new light on the pathogenesis of PC and identify potential therapeutic strategies. Despite the reliance on in vitro cell models based on interfollicular-derived keratinocytes, palmoplantar skin is quite distinct. It is thicker and hairless and has a distinctive, alternating, keratin expression profile (Swensson and Eady, 1996). In addition, signaling pathways can be differentially regulated in interfollicular and palmoplantar skin (Arcidiacono et al, 2018; Maruthappu et al, 2017). Therefore, current in vitro skin disease models are not ideal and may not be relevant for studying PPKs. Furthermore, the underlying biological and molecular mechanisms in palmoplantar skin are not well-understood because of the paucity of studies in both humans and mice. Toward bridging this knowledge gap, single-cell RNA-sequencing datasets of normal human palmoplantar skin have been performed and will provide a key resource/reference tool in understanding PC and PPK disease processes (Wiedemann et al, 2023).

In addition, knowledge is lacking in palmoplantar biology from development to adulthood and relating these data to time of onset and keratoderma patterns across distinct PC/PPKs. Studies that analyze patient biopsies from unaffected and callused palm/sole and other relevant clinical sites, such as cysts, are needed. To understand the development of the PPK, biopsies could be collected from individuals carrying a PC-associated variant before the onset of calluses. Although age of consent may make mouse models appealing in some research settings, tape strips can be used on a child's palmoplantar skin to address some of these challenges (Hughes et al, 2021).

To date, RNA array technology has only been used to a limited extent in human and mouse PCs. These include a gene expression dataset derived from 7 human PC samples (Cao et al, 2015) and a microarray dataset generated using forepaw skin from *K16*-knockout mice (Zieman et al, 2019). To address the inadequacy of existing datasets, bulk and single-cell RNA sequencing should be performed on new samples. The relatively new spatial RNA-sequencing technology may be the tool of choice for these studies because this method allows high-resolution RNA expression mapping of tissue sections, including different areas of the epidermis, dermis, and sweat glands. Biological material should be leveraged to a much greater degree in a variety of RNA, protein, immune, and lipid-based investigations.

Other omic approaches should be applied as well, including phosphoproteomics aimed at identifying possible kinase targets, metabolomics, and lipidomics (Migliozzi et al, 2023). Studies aimed at delineating epigenetic changes (eg, DNA methylation or microRNA profiling) could help identify additional therapeutically actionable pathways (Velasco and Francastel, 2019). To investigate systemic immune effects of PC/PPK-associated variants, human PBMCs from patients with PC/PPK and controls could be subjected to a panel of immune markers using the Cytometry by Time-Of-Flight platform (a type of mass cytometry used to quantify labeled targets in single cells). Spleen and lymph nodes from mouse models should also be processed and analyzed as part of this line of investigation.

Advanced bioinformatics tools may be used to correlate the various datasets expected to be generated, which may reveal PC/PPK-driven signaling pathways, transcription factor–linked networks, and potential ligand–receptor interactions, all of which could inform new therapeutic strategies. The impact of datasets that are used for these purposes should be enhanced by the ability to take subsequent serial tissue sections for follow-up protein immunohistochemistry, including multiplex biomarker spatial imaging (eg, Cell Dive) and proximity ligation analyses (Gerdes et al, 2013; Söderberg et al, 2006). Protein studies will be particularly useful for exploring nerve afferents in the epidermis, although these could be limited by the near absence of available antibodies to identify subsets of nerve afferents.

Eventually, these various efforts should lead to the establishment of publicly available datasets, which could in turn serve to integrate these data with clinical features and thereby not only point at novel therapeutic targets but also improve the quality of PC diagnosis and genetic counseling for families at risk for PC through the identification of modifier traits.

OPTIMIZING NEW LABORATORY MODELS, DEVICES, AND OTHER EMERGING TECHNOLOGIES

Laboratory studies of pain mechanisms should take advantage of the increased availability of mouse models of PPK pain (García et al, 2011; Kerns et al, 2016). However, an ideal PC-transgenic mouse model should be genetically relevant, feature key symptoms, and have lesions associated with this disease. At present, no existing published mouse model combines genetic and phenotypic relevance for any of the key PC symptoms. For instance, although it mimics the genesis of PPK-like lesions in foot pad skin, the *K16*-null mouse is not genetically relevant to most cases of PC, thereby limiting its use beyond discovery research (Lessard and Coulombe, 2012). Current efforts are dedicated to developing better mouse models for PC and other PPKs.

