Published in final edited form as:

Curr Opin Hematol. 2020 January ; 27(1): 18–26. doi:10.1097/MOH.0000000000000558.

Registries for Study of Non-Malignant Hematological Diseases: The Example of the Severe Chronic Neutropenia International Registry

David C. Dale¹, Audrey Anna Bolyard², Laurie A. Steele¹, Cornelia Zeidler³, Karl Welte⁴,
Severe Chronic Neutropenia International Registry

¹University of Washington, Department of Medicine, Seattle, WA

²University of Washington, Severe Chronic Neutropenia International Registry, Seattle, WA

³Hannover Medical School, Department of Molecular Hematopoiesis, Hannover, Germany

⁴University Hospital Tübingen, Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation, Tübingen, Germany

Abstract

Purpose of the review: Registries provide “real world” perspectives on the natural history and outcomes for many clinical conditions. The purpose of this review is to identify registries for non-malignant hematological disease and to describe the operation of a successful long-term registry for patients with severe chronic neutropenia.

Recent findings: There was an upswing in registries about 20 years ago, based on optimism about their utility to improve patient care. To show value, registries must define outcomes for populations of patients with specific medical conditions and the effects of treatment. This is challenging for many reasons. The SCNIR is an example of a successful registry. This report describes underlying reasons for its success.

Summary: Registries are important to organize and analyze clinical information across geographic, ethnic and social boundaries. They are also challenging to organize, administer and support.

Keywords

Registries; neutropenia; severe chronic neutropenia; clinical outcomes research

Introduction

Registries are organized collections of information about individuals with a common condition. [1–4] There is great diversity in medical registries. In general, the utility of a

CORRESPONDING AUTHOR: David C. Dale, MD, University of Washington, Box 356422, 1959 NE Pacific St., Rm AA522, Seattle, WA 98195, Tel: 206-543-7215, Fax: 206-685-4458, dcdale@uw.edu.

Conflicts of Interest

David Dale receives research support from and is a consultant for Amgen, the company which manufactures G-CSF

registry depends on it having a clearly defined purpose, strict enrollment criteria and methods for analysis of the collected data. Registries are potentially very useful to determine the comparative effectiveness of tests and treatments in a “real world” setting. In hematology, enrollment criteria are usually a clinically defined entity, e.g., clinical syndrome or abnormal laboratory test. Broad categories are: anemia or type anemia, thrombocytopenia, leukopenia or a genetic variant. Enrollment criteria work best if they are easily used by family physicians and general internists, so that the enrolled patients are representative of the population of affected individuals. A recent study emphasized the importance of defining enrollment criteria and harmonizing outcome measures that are meaningful for both patients and providers. [5] Registries are particularly useful for gathering information about rare diseases, because few clinicians or researchers have enough information from their small group of subjects to describe the condition or treatment outcomes accurately. [6]

Registry data are far more useful if they come from diverse geographic locales, i.e., through cooperation of multiple countries, clinics, and physicians as well as including patients from many different backgrounds. A recent review of multinational registries suggested that coordinated collection of common data on standard case report forms at multiple sites is more likely to be successful than networks of individual registries operating independently at a national or regional level. [6] However, it is also important to be able to interpret registry data locally. For example, a Turkish Registry recently reported that homozygous mutations in the *HAX1* gene are the most frequent cause for congenital neutropenia in Turkey, based on data from 216 patients from 28 pediatric centers (36%). [7] However, locales differ, and there are very few patients with *HAX1* associated neutropenia in the US (data on file).

Registries with longitudinal data, i.e., serial information gathered over months or years, are particularly important to establish the natural history, responses to treatments and treatment-related adverse events. Registries are also useful as a resource for recruitment of patients to clinical trials. The patients in a registry with longitudinal data provide useful baseline data on the condition and responses to previously available therapies, thus giving the clinical trial a very useful “head start.” Generally, registry data are owned and controlled by the sponsor of the Registry, with an institutional review committee or governance committee overseeing how data can be used and shared. [4, 6]

Patient data include medical and family history, physical examination findings, and routine and genetic laboratory results. All this information is protected and private, subject to local institutional review board (IRB) and national regulations. To some degree, privacy concerns represent a barrier to aggregation and exchange of registry data. De-identifying and anonymizing clinical information, usually allows registry data to be used for research purposes.

