Pachyonychia Congenita Project
Fighting for a cure. Connecting & helping patients. Empowering research.
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2018 ANNUAL REPORT FOR PACHYONYCHIA CONGENITA PROJECT

ABOUT PACHYONYCHIA CONGENITA

Pachyonychia Congenita (PC) is an ultra-rare, genetic, autosomal dominant skin disorder. PC is caused by a mutation in any one of five keratin genes: *KRT6A, KRT6B, KRT6C, KRT16*, *KRT17*. Over 116 specific mutations have now been identified. The gene and mutation affect the condition for each PC patient.

THE MOST COMMON FEATURES OF PC INCLUDE:

1. **Painful calluses and blisters** on the soles of the feet (focal plantar hyperkeratosis). Pain is one of the distinct characteristics of PC. Blisters are found under the callus in PC patients. Calluses may also form on the palms of the hands (palmar hyperkeratosis).
2. **Thickened Nails** (hypertrophic nail dystrophy) although not all nails are affected in all patients with PC.
3. **Cysts** of various types (including steatocystoma and pilosebaceous cysts). In some forms of PC, this is the most dominant, painful and problematic characteristic.
4. **Follicular hyperkeratosis** (FHK or bumps around hairs at friction sites such as waist, hips, knees, elbows). Most common in children and lessens after teenage years.
5. **Leukokeratosis of the oral mucosa** (white film on tongue and inside cheeks). This is not painful, but is often misdiagnosed as thrush or as leukoplakia.

ABOUT PC PROJECT

PC Project was founded in 2003 as a 501(c)3 public charity in the USA. PC Project staff work together with medical professionals, scientists, PC patients and family members to make a difference for those suffering with Pachyonychia Congenita. PC Project makes effective use of the limited budget to serve patients in over 60 countries around the world and to facilitate research.

MISSION STATEMENT:

Fighting for a cure. Connecting and Helping Patients. Empowering research.

To find effective treatments for those suffering from Pachyonychia Congenita, PC Project actively sponsors two major efforts:

1. The International Pachyonychia Congenita Research Registry (IPCRR).
    - Free genetic testing for those diagnosed with PC or similar disorders.
    - Annual Patient Support Meetings and other patient support services.
2. The International Pachyonychia Congenita Consortium (IPCC).
    - Research grants, clinical studies and clinical trials.
    - Annual Scientific meetings.
    - Publications of PC data and research.

SUMMARY OF 2018 PROGRAMS AND SERVICES

INTERNATIONAL PACHYONYCHIA CONGENTIA RESEARCH REGISTRY (IPCRR)

The IPCRR patient registry is the key to all patient services. Through the registry, each patient has an opportunity to contribute data about their condition and to receive important services. Isolation is a major burden for those with rare diseases and through the IPCRR, patients can connect with other patients and specialists who understand PC. Those in the IPCRR are offered free genetic testing. The testing is performed using a saliva collection kit provided by PC Project at no cost to patients. Physician consultations, support by PC advocates, assistance with applications for disability or work accommodations and other services are provided for those in the IPCRR.

There were 1982 patients in the IPCRR at the end of 2018 with 864 of those being genetically confirmed with PC. The following statistics were noted for the IPCRR in 2018:

- 115 patients contacted PC Project for the first time
- 74 saliva kits were sent for genetic testing
- 49 individuals received genetic testing results

PATIENT SUPPORT MEETING

London, England. PC Project held its annual Patient Support Meeting.
On October 19-21, 2018, at the Park Inn by Radisson London Heathrow, 140 Pachyonychia Congenita patients, caregivers, scientists, clinicians and representatives from industry partner, Palvella Therapeutics, gathered to share knowledge, encouragement and love. Many individuals made this PC Patient Support Meeting a success, including local organizers, Kate Fairbrother and Julie Peconi as well as European PC Patient Advocates Tom Baker, Kieren Eyles, Philip Gard, Melanie Hettler, Pamela Ibáñez Triguero, and Katri-Anna Lehto,

This Patient Support Meeting was sponsored by PC Project and from grants by Palvella Therapeutics and Novartis Pharmaceuticals UK Limited.

PC PROJECT PUBLICATIONS

PC NewsBrief. Each month PC Project sends out its monthly newsletter, the PC NewsBrief, to over 1000 recipients. The newsletter contains articles about meetings, clinical studies and trials, photos of PC Patients, updates on PC Project and tips for patients and family members who care for someone with Pachyonychia Congenita.