These models present an opportunity for detailed molecular, immunological, cellular, and physiological studies of PPK pain and initial testing of candidate therapies. Findings from these studies should be correlated with human data and would benefit from input received from regular meetings of PC-focused experts in PC-related pain.

These and other studies should focus on potential mechanistic contributors to pain, including structural lesions, subepidermal blisters, and decreased intraepidermal nerve fiber density (Pan et al, 2016). Although recent studies have shown that epidermal keratinocytes are involved in sensory transduction (Lumpkin and Caterina, 2007; Samuelov et al, 2020), the underlying mechanisms and extent of their role remain poorly understood. Novel coculture models involving

keratinocytes and sensory neurons have revealed information on these interactions and should be pursued further (Talagas et al, 2020). Another area of great relevance to PC would be coculture models designed to explore the interplay between epidermal keratinocytes and cellular effectors of innate immunity (Huth et al, 2019).

Various pharmacological pain therapies, device-based pain therapies (eg, engineered physical dressings, footwear, electrical stimulators), and disease-modifying approaches (eg, gene silencing, signal transduction manipulation, small molecules, biologics) should be considered for investigation in the PC setting, and the most promising of these should be prioritized for safe, objective, and statistically robust clinical evaluation in the setting of PC.

PROMOTING MOLECULAR THERAPIES AND DRUG REPURPOSING IN PC

In recent years, despite the gaps in knowledge, new therapeutic approaches are being investigated in patients with PC. Most novel approaches involve various forms of drug repurposing, as detailed below.

Small inhibitory RNAs

The ability of small inhibitory RNAs (siRNAs) to selectively and potently inhibit gene expression at the mRNA level has been established (Adams et al, 2021; O'Donoghue et al, 2022). Several siRNAs have been developed that inhibit PC targets in cell culture models (Hickerson et al, 2016; Leachman et al, 2010, 2008). One of these, TD101, was tested in a phase 1b study and reverted a small area of plantar callus to healthy-appearing skin in a prospective, double-blind, split-body, vehicle-controlled study of a single patient with PC (Leachman et al, 2010). In this trial, the pain associated with administration of intralesional TD101 required pain medication (including a local nerve block), which is why ultimately only 1 patient completed the study. A large volume of siRNA had to be administered (up to 2 ml), and this may have led to high pressure that facilitated siRNA uptake by keratinocytes but also exacerbated the local pain (Hickerson et al, 2011; Leachman et al, 2008). Efforts are currently being directed at developing delivery systems that are more acceptable to patients as well as more sophisticated, chemically modified siRNAs relevant to PC (Sallam et al, 2021).

Sirolimus

The mTOR inhibitor sirolimus (rapamycin) selectively inhibits K6 expression in a specific cell culture model (HaCaT keratinocytes) and was evaluated in an off-label oral study of 3 patients, which showed reduced neurovascular structures, reduced plantar keratoderma, and improved QOL (Hickerson et al, 2009). Despite encouraging improvement of PC symptoms, the 3 patients experienced debilitating side effects. Improvement in hyperkeratosis was reported in 2 patients with PC using topical 1% sirolimus ointment (Teng et al, 2018). A pivotal phase 2/3 trial of QTORIN 3.9% rapamycin gel (VALO study), opened to patients with K6A, K6B, and K16 PC, was completed. In the phase 2 portion of the open-label study using rapamycin gel with 71 patients, responders who achieved a statistically significant improvement on the Patient Global Assessment of Activities Difficulty (PGA-AD) primary endpoint moved directly to phase 3. In the phase 3 portion of the VALO study, the pooled QTORIN rapamycin arms did not show a treatment effect on the PGA-AD primary endpoint when compared to vehicle gel. Moreover, a recent separate phase 3 placebo-controlled double-blind trial (VAPAUS study; opened to patients with K6A, K6B, K6C, and K16 PC) with 87 patients did not meet the primary endpoint. QTORIN 3.9% rapamycin gel was well-tolerated in all trials, but the results did not show evidence that this formulation of sirolimus is effective in PC.