Physician scientists have recorded longitudinal patient data for a long time; Norway began a registry of patients with leprosy around 1850. [8] In 1997 the US Congress required the National Institute of Health to create a registry of clinical trials. Beginning in 2007, Congress required phase 2, 3 and 4 drug and medical device trials to be registered in ClinicalTrials.gov. This led to a surge in new registries. A recent review of characteristics and trends in patient registries in the life science industry reported that the majority of

registries have focused on medical device studies, drug evaluations and the utility of medical procedures. [9] The majority, 69 percent, were for cardiology, endocrine, oncology and musculoskeletal and connective tissue diseases.

Registries for non-malignant hematological diseases are relatively recent; many began in the 1990's. Table 1 lists key features for some of these registries. [10–33] Each registry has its own origin, support, organization, results and future. The history and development of the SCNIR is illustrious of a contemporary medical registry.

Origin

The Severe Chronic Neutropenia International Registry (SCNIR) is an example of a registry started to expand knowledge about an uncommon medical condition after discovery of a broadly effective new therapy. Its origins rest with the purification of the granulocyte colony-stimulating factor (G-CSF) protein [33], the cloning of the gene for G-CSF [34] and phase 2 clinical trials showing that daily subcutaneous injections of this cytokine could elevate blood neutrophils in patients with congenital, cyclic and idiopathic neutropenia [35–38]. A subsequent phase 3 trial proved its effectiveness. [39] When these trials began in the late 1980's, severe neutropenia was already a well-recognized clinical marker for susceptibility to infections, particularly for patients receiving myelosuppressive chemotherapy for cancer. The causes and consequences of severe chronic neutropenia (SCN) were not well understood. For the initial clinical trials, the enrollment criteria were relatively simple, i.e., patients were enrolled if they had an absolute neutrophil count (ANC) continually or intermittently $< 0.5 \times 10^9/L$ during a three month period. This allowed enrollment of patients with cyclic, autoimmune and idiopathic neutropenia, as well as severe congenital neutropenia. Patients with neutropenia due to chemotherapy or well-defined autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus were excluded because of the clinical complexity of these disorders. It was fortunate that the enrollment criteria were easy for most clinicians to use, so referrals came from many sources. Some clinicians recognized that SCN might predispose patients to development of myeloid malignancies, but the markers for risk of malignant transformation were unknown. Bone marrow evidence that the patient did not have leukemia or myelodysplasia was therefore required for enrollment. The designers of the initial trials were concerned that G-CSF might stimulate proliferation of malignant myeloid cells.

The SCNIR opened in 1994 as a follow-up study to the phase 3 trial. The European Medical Agency (EMA) and the US Food and Drug Administration (FDA) required a five-year follow-up study as a condition for approval of marketing of G-CSF/Filgrastim to prevent infections in SCN. The agencies were concerned about long-term adverse effects of administration of this growth factor, including its potential effects on growth and development of children. To satisfy this requirement, the manufacturer (Amgen, Inc, Thousand Oaks, CA, USA) sponsored beginning the SCNIR. This was fortuitous, because patients enrolled in the SCNIR provided the clinical data and biological samples for research defining many of the genetic, molecular and cellular mechanisms of SCN and their clinical consequences. [13, 39–62]

There were many barriers beginning this registry. SCN is rare; best estimates are only a few patients per million population, so most clinicians will never see a patient with SCN. [53] Where would we find patients for the registry? Because the steps to making a diagnosis of severe chronic neutropenia are not well known, what help could a registry provide? How would clinicians, families and patients learn about appropriate treatment with G-CSF?

These questions and the lack of clear answers provided the foundation for beginning the SCNIR. The questions were also the rationale for easily obtaining initial cooperation of patients and their healthcare providers. The bigger challenge was maintaining the voluntary efforts of patients, families, physicians and others over many years so that the natural histories were accurately recorded and the effects of treatment assessed correctly. These issues are the same for all of the long-term patient registries listed in Table 1.

Support:

The SCNIR began with corporate support through a five-year contract with Amgen, Inc, Thousand Oaks CA. The obligation for the company to conduct a follow up, long term observational trial in order to market Neupogen for the SCN indication was critical. After five years, with success in collecting and reporting follow-up information, the Amgen Foundation supported the Registry for another five years. The SCNIR then received grant funding from the NIH/NIAID through its R24 research resource program for the subsequent 15 years with continued funding requested. Additional support has come from patients and parents and through the Ella Jewel Foundation and other gifts and research contracts. Table 1 lists support for other registries. Almost all have depended on a mix of corporate, grant and private funding.

