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Prevalence of Diagnosed/Highly Symptomatic Pachyonychia Congenita (PC) Patients Managed Annually by US Dermatologists-National Real World Occurrence (RWO) Physician Study

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Abstract

Background: Pachyonychia Congenita (PC) is a chronically debilitating and lifelong genetic disease that typically causes constant, disabling pain. PC appears to be rare, but its prevalence is unsubstantiated by large-scale epidemiologic studies. We conducted the first national prevalence study of a cohort of PC patients, those managed annually by US dermatologists.

Methods: Potential study participants were randomly selected from a national panel of patient-care dermatologists and invited to participate in a brief study of a patient condition that would be disclosed at the study website.

Results: Of the 423 dermatologists contacted, 400 participated, of whom 53% reported managing at least one PC patient during the past 12 months, an annual prevalence of 6.4/10,000 patients (extrapolated to 8,900 to 9,800 nationally), according to the study model.

Conclusions: Study findings indicate PC is likely to be far more prevalent than previous estimates in the literature and that the frequency and level of disability caused by pain-related symptoms may be under-recognized by the treating dermatologist. Additional research is needed to determine the extent to which PC diagnosis has been or could be genetically confirmed.

Keywords Pachyonychia Congenita (PC); Prevalence; Real World; Epidemiologic survey

Introduction

Pachyonychia congenita (PC) is a rare, chronically debilitating, and lifelong genetic disease in which severe plantar pain is the most debilitating feature and which causes many PC patients to rely on canes, crutches, wheelchairs or other ambulatory aids to reduce plantar pain from walking [1-3]. PC is thought to be rare, but its prevalence is unsubstantiated by large-scale epidemiologic studies. The prevalence of PC has been estimated at 5,000 to 10,000 cases worldwide (Figure 1). This value, however, is based on an order-of-magnitude estimate supplied in a personal communication more than a decade ago. No epidemiologic study was performed to generate this value [4].

In the absence of previous population-based studies, it is useful to note that a registry has been created by the Pachyonychia Congenita (PC) Project, a non-profit organization initially founded in 2003 that is dedicated to finding treatments and a cure for PC and connects patients, researchers, and physicians in nearly 60 countries to help those with PC [5]. The PC Project registry had accrued more than 2,000 patients globally as of April 2019 [6]. Though PC Project has made significant strides in advancing scientific research, the registry is -neither designed-nor resourced to achieve complete ascertainment of the prevalent population.

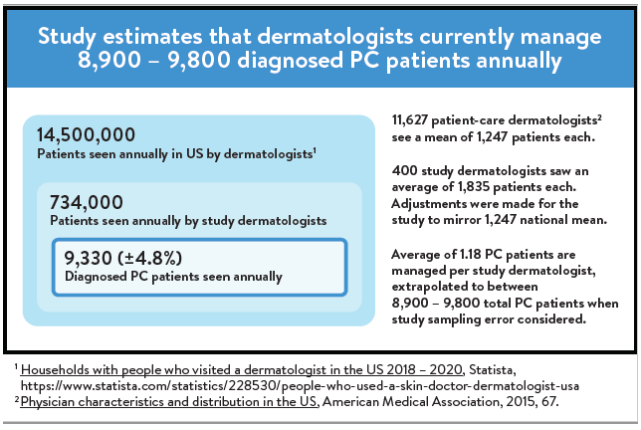


Figure 1: Dermatologist-managed PC: Current Estimated Studies.

Given the limitations of existing published data, the prevalence of PC remains an open question. This is the first study designed to estimate the national prevalence of a pachyonychia congenita cohort, specifically, the number of diagnosed PC patients managed annually by dermatologists in the United States.

Materials and Methods

We conducted a national, retrospective, observational survey of patient-care dermatologists in the United States to collect data on the extent to which patients diagnosed with PC are being managed for the condition. The basic approach was to:

- Obtain a representative sample of patient-care dermatologists (a key specialty that manages the target condition),
- Determine the proportion of dermatologists who manage PC,
- Determine the volume of PC patients each of these dermatologists, on average, manages annually and
- Extrapolate these findings to the national universe of dermatologists and the corresponding prevalence of their PC-managed patients.

This physician-based methodology and its variants have been successfully used to estimate the size of various patient cohorts on national and multi-national levels [7-9]. The study was conducted between August 10 and September 5, 2018.

