Pachyonychia Congenita Project

15 March 2005

Use of Articles in the Pachyonychia Congenita Bibliography

The articles in the PC Bibliography may be restricted by copyright laws. These have been made available to you by PC Project for the exclusive use in teaching, scholarship or research regarding Pachyonychia Congenita.

To the best of our understanding, in supplying this material to you we have followed the guidelines of Sec 107 regarding fair use of copyright materials. That section reads as follows:

> Sec. 107. - Limitations on exclusive rights: Fair use
> Notwithstanding the provisions of sections 106 and 106A, the fair use of a copyrighted work, including such use by reproduction in copies or phonorecords or by any other means specified by that section, for purposes such as criticism, comment, news reporting, **teaching (including multiple copies for classroom use), scholarship, or research**, is not an infringement of copyright. In determining whether the use made of a work in any particular case is a fair use the factors to be considered shall include - (1) the purpose and character of the use, including whether such use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the amount and substantiality of the portion used in relation to the copyrighted work as a whole; and (4) the effect of the use upon the potential market for or value of the copyrighted work. The fact that a work is unpublished shall not itself bar a finding of fair use if such finding is made upon consideration of all the above factors.

We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

2386 East Heritage Way, Suite B, Salt Lake City, Utah 84109 USA
Phone +1-877-628-7300 • Email—Info@pachyonychia.org
www.pachyonychia.org

Significance of Patient Registries for Dermatological Disorders

Mark P. de Souza[1] and Vanessa Rangel Miller[2]

Patient registries for dermatological disorders are important sources of data for researchers, clinicians, and patients. The majority of registries are maintained by academic investigators with funding from federal agencies. However, these registries are fragmented and are maintained only as long as federal funding exists. Patient organizations and companies can serve as alternative sources of funding for registries.

Journal of Investigative Dermatology (2012) **132,** 1749–1752. doi:10.1038/jid.2012.168

Patient registries are databases containing personal, medical, social, and financial data reported by a healthcare professional or by a patient or caregiver. For rare disorders, registries provide important epidemiological data to researchers (e.g., incidence and prevalence, symptoms, and severity to characterize the disorder), healthcare professionals (e.g., standard of care, diagnosis and prognosis), and registry participants (e.g., research projects, clinical trials with potential treatments). Registries can support policy initiatives and advocacy, and they provide data that often lead to deeper engagement among patients, families, researchers, doctors, and others in the healthcare community.

Objectives of patient registries

There are several objectives of patient registries:

(1) Characterize and describe the experiences of affected individuals.
(2) Identify patients and treating physicians.
(3) Assist the development of clinical care guidelines and improvements in care quality and disease outcomes.
(4) Facilitate basic, translational, and clinical trials, including those testing new therapies.
(5) Encourage research, including genotype–phenotype correlations, and publication.
(6) Collect and store DNA and other biological/tissue samples from affected and unaffected family members.
(7) Collect post-marketing surveillance data for approved drugs.

Registries can capture data reported by healthcare professionals or by patients or their caregivers. The data may be collected in an anonymous manner or in an identified manner with necessary informed consent, data protection, and security measures compliant with current privacy and security regulations, e.g., the Health Insurance Portability and Accountability Act of 1996. De-identified data may be available to qualified researchers who analyze data from the registry in preparation of a research publication or clinical study. The capture of and access to data for analysis has greatly improved with the shift in data collection, storage, and controlled retrieval from cumbersome, paper-based registries to efficient web-based electronic databases.

Quality control, updates, and accessibility are critical

Quality control of the registry data is paramount, and many registries have dedicated nurses, curators, genetic counselors, or researchers who assist the principal investigator to ensure that data are complete and accurate. Although data collected by a healthcare professional tend to be more accurate than patient- or caregiver-reported data (Kehoe *et al.*, 1994), both types of data collection are important, especially for rare diseases, as there is often a paucity of information in the literature. Patients or caregivers with a rare disease are frequently highly motivated to contribute data to a registry and can provide first-hand information, e.g., the personal, social, and financial costs of a rare disease, that is not easily accessed by healthcare professionals or not generally reported in the literature (Rangel *et al.*, 2012). Registry curators review collected data and resolve inconsistent responses, a vital step in ensuring the accuracy of the data collected in patient-entered registries.