Statins

Statins were initially identified as K6A inhibitors after screening a chemical library using a cell-based reporter gene assay for inhibitory effects on *K6A* promoter activity and K6A protein expression, mediated by signal transducer and activator of transcription 1 transcription factor, through the geranylgeranylation pathway (Zhao et al, 2011). In addition, studies of virally transformed PC keratinocyte cell lines using fluorescence and biochemical-based assays have shown impaired clearance of old mitochondria and autolysosome recycling, resulting in thickening of epidermal layers; statins have been shown to modulate autophagy and mitophagy, shown to underlie cardioprotection in mouse models (Andres et al, 2014; Ashrafizadeh et al, 2020). Statins have also been shown in rat models to activate antioxidant KEAP1—NRF2 signaling (Habeos et al., 2008), which has been implicated in the pathogenesis of PC-like keratoderma in a mouse model (Kerns et al, 2016; Zieman and Coulombe, 2020).

Case reports have suggested improvement of PC keratoderma in 2 pediatric patients treated with rosuvastatin and an adult patient treated with simvastatin, all with *K6A* mutations, with reductions in Children's Dermatology Life Quality Index (CDLQI), hyperkeratosis, and blistering (Abdollahimajd et al, 2019; Frommherz and Has, 2020; Sharma et al, 2022). However, results in adult patients using statins have been mixed, with some anecdotally experiencing no change (Theocharopoulos and O'Toole, 2019). This could be because statins have different potencies in 3-hydroxy-3-methylglutaryl coenzyme A inhibition; for instance, rosuvastatin is more potent than simvastatin or atorvastatin in this regard. Statins may be more beneficial for pediatric patients, who generally experience less plantar pain than adults. However, potential benefits should be balanced with common side effects of myalgia as well as the potential for long-term risks, including diabetes (Ruscica et al, 2023).

Botulinum toxin

To our knowledge, >20 patients with PC have been treated with plantar injections of botulinum toxin (BTx) with marked improvement in pain and functionality in most cases and varying degrees of impact on callosities. A protocol has been published for clinical use describing good outcomes in 5 patients with PC (Koren et al, 2020). An ultrasound-guided nerve block was performed by an anesthesiologist before the BTx injections were performed, and a course of injections every 100 days was recommended, suggesting that this treatment is only suitable in healthcare systems that will provide appropriate resources for the procedure.

Several mechanisms have been suggested that underlie the beneficial effect of BTx in PC. First, BTx prevents fluid

accumulation within blisters located underneath the calluses of patients with PC (Swartling et al, 2010). Second, BTx may block neurotransmitter release by type C fibers and thereby reduce pain (Gazerani et al, 2009). Third, BTx may inhibit vasodilation and neurogenic inflammation (Swartling et al, 2010).

Capsaicin

Capsaicin is a TRPV1 agonist that induces topical analgesia by exciting and then desensitizing sensory nerves. Cutaneous 8% capsaicin patches (Qutenza 179 mg) have been used for compassionate treatment of painful plantar keratoderma in an adult patient with severe PC (O'Toole et al, 2014). Two applications were made 10 months apart on both soles. Tolerance was acceptable, and pain improved by 20% (first application) and 10% (second application) for 4 months. However, there was little or no effect on the patient's QOL as measured by Dermatology Life Quality Index (DLQI) and pruritus; painful attacks along with walking distance remained unchanged. Overall, this treatment was relatively well-tolerated but had modest clinical benefit.