Selection and description of participants

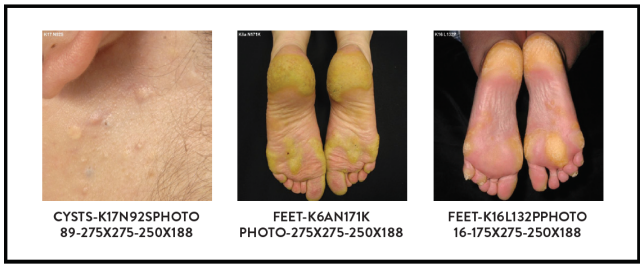
Potential study participants were randomly selected from a national master file of patient-care dermatologists developed and constantly updated by Medefield, a global physician research company. Selected dermatologists were sent an invitation electronically to participate in "a brief national study of a patient condition that would be disclosed at the study website." This procedure was used to minimize the loss of quantifiable responses from physicians who manage no PC patients and might self-select out of the study before being study qualified or disqualified, which could bias the resulting national prevalence estimates of our PC patient cohort. A total of 400 dermatologists accessed the study website. A study-eligible dermatologist was required to be actively managing the care of patients but not required to have ever managed a patient's PC. Of the 423 patient-care dermatologists invited to the study site, 400 participated in the study (94.6%).

To determine how well our sample of patient-care dermatologists matched the corresponding universe of dermatologists nationally, we compared the respective distributions by US Census Bureau regions. Table 1 reveals that our sample of dermatologists closely mirrors the corresponding geographic distribution of the national universe of dermatologists (Table 1).

Region	National (%)	Study (%)
Northeast	23%	23%
Midwest	18%	18%
South	33%	34%
West	26%	25%
National n = 11,627 dermatologists Study n = 400 dermatologists		

Table 1: Distributions of patient-care dermatologists in the US and study by US Census Bureau region.

After qualification for the study, dermatologists were informed that the purpose of our study was to understand the number of patients managed who are diagnosed or symptomatic with plantar keratodermas and thickened nails and were shown the patient examples pictured in Figures 1 and 2. Physicians were then asked to indicate the number of patients managed in the past 12 months "with plantar keratodermas and/or thickened nails" and the number "diagnosed with Pachyonychia Congenita (PC)" (Figures 2 and 3).



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https://www.pachyonychia.org/pc-images/

Figure 2: Images of PC symptoms displayed to study physicians.

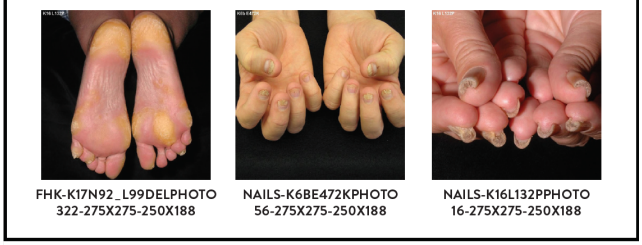

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Figure 3: Images of PC symptoms displayed to study physicians.

Statistical Analysis and Prevalence Model

We used descriptive statistics to examine physician demographic and patient- volume characteristics. Significant differences ($p < 0.05$) were evaluated using independent samples t-tests for comparison of the means of two independent groups on a continuous dependent variable and Chi-square test for homogeneity to determine if a difference exists between the binomial proportions of two independent groups on a dichotomous dependent variable. We also developed an

analytical model that provides an estimate of the total number of dermatologist-treated PC patients nationally. A step-by-step description of this model and resulting outputs are presented in the next section. Data were analyzed using IBM SPSS Statistics 23.

Results

Table 2 describes the practice characteristics of the study population, composed of 400 patient-care dermatologists. The mean self-estimated total number of unique patients reportedly managed by study physicians in past 12 months was 1,835 (SD 159.2) of whom the mean number reportedly diagnosed with plantar keratodermas and/or thickened nails was 46.8 (SD 44.5) and 70.1 (SD 75.4) for patients diagnosed with palmar keratodermas, follicular hyperkeratosis, or leukokeratosis that are unrelated to another known disease. About half of study physicians (53%) reported managing at least one PC-diagnosed patient in the past 12 months; two-thirds of these physicians (68%) reported managing only one or two PC patients (mean 1.18 SD 1.48). In addition to these currently managed PC patients, almost half of study physicians (45.8%) reported managing PC for an additional 1 to 8 PC patients in the past five years (Mean 1.8 SD 2.3).