IPCC Newsletter. Dr. Edel O'Toole became the editor for this publication in January 2018. All members of the International Pachyonychia Congenita Consortium (IPCC) receive the quarterly published IPCC News Brief. The newsletter includes updates on clinical studies and trials, recent publications, genetic testing information, annual meeting information and updates on the International Pachyonychia Congenita Research Registry (IPCRR)

INTERNATIONAL PC CONSORTIUM (IPCC)

The IPCC connects physicians and scientists with an interest in keratin disorders who agree to work collaboratively in areas that relate to progress for PC research and therapies. There are several hundred members of the IPCC and about 50 who are actively exchanging and assisting with research.

IPCC STRATEGIC PLANNING SESSION

The 15th IPCC meeting was a special strategic planning session with PC Project's Medical and Scientific Advisory Board Members and invited guests in Orlando, Florida, at Rosen Shingle Creek, before the official IID (International Investigative Dermatology) conference. This planning meeting was to discuss ways to move PC Project forward. In attendance from the IPCC: Eli Sprecher, Pierre Coulombe, David Hansen, Roger Kaspar, Wes Kaupinen, Birgit Lane, Edel O'Toole, Dennis Roop, Frances Smith (remotely). From PC Project: Jack Padovano, David Schwartz, Janice Schwartz, Mary Schwartz.

IPCC GENETICS TEAM AND IPCC STEERING COMMITTEE

PC Project meets with its Genetics Team once a month via web meetings in order to guide genetic testing, help with 'unresolved cases' and review cases who join the International PC Research Registry (IPCRR). During the monthly web meeting, cases are reviewed to try to establish a genetic testing target. If the target is not Pachyonychia Congenita, every effort is made to find a resource for testing for the patient. The members of our Genetics Team volunteer their time and are vital to the mission of PC Project. Once cases are reviewed, the committee then discusses and advises PC Project concerning goals and other actions concerning research, patients and various subject in which PC Project needs guidance.

Members include:
Philip David Gard, MD
C. David Hansen, MD
Edel A. O'Toole, MD, PhD, FRCPI, FRCP
Frances J.D. Smith, PhD (Chair)
Eli Sprecher, MD, PhD
Alain Hovnanian, MD, PhD

PC PROJECT KEY ACCOMPLISHMENTS IN 2018

ETERNALLY-LED PATIENT FOCUSED DRUG DEVELOPMENT MEETING WITH FDA OFFICIALS

With over 100 PC patients participating in person or via a live webcast, PC patients successfully communicated to key FDA officials the impact of PC on their lives, how they manage their PC and what a meaningful treatment will look like. Patient input and experiences were expressed through panel presentations, live polling and audience participation. Patients who attended remotely submitted their answers to open-ended questions online.

All answers were incorporated into the official Voice of the Patient Report for FDA. An impressive number of FDA officials attended the meeting: 24 in person; 18 via the webcast. This was a record amount of FDA officials to attend an EL-PFDD meeting.

PC Project submitted a "Voice of the Patient Report" to FDA from the Externally-led Patient Focused Drug Development (EL-PFDD) Meeting. This report is on the FDA website as an official record which captures the definitive voices of real patients about the impact of PC on their lives.

Why was this meeting so important for PC patients, FDA officials, industry partners, scientists, and clinicians?

1) FDA officials who listened at the meeting will make critical decisions regarding future treatments for PC.

2) While FDA officials will seek out medical literature and input from clinical experts, most FDA reviewers will have little if any personal knowledge of PC from their time in practice. Neither the published literature, nor the clinical expertise can fully capture the experiences of what patients experience day-to-day. It is only patients (and their caregivers) who have that knowledge to share.

3) There isn't always unity between patients and clinicians on what the most pressing unmet medical needs are, especially when a disease is as ultra-rare as PC. PC patients were able to express to FDA officials what those unmet needs are in a compelling way. The Voice of the Patient Report from this meeting will be used by FDA as a standard for PC.

4) FDA needs to know it is designing clinical trials that will generate empirical evidence on outcomes that are important to PCers. What a patient describes as the greatest burdens of a condition can lead to the appropriate selection of outcome (baseline) measures. Knowing about the day-today impact of PC can help determine when and how to implement outcome measures in clinical trials.

5) Patient input at the meeting also focused on patient preferences for future treatments. FDA recognizes that it is a judgement call as to whether the benefits of a drug outweigh the risks when it is making an approval decision. Thus, FDA heard the preferences of patients about future therapies; they can assign appropriate weight to those things that are most important to patients when balancing those benefits against the risks of a product.