Erlotinib and EGFR/TRPV3 pathway

The EGFR pathway was recently shown to be overactive in plantar skin lesions of 4 patients with severe PC. TRPV3 forms a functional complex with EGFR and is overexpressed in PC (Basset et al, 2023). Expression of TRPV3, EGFR ligands, and EGFRs was increased significantly, and EGFR downstream pathways, including mTOR and MAPK, showed enhanced activation. In 3 patients, pharmacological inhibition of EGFR with oral erlotinib was well-tolerated and led to significant reductions in pain and plantar and nail hyperkeratosis, resulting in marked improvement in patients' QOL, as measured by DLQI score, and activity/pain, as measured by the Foot Function Index (Basset et al, 2023). Oral erlotinib was administered to 2 additional patients with PC, with a reduction in pain and improvement in QOL (Greco et al, 2022). Erlotinib represents a promising treatment for PC (Coulombe and Orosco, 2023), although risk—benefit must be considered, including side effects and likely improvement. Placebo-controlled trials are required. Of note, a phase 1B open-label trial of a topical application of a specific and potent TRPV3 antagonist is in progress (see https://classic.clinicaltrials.gov/ct2/show/NCT05435638).

Clearly, these various approaches, despite showing promising results, should be evaluated formally in controlled studies. The design of these studies should take into consideration issues that have emerged during the course of the various clinical trials reviewed earlier, including a high placebo effect, the importance of practical and clinically relevant efficacy endpoints, and the challenges of topical drug delivery. Of note, the fact that most of the suggested therapies for PC involve different mechanisms suggests that the possibility of combined treatment modalities should be considered.

DEVELOPING NOVEL REGULAR AND TECHNOLOGY-BASED OUTCOME MEASURES

Clinically relevant, quantifiable, and reliable outcome measures are critical to the successful evaluation of new therapies for PC.

Pain

Intensity of pain at rest, standing, and ambulation is positively correlated with PC severity, and pain has a significant impact on QOL and psychosocial well-being among patients with PC. Apart from the role of physical activity in driving pain levels, pain also varies depending on changes in humidity and temperature as well as a patient's physiological, mental, and health status (Smith et al, 2006). The ability to accurately quantify pain reduction in response to treatment is critical in assessing the efficacy of management and therapeutic strategies that target this aspect of PC. However, challenges with this outcome stem from the qualitative/subjective nature of pain and the accompanying self-reported measures that are often used to measure it. Although pain evaluation presents difficulties in the research setting, several validated instruments have been developed, including the Patient Reported Outcomes Measurement Information System (PROMIS) tools for pain intensity and pain interference from the U.S. National Institutes of Health (Cook et al, 2013). Concurrent symptoms stemming from chronic pain, including fatigue, sleep disruption, psychological stress, and effect on social (eg, peer relationships) and mental health (eg, stigma, anxiety and depression) can also be assessed using adult or pediatric (and proxy) PROMIS tools that focus on these metrics. In addition, computerized adaptive tests can be incorporated to minimize questions that need to be completed by participants to improve response rate (Wainer and Dorans, 2000). Electronic diaries are used frequently in clinical trials to capture self-reported pain information. However, the quality and completeness of data obtained with these tools can be affected by the level of protocol compliance and recall bias. As a result, there has been growing interest in using automated technology and data analytics to capture pain-related biometrics, such as pulse, blood pressure, and respiration rate. This stems from the observation that increased pain can be associated with corresponding increases in blood pressure and pulse rate (Johnson et al, 2019). Continuous data capture with wearable sensors may therefore be a strategy to mitigate or eliminate diary-related compliance and recall bias issues in PC research. However, additional work needs to be done to correlate these measures with patient self-reported pain and level of activity, medication administration, and overall state of health. This foundational work is necessary to ensure that if these measures are used in clinical trials, they are valid, accurate, and clinically meaningful in the PC setting.

Although accurate measure of pain intensity is important, it should not replace an assessment of QOL. Commonly used QOL tools in dermatology, DLQI and CDLQI, can compare the impact of PC with that of other skin disorders (Basra et al, 2008). A validated PC-specific QOL tool has also been developed (Abbas et al, 2015).