Organization:

The SCNIR operates from the Department of Medicine, University of Washington, Seattle WA; Department of Molecular Hematopoiesis, Hannover Medical School, Hannover, Germany; Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation, Tübingen, Germany; and St. Vincent Hospital, University of Melbourne, Melbourne, Australia and at numerous other sites. Its long-term Co-Directors are Drs. David Dale (Seattle) and Karl Welte (Tuebingen). An International Advisory Board composed of 12–14 members, specialists in pediatric and adult hematology and a patient representative, guide its work. The Advisory Board meets annually in conjunction with the annual meeting of the American Society of Hematology (ASH). There are three standing committees: Executive, Research, and Education which meet during the year to consider clinical issues and research requests and opportunities. In Europe a Liaison Physicians Group (LLP) with members from all European countries including Russia and several countries in the Middle East meets annually to discuss clinical and research programs. The SCNIR maintains relationships with nearly 1000 referring physicians who provide care to the enrolled patients. More than 70 Investigational Review Boards (IRBs) have approved the SCNIR protocol, consent and data forms. Patients, families and physicians may directly contact the offices of the Registry with clinical questions. A strength of the SCNIR is its team of cooperating staff,

physicians and scientists and its relations with industry. We believe cooperation and a shared mission are essential for any registry to be successful.

Clinical Data Collection and Analysis

Patient information flows from interested physicians and patients to the Registry offices utilizing standardized forms available by mail and via the internet at the SCNIR websites (<http://depts.washington.edu.registry> [SCNIR USA]; <https://severe-chronic-neutropenia.org> [SCNIR Europe]). After obtaining preliminary referral information, most US patients currently are consented by phone/teleconference by a Research Nurse, using procedures approved by the IRB at the University of Washington. In other countries, physician-physician communication is more common. Annual follow-up information usually comes directly from patients to the SCNIR offices with most US patients taking the responsibility of sending in laboratory data reports obtained from the physicians' office or laboratory. This work helps patients to learn about neutropenia, its complications and treatments through handling and communicating this information. Participation also communicates to patients a sense of belonging to and being part of the SCNIR. Over many years we have found that physicians and physicians' office staff appreciate being unburdened from this activity. All data are handled confidentially, consistent with HIPPA regulations. In Europe and elsewhere similar practices apply.

Early on the SCNIR supported creation of biological repositories at several sites to study the cellular mechanisms and genetic causes of SCN. Our first discovery was that mutations in *ELANE* are the most common cause for cyclic (CyN) and severe congenital neutropenia (CN). This work rested on careful family histories, collections of their blood and bone marrow samples and improving methods for genetic sequencing. Over the next two decades, the SCNIR provided the stimulus and materials for many subsequent discoveries of causal mutations for CN. The risk of evolution to myelodysplasia and leukemia (MDS/AML) was known before G-CSF and the SCNIR, but because of the risk of death from infections, few patients survived long enough to develop leukemia. The database of the SCNIR defined the risk of leukemic transformation and the most vulnerable patients. The increasingly wide use of G-CSF to treat SCN has prevented any definitive study to determine if it contributes to the risk of leukemia. Soon after beginning the SCNIR, we appreciated its value for providing educational support to patients and families. The clinical database and, where possible, genotype-phenotype analyses are now key resources for providing this support.

As an observational study; a registry lacks the rigor of a randomized trial. The original studies demonstrating the effectiveness of G-CSF treatment for SCN precluded most other options for subsequent, single agent, randomized, clinical trials. It is difficult to compare data from patients in the SCNIR with national and international data because healthcare systems in most countries do not collect and maintain data on chronic neutropenia. Specifically, the prevalence of severe chronic neutropenia by clinical and genetic diagnosis, for vulnerable populations, with historical outcome data, etc. is simply not available. The SCNIR has sought to overcome these weaknesses through consistent enrollment and follow-up policies.