6) Finally, FDA saw real patients, with real pain and challenges. FDA officials have learned not only about PC, but that PC is a disease that needs effective treatments to reduce or eliminate the debilitating, painful burdens PCers live with every single day.

PC Project appreciates the IPCC members who were able to attend the meeting in person – Drs. Anna Bruckner (who gave the PC clinical overview), C. David Hansen, Roger Kaspar, Sancy Leachman and Joyce Teng. PC Project also appreciates James Valentine (consultant and moderator) and the support of its industry partner, Palvella, including CEO Wes Kaupinen and members the Palvella team.

TOPICAL RAPATANE CLINICAL TRIAL

PC Project and Palvella continued throughout 2018 to work closely over the last several months to prepare for the imminent initiation of the Phase 2/3 study evaluating PTX-022 (novel, high strength topical rapamycin, optimized for dermal targeting) for the treatment of PC. Significant progress was made in 2018, the most important of which was: i) The selection of a final formulation to be evaluated in the Phase 2/3 clinical study; ii) Decisions around which efficacy endpoints to prioritize for the study. Notably, the final formulation was architected specifically for the PC patient population, and it was selected after a rigorous testing program that included more than 20 prototype formulations evaluated by Palvella and their formulation partner MedPharm, a leading global topical formulation development company based in London, UK.

With regards to efficacy endpoints, hundreds of PC patients willingly participated in qualitative and quantitative surveys to help narrow to specific efficacy endpoints. PC is truly a condition where the patients are the experts in the disease, and hence, the 'voice of the patient' will play a central role in the Phase 2/3 study. In addition to the tremendous response from PC patients, a Global Pachyonychia Congenita Working Group comprised of clinicians with expertise in PC as well as rare disease regulatory experts was assembled more than 16 months before, and that group worked diligently to iteratively narrow to efficacy endpoints for the study.

In addition, November 12, 2018, Palvella announced FDA granted Fast Track Designation for the advancement of PTX-022 (novel, high strength rapamycin topical formulation, optimized for dermal targeting) for the treatment of PC.

Here is a press release that includes additional information about the progress of the clinical trial:

FIRST-EVER PHASE 2/3 CLINICAL STUDY IN PACHYONYCHIA CONGENITA TO COMMENCE IN EARLY 2019 By: Wes Kaupinen, CEO, Palvella Therapeutics On December 18th, Palvella Therapeutics issued a press release highlighting the receipt of a $10 million investment from Ligand Pharmaceuticals to support the Phase 2/3 study of PTX-022 (QTORIN™ rapamycin formulation) for the treatment of Pachyonychia Congenita. Ligand Pharmaceuticals is a publicly traded company that has a track record in partnering with leading biopharmaceutical companies to develop some of the world's most important medicines. The 2018 represents a year of noteworthy progress for PC Project and Palvella Therapeutics, with the following milestones achieved:

- The historic FDA patient-focused drug development meeting on PC where PC patients courageously shared their personal stories of living with PC with 42 FDA officials
- The publication in Clinical and Experimental Dermatology by Dr. Joyce Teng and colleagues reporting two PC patients treated with topical rapamycin cream who experienced rapid improvement of pain and ability to ambulate
- FDA's granting a Fast Track Designation which recognizes PC as a serious disease with an unmet medical need
- Ligand's investment of $10 million which will accelerate the Phase 2/3 study of PTX-022 in PC 2019 promises to be an exciting year with the commencement of the Phase 2/3 clinical study which will initially be focused at several sites in the US. Sincere thanks to all who have contributed over many years to the advancement of this program.

PC AWARENESS MONTH

During the month of June 2018, PC Project encouraged its worldwide community to participate in PC Awareness Month. During this month, PC Project executed The PC Project Giving Challenge in order to obtain monthly donors whom we call "PC Love Builders". This campaign resulted in 66 people donating to PC Project. We welcomed 53 monthly sustaining donors to the PC LOVE BUILDERS family and received 13 one-time donations.

GIVING TUESDAY

A PC awareness and fundraising campaign was initiated and executed via email and social media worldwide on November 27, 2018 through the greater Giving Tuesday campaign. With the help of over 350 donors, PC Project surpassed its Giving Tuesday goal and raised more than $90,000 for PC patients. This amount was matched totaling over $160,000 for PC patient services and research. The support is proof that combined efforts, big or small, equal impressive results.