Ambulation

A pivotal functional outcome measure for PC trials is ambulation. Existing tools such as the 6-minute walk and standing pain are not suitable for PC trials because they are assessed at a single point in time. As a result, these measures do not address PC-specific, daily fluctuations in function that need to be assessed in a clinical trial aiming to improve foot

function. To address these challenges, wearable devices that allow continuous measurement of gait and movement might be a better choice for assessing foot function and ambulation in the PC setting, and these outcomes should be incorporated into therapeutic trial designs. However, many fitness devices currently on the market have not been validated for research purposes, whereas others are not suitable for use in a functional assessment of PC. It is for this reason that research focused on validation and/or development of wearable technologies, especially technology that captures gait that can be used in robust trials of physical function in the PC setting, will be of tremendous long-term therapeutic benefit for patients with PC.

A validated PC-specific functional measurement, PGA-AD, is a daily patient-reported outcome that assesses the difficulty in carrying out activities on their feet. In the VAPAUS trial, there was no difference between placebo and treatment groups using this patient-reported outcome measure (see https://palvellatx.com/2023/07/20/palvella-therapeutics-reports-topline-results-from-pivotal-phase-3-vapaus-study-of-qtorin-rapamycin-pachyonychia-congenita/).

Additional outcomes

Imaging techniques such as high-frequency ultrasound or optical tomography may be used to objectively ascertain plantar skin and nail thickness. Biomarkers are not yet available but should be identified to facilitate follow-up of patients under treatment. Finally, qualitative measures should also be considered (Pascual et al, 2023).

SUMMARY

By identifying and promoting a clear set of PC research priorities, the PC Research Agenda can be a shared roadmap for funding organizations, new and established investigators, patients, families, and advocacy organizations as these stakeholders work together toward improved outcomes for all people affected by PC.

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CONFLICT OF INTEREST

ASP served as an investigator (payment to institution) for AbbVie, Applied Pharma Research, Dermavant, Eli Lilly, Incyte, Janssen, Krystal, Regeneron, and UCB; as a consultant with honorarium for Aegerion Pharma, Azitra, BioCryst, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Johnson & Johnson, Krystal, LEO Pharma, Novartis, Primus, Regeneron, Sanofi/Genzyme, Seanergy, TWI Biotechnology, and UCB; and in Data Safety Monitoring Boards for AbbVie, Abeona, Galderma, and InMed. BS is the Chief Scientific Officer of and a shareholder in Palvella Therapeutics. EAOT received research funding from Palvella Therapeutics, Kamari Pharma, Leo Foundation, and Unilever (unrelated to PC); is/was chief investigator for Kamari Pharma and Palvella Therapeutics and a consultant for Kamari Pharma, Palvella Therapeutics, and Azitra (funding was received by university/hospital only); is on the steering group of Pachyonychia Project. ES has received consultation fees from SolGel, and his department has received financial support from Pierre Fabre, Kamari, Biomx, Amryt, and Medison Pharma. JT served as investigator for Arcutis, Castle Creek, Eli Lilly, Janssen, LeoPharm, Novartis, Palvella Therapeutics, Pfizer, Regeneron, Syneos, Timber Pharmaceuticals, and Twi Biotech and as consultant for Abeona, AFT, Amryt, AUCTA, Biocryst, BridgeBio, Castle Creek, Coterie, GLG, Guide Point, Innova, Kamari, KrystalBio, LeoPharm, Lifemax, Menlo Therapeutics, Mitsubishi, NobelPharm, Novartis, Palvella Therapeutics, Pfizer, Pierre Fabre, Regeneron, Rarebase, Syneos, Timber Pharmaceuticals, Topicals, and Twi Biotech. MdB's position is funded by Chang Zuckerberg Initiative and the Leo Foundation. MJC has previously received access to biopsy specimens and letters of support for grant proposals from the Pachyonychia Congenita Project. RLK has ownership in Ayni Therapeutics. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: EAOT, DPK, MC, MdB, DH, RPH, AH, RK, EBL, ASP, JS, BS, JT, MT, PAC, ES; Data Curation: EAOT, DPK, MC, MdB, DH, RPH, AH, RK, EBL, ASP, JS, BS, JT, MT, PAC, ES; Project Administration: JS; Writing – Original Draft Preparation: EAOT, DPK, JS, PAC, ES; Writing – Review and Editing: EAOT, DPK, MC, MdB, DH, RPH, AH, RK, EBL, ASP, JS, BS, JT, MT, PAC, ES

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