Recently the SCNIR reported outcomes for 1672 neutropenic patients observed in aggregate for 17,577 person years. 70 patients had developed myelodysplasia or acute myeloid leukemia. Ninety-nine percent had hereditary neutropenia. There were 12 patients who had developed T-cell lymphoproliferative disorders, chiefly patients with autoimmune or idiopathic neutropenia. The diagnosis of cyclic neutropenia or chronic idiopathic/autoimmune neutropenia portended a favorable prognosis based on 10,482 person years of observation. Outcomes for patients developing leukemia, have improved in recent years, attributable to improvements in combination chemotherapy and stem cell transplantation.

The future for registries for clinical care, education and research

In 2006 the European Medicines Agency (EMA) established the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) to facilitate collection of information about safety and benefit/risk. [9] In 2012 the US agency for health research and quality (AHQR) established a registry to collect comprehensive data on patient registries, but this program was recently discontinued. It is an uncertain time for registries, in part because it is so difficult to collect and analyze long-term clinical data. We believe that the future for registries depends on good planning, cooperation and evidence showing their utility as a resource to improve patient care.

Ideally it would be possible to analyze comprehensive banks of clinical and genetic data to learn far more about diseases and syndromes than can be learned from patient registries. However, we believe that for the immediate future there are many more barriers and constraints to “big data studies” than for registries to define the natural history, disease mechanisms and novel therapies for many diseases. Focused research groups are more skillful to collect relevant information and patients are more likely to cooperate with researchers with defined interest in their well-being. The SCNIR is currently focused on expanding the spectrum of genetic causes and mechanisms for congenital neutropenia, understanding the natural history of idiopathic neutropenia and finding novel therapy for these conditions. Despite many challenges, we believe registries are effective organizations to improve patient care if they are adequately staffed and supported.

ACKNOWLEDGEMENTS

Ellis Yoo of the Severe Chronic Neutropenia International Registry (SCNIR) assisted with the data collection for the registry table. I would also like to thank Tracy Marrero and Emily Tran of the SCNIR and the members of the SCNIR advisory board, LLP physicians, parents and friends of the SCNIR, patients and the Ella Jewel Foundation.

Financial Support

This work was funded by the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), Grant #5R 24AI049393

REFERENCES

1. Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; 2019 9 Available at: <https://www.ncbi.nlm.nih.gov/books/NBK49444/>**A very important comprehensive review of medical registries

2. deGroot S, van der Linden N, Franken MG, et al. Balancing the optimal and the feasible: a practical guide for setting up patient registries for the collection of real-world data for health care decision making based on Dutch experiences. *Value Health*. 2017;20:627–636. [PubMed: 28408005]
3. Glicklich R Patient Registries. Quintiles Outcome. 2012 Available at: <https://www.pcori.org/assets/11-Gliklich-Slides-Registries.pdf>
4. National Institutes of Health. NIH Clinical Research Trials and You: List of Registries. Last reviewed Sept 3, 2019 Available at: <https://www.nih.gov/health-information/nih-clinical-research-trials-you/list-registries>
5. Gliklich RE, Castro M, Leavy MB, et al. Harmonized outcome measures for use in asthma patient registries and clinical practice. *J Allergy Clin Immunol*. 2019;144:671–681. [PubMed: 30857981]
6. Leavy MB. Multinational Registries: Challenges and Opportunities: Addendum to Registries for Evaluating Patient Outcomes: A User's Guide, 3rd ed. [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US); 2018 Feb. Available at: <https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition/white-paper-2016-1> **It is a useful guide for developers of medical registries
7. Yılmaz Karapınar D, Patiro lu T, Metin A, et al. Homozygous c.130–131 ins A (pW44X) mutation in the HAX1 gene as the most common cause of congenital neutropenia in Turkey: Report from the Turkish Severe Congenital Neutropenia Registry. *Pediatr Blood Cancer*. 2019;66:e27923. [PubMed: 31321910]
8. Irgens LM. The origin of registry-based medical research and care. *Acta Neurol Scand Suppl*. 2012;195:4–6.
9. Travers K, Sallum RH, Burns MD, et al. Characteristics and temporal trends in patient registries: focus on the life sciences industry, 1981–2012. *Pharmacoepidemiol Drug Saf*. 2015;24:389–398. [PubMed: 25079108] **A summary report on the utility of medical registries
10. Niss O, Lorschach RB, Christakopoulos GE, et al. The first registry for patients with congenital dyserythropoietic anemia in North America: Design and preliminary results. *Blood*. 2017;130:2210.
11. Lipton JM, Atsidaftos E, Zyskind I, Vlachos A. Improving clinical care and elucidating the pathophysiology of Diamond Blackfan anemia: update from the Diamond Blackfan Anemia Registry. *Pediatr Blood Cancer*. 2006;46:558–564. [PubMed: 16317735]
12. Butturini A, Gale RP, Verlander PC, et al. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. *Blood*. 1994;84:1650–1655. [PubMed: 8068955]
13. Dale DC, Cottle TE, Fier CJ, et al. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol*. 2003;72:82–93. [PubMed: 12555210] **Important paper covering the early years of the Severe Chronic Neutropenia International Registry
14. Rosenberg PS, Zeidler C, Bolyard AA, et al. Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy. *Br J Haematol*. 2010;150:196–199. [PubMed: 20456363]
15. Carlsson G, Fasth A, Berglöf E, Lagerstedt-Robinson K, Nordenskjöld M, Palmblad J, Henter JI, Fadeel B. Incidence of severe congenital neutropenia in Sweden and risk of evolution to myelodysplastic syndrome/leukaemia. *Br J Haematol*. 2012;158:363–369. [PubMed: 22624626]
16. Donadieu J, Michel G, Merlin E, et al. Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: experience of the French neutropenia registry. *Bone Marrow Transplant*. 2005;36:787–792. [PubMed: 16151425]
17. Desplantes C, Fremont ML, Beaupain B, et al. Clinical spectrum and long-term follow-up of 14 cases with G6PC3 mutations from the French Severe Congenital Neutropenia Registry. *Orphanet J Rare*. 2014;9:183.
18. Beaussant Cohen S, Fenneteau O, Plouvier E, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. *Orphanet J Rare Dis*. 2012;7:71. [PubMed: 23009155]
19. Farruggia P, Fioredda F, Puccio G, et al. Idiopathic neutropenia of infancy: Data from the Italian Neutropenia Registry. *Am J Hematol*. 2019;94:216–222. [PubMed: 30456824]