MEETINGS ATTENDED IN 2018 FOR LEARNING AND PROMOTING PC

Pediatric Society of Investigative Dermatology – July Lake Tahoe

PC Project attended and participated with the Society for Pediatric Dermatology (SPD) at the annual meeting July 12-14, 2018 at Lake Tahoe. As the only patient advocacy group to be invited, this was a not-to-be-missed opportunity for PC Project to network and raise awareness among the 430 attendees.

Dr. Eulalia Baselga, the director of the Pediatric Dermatology unit at Hospital de la Santa Creu in Spain, who has referred patients to PC Project and who attended the 2016 Spain and 2016 Edinburgh Patient Support Meetings, shared her positive experiences from attending PC Patient Support Meetings.

Dr. Tracy Funk, Assistant Professor, Dermatology and Pediatrics at Oregon Health & Science University, who works with Dr. Sancy Leachman who was influential in PC Project's creation and a founding member of the International PC Consorium (IPCC), gave an informative 30- minute presentation called, "Update on Pachyonychia Congenita." Dr. Funk also encouraged scientists and clinicians to learn more from PC Project.

PeDRA Annual Meeting – October 2018 PC Project was one of three patient advocacy organizations invited to present at dinner session at the 2018 PeDRA Annual Meeting in Colorado, October 25-27, 2018. The session was focused on the value of collaborations between patient advocacy groups and industry. Holly Evans, PC Project Patient Support Officer, presented the pathways PC Project has taken to help develop effective endpoints for clinical trials for Pachyonychia Congenita. This process has included patient focus groups and a number of patient surveys. Working with patient groups helps drug developers understand what kind of treatment is meaningful to patients. Working together to find effective ways to measure the efficacy of a drug is critical for both industry and patient advocacy groups.

RESEARCH ARTICLES PUBLISHED

During 2018, PC Project and IPCC Members collaborated in publishing numerous research articles (https://www.pachyonychia.org/research-articles/) in leading journals including:

Title: Painful Callosities in a young boy
Journal: Pediatr Dermatol
Authors: Arake Zanatta D, Taniguchi Abagge K, Franca Souza Gomes Vial I
Volume: 35, Issue: 4, Pages: 509-510

Title: A recurrent mutation in the KRT17 gene responsible for severe steatocystoma multiplex in a large Chinese family.
Journal: Clin Exp Dermatol
Authors: Wang J, Li J, Li X, Lei D, Xiao W, Li Z, Zhang S, Li M
Volume: 43, Issue: 2, Pages: 205-208

Title: Striate palmoplantar keratoderma resulting from a missense mutation in DSG1
Journal: Br J Dermatol
Authors: Vodo D, O'Toole EA, Malchin N, Lahav A, Adir N, Sarig O, Green KJ, Smith FJD, Sprecher E
Volume: 179, Issue: 3, Pages: 755-757

Title: Novel treatment of painful plantar keratoderma in pachyonychia congenita using topical sirolimus.

Journal: Clin Exp Dermatol
Authors: Teng JMC, Bartholomew FB, Patel V, Sun G
Volume: 43, Issue: 8, Pages: 968-971

Title: Skin fragility, woolly hair syndrome with a desmoplakin mutation - a case from India.
Journal: Int J Dermatol
Authors: Peter DCV, Thomas M, Wilson NJ, Smith FJD
Volume: 57, Issue: 9, Pages: e73-e75

Title: Nociceptin/orphanin FQ opioid peptide-receptor expression in pachyonychia congenita.
Journal: J Peripher Nerv Syst
Authors: Pan B, Schroder W, Jostock R, Schwartz M, Rosson G, Polydefkis M
Volume: 23, Issue: 4, Pages: 241-248

Title: A novel APC mutation identified in a large Chinese family with familial adenomatous polyposis and a brief literature review
Journal: Mol Med Rep
Authors: Pang M, Liu Y, Hou X, Yang J, He X, Hou N, Liu P, Liang L, Fu J, Wang K, Ye Z, Gong B
Volume: 18, Issue: 2, Pages: 1423-1432

Title: Plantar pain in pachyonychia congenita
Journal: Br J Dermatol
Authors: Krupiczojc MA, O'Toole EA
Volume: 179, Issue: 1, Pages: 11-12

Title: The non-neuronal and nonmuscular effects of botulinum toxin: an opportunity for a deadly molecule to treat disease in the skin and beyond.
Journal: Br J Dermatol
Authors: Grando SA, Zachary CB.
Volume: 178, Issue: 5, Pages: 1011-1019

Title: Facial cystic lesions and onychodystrophy
Journal: Pediatr Dermatol
Authors: Sabogal Gomez MV, Gozalez V, Martin JM
Volume: 35, Issue: 4, Pages: 517-518

Title: Pachyonychia congenita: a case report of a successful treatment with rosuvastatin in a patient with a KRT6A mutation
Journal: British Journal of Dermatology
Authors: Abdollahimajd F, Rajabi F, Shahidi-Dadras M, Saket S, Youssefian L, Vahidnezhad H, Uitto J.