Recruitment of patients for clinical trials can often take a long period of time, especially for rare disorders. This can slow down the development of new therapies and increase development costs. An up-to-date registry can accelerate the process (Nurok *et al.*, 2010) and reduce the time and costs of reaching full recruitment, by targeted communication with prescreened patient participants and providing data to expedite study planning and feasibility assessments. To maintain the utility of registries as a tool to facilitate research over time, it is important that participants' profiles be regularly updated.

In the past, maintaining an up-to-date registry was a major responsibility of the Registry Coordinator or the Principal Investigator, accomplished during patient visits or via telephone. With web-based registries, the logistics of updating the registry are greatly facilitated. For example, automated emails can be sent by the online registry via the Registry Coordinator on a periodic (e.g., annual, quarterly, or other) basis to prompt participants to provide missing information and update critical data points. A regular update of participant profiles can often provide researchers with valuable longitudinal data, establish baselines and natural history for rare disorders, and facilitate cost-effectiveness comparisons of therapies once they are available.

Accessibility of data in a patient registry is critical to generating a better

[1]*Lotus Tissue Repair, Cambridge, Massachusetts, USA and* [2]*Patient Crossroads, Innolyst, San Mateo, California, USA*

Correspondence: Mark P. de Souza, Lotus Tissue Repair, 1 Mifflin Place, Suite 400, Cambridge, Massachusetts 02138, USA. E-mail: mark@lotustr.com

Epidermolysis Bullosa (EB) Registries: A Case Study

The US National EB Registry (NEBR) provided a wealth of clinical, laboratory, and epidemiological data on patients with all forms of EB (Fine *et al.*, 1999). This registry was funded by the National Institutes of Health (NIH) from 1986 to 2002. Unfortunately, this paper-based registry ceased operations despite the best efforts of the investigators and the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) of America, the EB patient association, to obtain funding to continue the pioneering research enabled by the NEBR.

As the NEBR ceased operations, individual EB centers in the United States have maintained their own EB patient registries, as do EB centers in the European Union, Japan, Chile, and Mexico. A group of European investigators recently launched a registry that collects phenotypic and genotypic information on dystrophic EB (DEB) patients described in the literature and unpublished data from investigators who have characterized DEB patients (van den Akker *et al.*, 2011). Genotypic and phenotypic data from DEB patients in other registries, e.g., the Australasian EB registry (Kho *et al.*, 2010), are being added to the European registry.

A US Clinical Research Consortium comprising ten EB centers in the United States recently launched a physician-reported registry for the clinical characterization of EB patients in the United States (http://dermatology.stanford.edu/gsdc/eb_clinic/trials/eb-ebcrc.html).

On 29 February 2012, DEBRA of America and DEBRA International launched EBCare (http://www.ebcare.org), an online registry with patient-reported data that will provide researchers with additional insights into EB symptoms from a patient's perspective while providing data on the financial, physical, emotional, and social burden of illness on patients and their families.

Information from the EB registries will help guide the design of new clinical studies, provide data on the quality of life of patients with EB, and help better quantify the burden of illness and the costs associated with EB treatment, which could help rationalize reimbursement of novel therapies for EB in today's budget-constrained environment.

understanding of a rare disorder. Unfortunately, many registries established by academic investigators are not readily accessible to patients or investigators outside the sponsoring investigator's facility, hospital, or university. Multiple registries for a single disease may emerge, and because no data collection standards exist investigators collect different data points using different methods and coding systems, squandering the potential value of a single well-controlled registry. Furthermore, owing to the expense of translation, registries are often available in only one language. For these reasons, the data collected for rare diseases tend to be fragmented, limiting pan-disorder analysis. Organizations such as Orphanet, NORD, and EURODIS, as well as the Office of Rare Diseases Research (ORDR, National Institutes of Health), are attempting to unify the existing, disparate registries for rare disorders, and, where none exist, to set up a single, broadly accessible registry for specific disorders. In addition, an information model and data standards have been proposed by the ORDR to aggregate patient registry data and support research across rare diseases (Office of Rare Diseases Research, 2012).