20. Khellaf M, Charles-Nelson A, Fain O, et al. Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients. *Blood*. 2014;124:3228. [PubMed: 25293768]
21. Acharya SS, Coughlin A, Dimichele DM; North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost*. 2004;2:248–256. [PubMed: 14995986]
22. Severinsen MT, Engebjerg MC, Farkas DK, et al. Risk of venous thromboembolism in patients with primary chronic immune thrombocytopenia: a Danish population-based cohort study. *Br J Haematol*. 2011;152:360–362. [PubMed: 20955411]
23. Kühne T, Berchtold W, Michaels LA, et al. Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. *Haematologica*. 2011;96:1831–1837. [PubMed: 21880634]
24. Iorio A, Olivocchione E, Morfini M, et al. Italian Registry of Haemophilia and Allied Disorders. Objectives, methodology and data analysis. *Haemophilia*. 2008;14:444–453. [PubMed: 18355268]
25. Acharya SS, Coughlin A, Dimichele DM; North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost*. 2004;2:248–256. [PubMed: 14995986]
26. Gathmann B, Binder N, Ehl S, et al. The European internet-based patient and research database for primary immunodeficiencies: update 2011. *Clin Exp Immunol*. 2012;167:479–91. [PubMed: 22288591]
27. Edgar JD, Buckland M, Guzman D, et al. The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008–2012. *Clin Exp Immunol*. 2014;175:68–78. [PubMed: 23841717]
28. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore)*. 2006;85:193–202. [PubMed: 16862044]
29. Hamilton JK, Paquin LA, Sullivan JL, et al. X-linked lymphoproliferative syndrome registry report. *J Pediatr*. 1980;96:669–673. [PubMed: 7188959]
30. Gathmann B, Binder N, Ehl S, et al. The European internet-based patient and research database for primary immunodeficiencies: update 2011. *Clin Exp Immunol*. 2012;167:479–491. [PubMed: 22288591]
31. Suarez F, Mahlaoui N, Canioni D, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. *J Clin Oncol*. 2015;33:202–208. [PubMed: 25488969]
32. Charrow J, Andersson HC, Kaplan P, et al. The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med*. 2000;160:283 [PubMed: 10668829]
33. Welte K, Platzer E, Lu L, et al. Purification and biochemical characterization of human pluripotent hematopoietic colony-stimulating factor. *Proc Natl Acad Sci U S A*. 1985;82:1526–1530. [PubMed: 3871951]
34. Souza LM, Boone TC, Gabrilove J, et al. Recombinant human granulocyte colony-stimulating factor: effects on normal and leukemic myeloid cells. *Science*. 1986;232:61–65. [PubMed: 2420009]
35. Jakubowski AA, Souza L, Kelly FK, et al. Effects of human granulocyte colony-stimulating factor in a patient with idiopathic neutropenia. *N Engl J Med*. 1989;320:38–42. [PubMed: 2462670]
36. Hammond WP 4th, Price TH, Souza LM, Dale DC. Treatment of cyclic neutropenia with granulocyte colony-stimulating factor. *N Engl J Med*. 1989;320:1306–1311. [PubMed: 2469956]
37. Bonilla MA, Gillio AP, Ruggeiro M, et al. Effects of recombinant human granulocyte colony-stimulating factor on neutropenia in patients with congenital agranulocytosis. *N Engl J Med*. 1989;320:1574–1580. [PubMed: 2471075]
38. Dale DC, Bonilla MA, Davis MW, et al. A randomized controlled phase III trial of recombinant human G-CSF for treatment of severe chronic neutropenia. *Blood*. 1993;81:2496–2502. [PubMed: 8490166]