N=400 dermatologists	
Variables (physician self-estimates)	
Number of total unique patients managed in past 12 months	
=< 1,000	10.00%
1,001 - 1,500	32.40%
1,501 - 1,700	31.50%
1,701 - 2,000	10.80%
=>2,001	15.30%
Mean	1,835
Median	1,700
Standard deviation	159.2
Number of unique patients managed in past 12 months who are diagnosed with plantar keratodermas and/or thickened nails	
=< 10	24.00%
Nov-25	19.30%
26 - 49	15.30%
50 - 99	25.40%
=> 100	16.00%
Mean	46.8
Median	32.5
Standard deviation	44.5
Number of unique patients managed in past 12 months managed for palmar keratodermas, follicular hyperkeratosis, or leukokeratosis which are unrelated to another known disease	
=<5	19.30%
Jun-25	21.00%
26 - 50	20.00%
51 - 150	24.70%
=>151	15.00%
Mean	70.1
Median	50
Standard deviation	75.4

Number of unique patients managed in past 12 months who are diagnosed with Pachyonychia Congenita (PC)	
0	47.00%
1	21.50%
2	14.80%
3	7.00%
4	3.30%
5	6.40%
Mean	1.18
Median	1
Standard deviation	1.48
Number of unique patients seen for PC in past 5 years in addition to those PC patients managed in past 12 months	
0	54.20%
1	2.80%
2	12.50%
3	9.00%
4	5.00%
5	7.50%
6	3.00%
7	2.70%
8	3.30%
Mean	1.76
Median	0
Standard deviation	2.34

Table 2: Practice characteristics of the study population.

Table 3 provides the distribution of physician-estimated symptoms observed in patients diagnosed with PC. The most frequently reported PC symptoms were thickened toenails (92%), thickened fingernails (90%), and calluses and blisters (76%).

N=400 dermatologists	
Variables (physician self-estimates)	
Thickened toenails	92.00%
Thickened fingernails	90.10%
Presence of calluses and blisters	75.90%
Plantar pain	68.90%
Difficulty performing activities on feet, including standing	62.30%
Ambulation impairment, including difficulty with walking	51.90%
Reliance upon ambulatory aids or alternative forms of mobility	24.50%

Neurovascular structures or cutaneous thromboses on feet	12.70%

Table 3: Symptoms observed in patients diagnosed with PC.

Figure 4 describes and presents the results of the 11-step dermatologist PC-managed prevalence model for the study cohort. According to model-derived estimates, US dermatologists manage PC for 9,330 PC patients annually (CI ±4.8%) or about 8,900 to 9,800 patients. The estimated prevalence of the dermatologist PC-managed cohort in the US is 6.4 PC patients per 10,000 patients managed.

Step	Description	Metric
1	Estimated number of total patients seen annually by all US dermatologists[1]	14,500,000
2	Number of patient-care dermatologists in the US[2]	11,627
3	Number of patients per dermatologist seen annually in the US (Step 1 / Step 2) (14,500,000 / 11,627)	1,247
4	Number of patient-care dermatologists in study (all full-time patient care)	400
5	Sum of all physician self-estimated total patients reportedly seen annually by dermatologists in study	734,000
6	Estimated number of study patients managed annually per dermatologist (Step 4 / Step 5) (734,000 / 400)	1,835
7	Adjustment needed for annual study physician total patient-load to mirror corresponding patient load of dermatologists nationally (Step 3 / Step 6) (1,247 / 1,835 = 0.68)	Multiply by .68
8	Mean number of physician self-estimated PC patients managed annually per study physician (SD 1.49)	1.18
9	Estimated number of PC patients managed annually in the US by all patient care dermatologists nationally (Step 8 x Step 2 x Step 7) (1.18 x 11,627 x .68)	9,330
10	Estimated range of PC patients managed annually by all patient care dermatologists nationally	8,900 – 9,800
11	Estimated prevalence of PC patients managed annually in the US by all patient care dermatologists (Step 9 / Step 1 / 10,000)	6.4 / 10,000 patients

[1] Households with people who visited a dermatologist in the US 2018 – 2020, Statista, https://www.statista.com/statistics/228530/people-who-used-a-skin-doctor-dermatologist-usa
[2] Physician characteristics and distribution in the US, American Medical Association, 2015.

Figure 4: Dermatologist-managed PC prevalence model.

Study physicians were asked, "Are you familiar with PC Project, a public US charity dedicated to patients with PC and providing free genetic testing?" Only 15.2% indicated awareness of PC Project, and only 40.8% of these physicians (9.0% of all physicians) expressed awareness that the organization offers free genetic testing to diagnose PC.

Discussion

Our study represents the first attempt using a nationally representative sample to estimate the prevalence of any pachyonychia congenita (PC) cohort in any country in the world. The prevalent population examined in this study is the cohort of PC-diagnosed patients managed annually by dermatologists in the United States.