Title: Pachyonychia Congenita (updated 2018)

Journal: Gene Reviews
Authors: FJD Smith, CD Hansen, PR Hull, RL Kaspar, WHI McLean, E O'Toole, E Sprecher

Title: The keratin 16 null phenotype is modestly impacted by genetic strain background in mice.
Journal: Exp Dermatol.
Authors: Abagail Zieman and Pierre A. Coulombe

Title: Striate palmoplantar keratoderma resulting from a missense mutation in DSG1
Journal: Br J Dermatol.
Authors: D. Vodo, E.A. O'Toole, N. Malchin, A. Lahav, N. Adir, O. Sarig, K. Green, F. J.D. Smith, E. Sprecher

Title: Sex Matters: Interfering with the Oxidative Stress Response in Pachyonychia Congenita
Journal: J Invest Dermatol.
Authors: RE Leube, N Schwarz
Volume: 138, Issue: 5, Pages: 1019-1022

Title: Genetic variants in pachyonychia congenita: associated keratins increase susceptibility to tooth decay
Journal: PLoS Genet
Authors: O Duverger, JC Carlson, CM Karacz, ME Schwartz, MA Cross, ML Marazita, JR Shaffer, MI Morasso
Volume: 14, Issue: 1,

Title: Sexual Dimorphism in Response to an NRF2 Inducer in a Model for Pachyonychia Congenita.
Journal: J Invest Dermatol
Authors: Michelle L. Kerns, Jill M.C. Hakim, Abigail Zieman, Rosemary G. Lu, and Pierre A. Coulombe
Volume: 138, Issue: 5, Pages: 1094-1100

Title: The keratin 16 null phenotype is modestly impacted by genetic strain background in mice.
Journal: Exp Dermatol
Authors: Abigail Zieman and Pierre A. Coulombe

2018 INCOME AND EXPENSE REPORT FROM 990 TAX RETURN

Total 2018 Income	**$ 843,672**	[Page 9, Line 12a]
Contributions	$ 800,723	[Page 9, Line 1f]
Fundraising Events	$ 0	[Page 9, Line 1c $0 plus Line 8c $0]
Investment Income	$ 39,054	[Page 9, Line 3]
Investment Gain/Loss	$ 3,185	[Page 9, Line 7da]

2018 Total Expenses	**$ 375,828**	[Page 10, Line 25, Col A]
Program Expenses	$ 315,941	[Page 10, Line 25, Col B]
General Expenses	$ 29,383	[Page 10, Line 25, Col C]
Fundraising Expenses	$ 30,504	[Page 10, Line 25, Col D]
Expenses over/under income	**$ 467,844**	[Page 1, Line 19, Current year]
Net Assets 2018 Total	**$1,799,449**	[Page 1, Line 22, Current year]

DONATED SERVICES AND VOLUNTEERS

In 2018 PC Project was greatly benefited by the help of volunteers. There were also many hours donated by physicians, scientists and professionals who provided their services and expertise to PC Project.

	Total Hours
DONATED SERVICES	
Physicians and Scientists	
IPCRR patient consultations	50
IPCC Genetics Team & Steering Meeting	70
IPCC Meeting	400
Patient Support Meeting	200
Program services & events	520
Program services (ED salary)	2080

PC PROJECT STAFF

Janice Schwartz, Executive Director
Holly A. Evans, Patient Support Officer
Frances J.D. Smith, Chief Geneticist
Joanne Udy, Bookkeeper

PC PROJECT BOARD OF TRUSTEES

Board of Trustee Members at the end of the year were:

Jack Padovano, Chair
Barbara Feinstein, Secretary
C. David Hansen, MD, Medical Advisor
Jason Hunter, Treasurer
James Rittle, Trustee
Janice Schwartz, Trustee

Board of Trustee meetings in 2018 were held on April 5, August 10 and November 9.