39. Horwitz M, Benson KF, Person RE, et al. Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological clock in cyclic haematopoiesis. *Nat Genet.* 1999;23:433–436. [PubMed: 10581030]
40. Dale DC, Person RE, Bolyard AA, et al. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. *Blood.* 2000;96:2317–2322. [PubMed: 11001877]
41. Rosenberg PS, Alter BP, Bolyard AA. Severe Chronic Neutropenia International Registry. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. *Blood.* 2006;107:4628–4635. [PubMed: 16497969]
42. Klein C, Grudzien M, Appaswamy G, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). *Nat Genet.* 2007;39:86–92. [PubMed: 17187068]
43. Boztug K, Appaswamy G, Ashikov A, et al. A syndrome with congenital neutropenia and mutations in G6PC3. *N Engl J Med.* 2009;360(1):32–43. Erratum in: *N Engl J Med.* 2011 Apr 28;364:1682. [PubMed: 19118303]
44. Dale DC, Link DC. The many causes of severe congenital neutropenia. *N Engl J Med.* 2009;360:3–5. [PubMed: 19118300]
45. Rosenberg PS, Zeidler C, Bolyard AA, et al. Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy. *Br J. Haematol.* 2010;150:196–199. [PubMed: 20456363]
46. Germeshausen M, Zeidler C, Stuhmann M, et al. Digenic mutations in severe congenital neutropenia. *Haematologica.* 2010;95:1207–1210. [PubMed: 20220065]
47. Boztug K, Rosenberg PS, Dorda M, et al. Extended spectrum of human glucose-6-phosphatase catalytic subunit 3 deficiency: novel genotypes and phenotypic variability in severe congenital neutropenia. *J Pediatr.* 2012;160:679–683.e2. [PubMed: 22050868]
48. Makaryan V, Kulik W, Vaz F, et al. The cellular and molecular mechanisms of neutropenia in Barth syndrome. *Eur J Haematol.* 2012;88:195–209. [PubMed: 22023389]
49. Skokowa J, Steinemann D, Katsman-Kuipers JE, et al. Cooperativity of RUNX1 and CSF3R mutations in severe congenital neutropenia: a unique pathway in myeloid leukemogenesis. *Blood.* 2014;123:2229–2237. [PubMed: 24523240]
50. Makaryan V, Rosenthal EA, Bolyard AA, et al., for the UW Center for Mendelian Genomics. TCIRG1 associated congenital neutropenia. *Hum Mutat.* 2014;35:824–827. [PubMed: 24753205]
51. Makaryan V, Zeidler C, Bolyard AA, et al. The diversity of mutations and clinical outcomes for ELANE associated neutropenia. *Curr Op Hematol.* 2015;22:3–11.
52. Myers KC, Davies SM, Shimamura A. Clinical and molecular pathophysiology of Shwachman-Diamond syndrome: an update. *Hematol Oncol Clin North Am.* 2013;27:117–128 [PubMed: 23351992]
53. Skokowa J, Dale DC, Touw IP, et al. Severe congenital neutropenias. *Nat Rev Dis Primers.* 2017;8:17032.
54. Dale DC, Bolyard AAB. An update on the diagnosis and treatment of chronic idiopathic neutropenia. *Curr Opin Hematol.* 2017;24:46–53. [PubMed: 27841775]
55. Dale DC, Bolyard AA, Marrero T, et al. Long-term effects of G-CSF therapy in cyclic neutropenia. *N Engl J Med.* 2017;377:2290–2292 [PubMed: 29211670]
56. Makaryan V, Kelley MK, Fletcher B, et al. Elastase inhibitors as potential therapies for ELANE-associated neutropenia. *J Leukoc Biol.* 2017;102:1143–1151. [PubMed: 28754797]
57. Xia J, Miller C, Baty J, Ramesh A, et al. Somatic mutations and clonal hematopoiesis in congenital neutropenia. *Blood.* 2018;131:408–416. [PubMed: 29092827]
58. Dale DC, Bolyard AA, Alter B, et al. Myelodysplasia, leukemia, lymphoid malignancies, and other cancers in patients with severe chronic neutropenia. (ASH Annual Meeting Abstracts). *Blood Annual Meeting Abstracts.* 2018;132(S1):16.
59. Dale DC, Bolyard AA, Marrero T, et al. Neutropenia in glycogen storage disease Ib: outcomes for patients treated with granulocyte colony-stimulating factor. *Curr Opin Hematol.* 2019;26:16–21. [PubMed: 30451720]
60. Steward CG, Groves SJ, Taylor CT, et al. Neutropenia in Barth syndrome: characteristics, risks, and management. *Curr Opin Hematol.* 2019;26:6–15. [PubMed: 30451719]