We found that management of PC by dermatologists is more common than one might expect based on previously published PC prevalence estimates, none of which used a nationally representative epidemiology study. About half the dermatologists in our study (53%) reported managing PC for one or more patients during the past 12 months, representing 8,900 to 9,800 patients, according to the study analytical model (Figure 4).

Our study also raises the possibility that the level of disability caused by pain-related symptoms may be under-recognized by the treating dermatologist. Study physicians mentioned pain as a symptom for only 69% of their PC patients. By contrast, pain was almost universal among 101 livestream respondents who participated in an in-person or online PC survey conducted during a 2018 Food and Drug Administration (FDA) externally led patient-focused drug development (EL-PFDD) meeting: 91% indicated that they typically feel some level of pain with every step that they walk [2].

We also found that study dermatologists were about 58 times more likely to report managing a patient for palmar keratodermas, follicular hyperkeratosis, or leukokeratosis that are unrelated to another known disease (mean 70.1 SD 75.4) than for PC (mean 1.2 SD 1.5). Thus, dermatologists appear to manage many non PC-diagnosed patients who have prominent symptoms of PC.

It is important to note that the current study was not designed to estimate the total national prevalence of PC, but rather the prevalence of a particular, though important, subset. Using the model's best PC patient estimate (9,330) and the estimated number of total patients managed annually by dermatologists (14,500,000), the estimated prevalence is 6.4 PC patients per 10,000 total dermatologist-managed patients.

These estimates must be viewed in light of several potentially serious study limitations. Among the most important limitations is a possible "study-participation" effect. This is a positive-response bias that could be caused if a physician unfamiliar with PC until viewing the patient-symptom pictures and descriptions presented in the electronic survey instrument realized that some of his/her previously undiagnosed PC patients should have been diagnosed with this condition. PC-diagnosed prevalence over estimation would occur if any these newly PC-diagnosed patients were added by the physician to the number of study-reported PC-patients that he/she manages. Other potentially serious biases include:

- Surveys are subject to sampling error and other possible survey-related biases;
- Recall errors, which may be minimized because most physicians had only two or fewer PC patients to recall;
- Possible duplication of patients if the patients have seen more than one dermatologist for management of PC in the last 12 months; and
- Possible lack of genetic confirmation of PC. It is important that dermatologists be aware that the PC Project provides free genetic testing [10].

Unfortunately, only 15.2% of study dermatologists were aware of the PC Project and 40.2% of those physicians (9% of total physicians) were not aware that the organization offers free genetic testing. These findings indicate that efforts are needed by various dermatology-supporting organizations to raise awareness of PC Project's free genetic testing and other contributions to PC-related scientific research, including its support of the first large-scale, randomized, placebo-controlled study of an experimental therapy for PC. At present there is no FDA-approved treatment for PC. The FDA recently has acknowledged pachyonychia congenita as a serious condition and has granted fast-track designation for the advancement of PTX-022

(QTORIN rapamycin) for the treatment of PC [11]. Additional information on PC Project and its services to physicians, patients, scientists, and others is contained in the Supplemental section of this article.

Conclusion

In conclusion, this research underscores the need for future research to determine the proportion of patients diagnosed with PC whose diagnoses are recorded in the patients' medical records, the proportion whose diagnosis is genetically confirmed, and the proportion of non-PC-diagnosed patients with PC-like symptoms and who would likely be diagnosed with PC if they received genetic testing. Research also is needed to determine the total national prevalence of PC patients, which requires including physician specialties other than dermatology and deduplication of patients who see multiple physicians for management of PC.

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Conflict of Interest

Jack R. Gallagher is an employee of Clarity Pharma Research, LLC, Spartanburg, SC, a scientific research organization that conducted the study, and declares that he has no conflicts of interest. David Lapidus is an employee of LapidusData, Inc., and declares that he has no conflicts of interest. Kylee Heap is an employee of Clarity Pharma Research, LLC, Spartanburg, SC, and declares that she has no conflicts of interest. Susan Carroll is an employee of Clarity Pharma Research, LLC, Spartanburg, SC, and declares that she has no conflicts of interest.

Ethics Approval and Consent to Participate

This article is based on previously existing observational data, and the research did not involve any new interventional studies of human or animal subjects performed by any of the authors. This retrospective study used deidentified data, and no personally identifiable health information was collected. Such studies are exempt according to 45CFR46.101(b)(4): Existing Data & Specimens - No Identifiers.

Availability of Data and Materials

The dataset generated during and/or analyzed during the current study is available from the corresponding author on reasonable request.

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