Greater cooperation among stakeholders needed to consolidate registries

Different stakeholders create and maintain patient registries for different reasons. In one survey of Orphanet, 95.3% of registries in Europe were sponsored by or hosted by academic institutions, 3.1% by companies, and 1.6% by patient organizations ($n = 514$ registries) (Orphanet, 2011). Although academic investigators may establish a registry for epidemiological research or clinical trial purposes, drug companies may set up a registry to comply with post-marketing surveillance requirements agreed upon with regulatory authorities. Patient or disease foundations may set up registries for advocacy, educational, or fundraising purposes.

Some countries, especially the Scandinavian countries, established national hospital registries several decades ago, and these registries are organized in a structured manner to provide access to administrative and clinical data. The Danish National Patient Register is probably the most comprehensive of these national registries (Lynge *et al.*, 2011).

Thus, for a single disease, there can be multiple registries organized by different academic institutions, patient organizations, federal agencies, or companies. For example, there are currently 29 patient registries for Duchenne Muscular Dystrophy in Europe listed on Orphanet, an online rare disease and orphan drug database (accessed April 4, 2012). Would it not be easier for patients, their caregivers, healthcare professionals, and researchers to have one centralized registry for DMD? Rare dermatologic diseases are not immune to registry proliferation because of their limited patient populations. Patient organizations, academic institutions, researchers, and companies could work together to set up a unified patient registry for each rare disorder.

Patient organizations, rare disease advocacy groups, and companies can provide funding for registries

There are a number of registries for dermatological disorders (Table 1). In the United States, the NIH has provided the funding for several patient registries in dermatology, including those for ichthyosis (1994–2004), alopecia areata (2000–2012), epidermolysis bullosa (1986–2002), and scleroderma (2001-current). Such government support was critical to providing much-needed epidemiological data for these disorders, especially for rare disease subtypes, and there have been several publications resulting from these registries. Unfortunately, it has been challenging for principal investigators, universities, and

Table 1 Selected patient registries in dermatological disorders

Disorder	Sponsor	Registry web site
Alopecia areata	National Alopecia Areata Foundation	http://www.mdanderson.org/education-and-research/departments-programs-and-labs/programs-centers-institutes/alopecia-areata-registry/index.html
Atopic dermatitis	National Institute of Allergy and Infectious Diseases	http://clinicaltrials.gov/ct2/show/NCT01494142
Cutaneous lupus	University of Texas Southwestern	http://www.utsouthwestern.edu/education/medical-school/departments/dermatology/research/cutaneous-lupus-registry
Ectodermal dysplasia	National Foundation for Ectodermal Dsyplasias, with funding from Edimer Pharmaceuticals	https://nfed.patientcrossroads.org/
Epidermolysis bullosa	Dystrophic Epidermolysis Bullosa Research Association funded by Lotus Tissue Repair	www.ebcare.org (patient-reported data)
	COL7 mutation database	http://www.deb-central.org/molgenis.do (physician-reported database of COL7A mutations)
Hereditary angioedema	Herediatry Angioedema Association, with funding from Dyax, CSL Behring, Shire, Viropharma	http://www.haea.org/get-involved/us-haea-scientific-registry
Icthyosis	Foundation for Ichthyosis and Related Skin Types	http://depts.washington.edu/ichreg/ichthyosis.registry/
Pachyonychia congenita	Pachyonychia Congenita Project	http://www.pachyonychia.org/
Pediatric eczema	Valeant Pharmaceuticals	https://enroll.thepeerprogram.org/followup/FollowupLogin.action
Psoriasis	Medical University, Graz	http://www.psoriasis-therapieregister.at
Scleroderma family registry and DNA repository at University of Texas	University of Texas, NIH	http://www.uth.tmc.edu/scleroderma_reg
Xeroderma pigmentosum	Xeroderma Pigmentosum Family Support Group	http://xppatientregistery.net/

Abbreviation: NIH, National Institutes of Health. The table does not include a number of registries for skin cancers.

patient organizations to sustain funding for these registries.