61. Dale DC, Dick E, Kelley M, et al. Family studies of WHIM syndrome. *Curr Opin Hematol*. 2019; in press
62. Warren JT, Wattanasirakul P, Spencer DH, Locke AE, et al. Heterozygous mutations of CLPB as a newly identified and frequent cause of severe congenital neutropenia. (ASH Annual Meeting Abstracts). *Blood* 2019.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Key Points:

- Medical registries serve to organize clinical information for longitudinal studies of their natural history and outcomes
- Registries are challenging to organize across international boundaries and their operation and funding are difficult
- The SCNIR is described in this review as an example of a successful registry now in operation for more than 25 years

Table 1

Registries for the study of non-malignant hematological diseases

ORGANIZATION	SPONSOR	GEOGRAPHIC COVERAGE	DATE OF INCEPTION	TOTAL # PATIENTS ENROLLED	REFERENCE/WEBSITE/EMAIL
ANEMIA					
Diamond Blackfan Anemia Registry (DBAR)	Northwell Health NHLBI/NIH DOD Diamond Blackfan Anemia Foundation ASH Bridge Grant	USA, Canada, Mexico	1992	850	[ref 11] https://www.dbar.org/
Congenital Dyserythropoietic Anemia Registry (CDAR)	Center for Pediatric Genomics, Cincinnati Children's Hospital	USA	2016		[ref 10] https://www.cincinnatichildrens.org/research/divisions/c/genomics/clinicians-researchers/projects/awards/kalfa
Registry of Congenital Dyserythropoietic Anemia (CDA)	Lille Catholic University	France	2017	Est 200	[ref 10] lanxiaux.amelie@ghicl.net
International Faconi Anemia Registry (IFAR)	Rockefeller University	International	1982	1278 families	[ref 12] http://lab.rockefeller.edu/smogorzewska/ifar/
Atypical Hemolytic-Uremic Syndrome (aHUS) Registry	Alexion Pharmaceuticals	International	2012	Est 2000	Ahus-registry@syneoshealth.com
Pyruvate Kinase Deficiency Global Longitudinal Registry (PEAK Registry)	Agios Pharmaceuticals, Inc.	International	2018	500	https://www.peakregistry.com/
Sickle-cell Disease Registry of the GPOH (SichReg)	University Hospital Heidelberg	Germany	2016	500	https://www.sichelzellkrankheit.info/patientenregister/
Registre des patients thalassémiques en France (Registre qualifié)	Assistance Publique-Hôpitaux de Marseille	France	2005	515	https://epidemiologie-france.aviesan.fr/en/epidemiology/records/registre-des-patients-thalassemiques-en-france-registre-qualifie
BLEEDING DISORDERS					
World Bleeding Disorders Registry	World Federation of Hemophilia	International	2018	1,000+	[see also ref 22] https://www.wfh.org/en/wbdr
Australian Bleeding Disorders Registry	National Blood Authority	Australia	1988	5,947	https://www.blood.gov.au/abdr
Swiss Hemophilia Registry	Swiss Hemophilia Network	Switzerland	2015	900 since 2017	[ref 25] manuela.albisetti@kispi.uzh.ch
NEUTROPENIA AND IMMUNODEFICIENCY					
Severe Chronic Neutropenia International Registry	University of Washington/NIH/NIAID	International	1994	839	[ref 13, 14, 15] https://depts.washington.edu/registry/