When NIH funding for the Alopecia Areata Research Registry ended on March 31, 2012, the National Alopecia Areata Foundation continued to fund the registry. However, likely because of limited funding, no additional samples are being taken for the biobank, although the data in the registry are still being maintained.

Patient foundations do not always have adequate funding to set up and support registries. In the editorial in this issue, Dr. Fleckman (2012) informs us that the National Registry of Ichthyosis and Related Disorders is ceasing operations owing to the withdrawal of support from its financial sponsor, the Foundation for Ichthyosis and Related Skin Types, a patient organization.

Other patient organizations have done a remarkable job of setting up and funding patient registries. We believe that the example set by the Cystic Fibrosis Foundation (CFF) should be aspirational for other rare disease foundations seeking to establish patient registries. In their 2010 patient registry report, the CFF claims 26,263 US participants, a remarkable 88% of the estimated 30,000 patients in the United States. The success of the cystic fibrosis (CF) patient registry is attributable to the considerable funding provided by the CFF, which is well capitalized, with $313 million in 2010 revenues, consisting of $118 million received in donations from the public, and the remainder from investments, pharmacy services, and royalties (Cystic Fibrosis Foundation, 2011).

In addition to capturing data from most patients in the United States, the CF registry also meets Food and Drug Administration (FDA) requirements, which enables the CFF (along with pharmaceutical industry drug manufacturers) to monitor the long-term safety of FDA-approved therapeutics. In addition, the US CF registry model is being adopted outside the United States. The CF foundations in the UK and New Zealand launched their CF registries in 2011.

Companies developing orphan drugs for rare dermatological disorders can benefit from the active participation of patients and disease advocacy organizations. Partnership among these stakeholders provides the opportunity to establish a trusted network and a foundation for research and registry activities. Companies developing and commercializing orphan drugs offer a potential source of long-term funding of international patient registries. These registries may be set up and maintained in collaboration with patient organizations or disease foundations. For example, in the past 18 months, two international patient registries for rare dermatological disorders were launched by patient foundations with corporate funding:

(1) The National Foundation for Ectodermal Dysplasias (NFED) launched the Ectodermal Dysplasias International Registry with funding from

Edimer Pharmaceuticals, a company developing EDI200, a protein therapy, to treat the symptoms of patients affected by X-linked hypohidrotic ectodermal dysplasia (https://nfed.patientcrossroads.org/).

(2) The Dystrophic Epidermolysis Bullosa Research Association (DEBRA) launched EBCare, the first online international patient-reported registry for all forms of epidermolysis bullosa (http://www.ebcare.org), with funding from Lotus Tissue Repair, a company developing recombinant collagen VII for treatment of dystrophic epidermolysis bullosa.

Multiple companies may jointly sponsor a shared registry for a specific disease, thereby sharing costs and reducing both patient fragmentation and patient survey fatigue, within a framework that protects intellectual property.

Unlike academic registries that are usually presented only in one language and in a few countries, company-sponsored registries are usually international registries that are translated into several major languages. For example, the NFED registry is currently available in English, Spanish, German, French, and Italian. Thus, well-funded, company-sponsored, multilingual registries can facilitate collection of data in a single unified database.

To address the unmet needs shared throughout the rare disease community, the NIH ORDR has recently launched the Global Rare Diseases Patient Registry and Data Repository (http://grdr.info) program (Rubinstein *et al.*, 2010). Through a pilot program, new registries will be developed using the PatientCrossroads web-based patient registry program (http://www.patientcrossroads.com), and an infrastructure will be developed to create a repository of patient natural history and biorepository information. The GRDR repository will enable analyses of data across rare diseases and will facilitate clinical trials and research studies, thereby accelerating rare disease research.

Although there is no single solution to securing sustained funding for patient registries, it is disappointing that registries that were maintained (with NIH support) for a decade or more are being terminated. We hope that academic institutions, patient organizations, and companies together can find solutions to keeping these important resources in service.

CONFLICT OF INTEREST

Lotus Tissue Repair funded the registry mentioned under the heading ''Epidermolysis Bullosa (EB) Registries'', and Patient Crossroads, Innolyst built several of the registries mentioned. Both authors are employees of companies mentioned in the commentary.

ACKNOWLEDGMENTS

The authors thank Jim Fordyce and Kyle Brown for reviewing the manuscript.

REFERENCES

Cystic Fibrosis Foundation (2011) 2010 Annual report. http://www.cff.org/UploadedFiles/aboutCFFoundation/AnnualReport/2010-Annual-Report.pdf

Fine JD, Johnson LB, Suchindran C *et al.* (1999) The epidemiology of inherited EB: findings within American Canadian and European study populations. Fine JD, Bauer EA, McGuire J, Moshell A In:(eds) *Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry*. Johns Hopkins University Press: Baltimore, 101–13

Fleckman P (2012) The National Registry for Ichthyosis and Related Disorder will cease operation after 2012. *J Invest Dermatol* 132:1745

Kehoe R, Wu S, Leske MC *et al.* (1994) Comparing self-reported and physician-reported medical history. *Am J Epidemiol* 139:813–8

Kho YC, Rhodes LM, Robertson SJ *et al.* (2010) Epidemiology of epidermolysis bullosa in the antipodes. the australasian epidermolysis bullosa registry with a focus on herlitz junctional epidermolysis bullosa. *Arch Dermatol* 146:635–40

Lynge E, Sandegaard JL, Rebolj M (2011) The Danish National Patient Register. *Scand J Public Health* 39:30–3

Nurok M, Eslick I, Carvalho CR *et al.* (2010) The International LAM Registry: a component of an innovative web-based clinician, researcher, and patient-driven rare disease research platform. *Lymphat Res Biol* 8:81–7

Office of Rare Diseases Research, National Institutes of Health (2012) *Common Data Elements*; http://rarediseases.info.nih.gov/PatientRegistry.aspx

Orphanet (2011) Disease Registries in Europe, Orphanet Report Series, Rare Diseases collection. http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

Rangel V, Martin AS, Peay HL (2012) Duchenne-Connect Registry Report. (Internet) PLoS Currents: Muscular Dystrophy. Available from: http://knol.google.com/k/vanessa-rangel/duchenneconnect-registry-report/3c8kwqirmpdbh/3

Rubinstein YR, Groft SC, Bartek R *et al.* (2010) Creating a global rare disease patient registry linked to a rare diseases biorepository database: Rare Disease-HUB (RD-HUB). *Contemp Clin Trials* 31:394–404

van den Akker PC, Jonkman MF, Rengaw T *et al.* (2011) The international dystrophic epidermolysis bullosa patient registry: an online database of dystrophic epidermolysis bullosa patients and their COL7A1 mutations. *Hum Mutat* 32:1100–7

See related article on pg 1869

Engineering a New Mouse Model for Vitiligo

Prashiela Manga[1] and Seth J. Orlow[1]

Although the precise mechanisms that trigger vitiligo remain elusive, autoimmune responses mediate its progression. The development of therapies has been impeded by a paucity of animal models, since mice lack interfollicular melanocytes, the primary targets in vitiligo. In this issue, Harris *et al.* describe a mouse model in which interfollicular melanocytes are retained by Kit ligand overexpression and an immune response is initiated by transplanting melanocyte-targeting CD8+ T cells.

Journal of Investigative Dermatology (2012) **132,** 1752–1755. doi:10.1038/jid.2012.140

Vitiligo

Melanocytes synthesize melanin, the pigment that provides color to skin, hair, and eyes, while protecting against sun-induced damage. Vitiligo causes a selective, progressive loss of melanocytes,

[1]*The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York, USA*

Correspondence: Seth J. Orlow, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, 560 First Avenue, H100, New York, New York 10016, USA. E-mail: seth.orlow@nyumc.org