ORGANIZATION	SPONSOR	GEOGRAPHIC COVERAGE	DATE OF INCEPTION	TOTAL # PATIENTS ENROLLED	REFERENCE/WEBSITE/EMAIL
French Congenital Neutropenia Registry	Hôpital Trousseau APHP	France	1995	503	[ref 16, 17, 18, 19] https://epidemiologie-france.aviesan.fr/en/epidemiology/records/french-congenital-neutropenia-registry
Italian Severe Chronic Neutropenia Registry	Meyer University Hospital, Florence, Italy	Italy	1995		[ref 20] https://severe-chronic-neutropenia.org/en (European Branch of the Severe Chronic Neutropenia International Registry)
Barth Syndrome Registry (BRR)	Barth Syndrome Foundation	United Kingdom, France, USA, Italy, Canada	2003	Est 200	[ref 48, 60] https://barthsyndromeregistry.patient.crossroads.org/
Shwachman-Diamond Syndrome (SDS) Registry	National Institutes of Health(NIH), Butterfly Guild, SDS America, SDS Project, SDS Foundation	USA	2008	est 250	[ref 17, 18] http://sdsregistry.org/
United States Immunodeficiency Network (USIDNET) Registry	NIH/NIAID	USA	1992	5346	[ref 29, 30; see also ref 28] https://usidnet.org/
European Society for Immunodeficiencies (ESID) Registry	ESID	International	1994	29265	[ref 27, 31; see also ref 32] https://esid.org/
AUTOIMMUNE					
Autoimmune Cytopenias: Midi-Pyrenees Registry (CARMEN)	University Hospital, Toulouse	France	2016	Est 800	moulis.g@chu-toulouse.fr
Data Registry of Auto Immune Hemolytic Anemia (DRAIHA)	Sanquin Research & Blood Bank Divisions	Netherlands		Recruiting	https://www.sanquin.org/research/ctr-studies/draiha
Severe Immune Cytopenia Registry	Medical University of Graz	Austria	2018	50	www.sic-reg.org
International ITP Registry	South Eastern Sydney Local Health District	Australia, Colombia, Korea, Kuwait, Malaysia, Singapore, Taiwan, Thailand, Turkey, Uruguay	2011	Est 500	[see also ref 23, 24] http://www.globalitp.org/index.php/about-itp/clinical-trials/53-the-international-itp-registry
ITP-Ritux Registry	Henri Mondor University Hospital	France	2010	255	[ref 21] https://clinicaltrials.gov/ct2/show/NCT01101295
Thrombotic Thrombocytopenic Purpura Registry	University Hospital Inselspital, Berne	Austria, Czechia, Germany, Japan, Norway, Switzerland, United States	2006	Est 450	https://ttpregistry.net/
The United Kingdom Thrombotic Thrombocytopenic	University College, London	United Kingdom	2009	Est 1000	https://www.uclh.nhs.uk/OurServices/ServiceA-Z/Cancer/CBD/TTP/TTPRegistry/Pages/Home.aspx

ORGANIZATION	SPONSOR	GEOGRAPHIC COVERAGE	DATE OF INCEPTION	TOTAL # PATIENTS ENROLLED	REFERENCE/WEBSITE/EMAIL
Purpura Registry (UK TTP Registry)					
OTHER					
Finnish Hematology Registry and Biobank	Finnish Assoc. of Hematology (FAH), Finnish Red Cross Blood Service & the Institute for Molecular Medicine Finland (FIMM)	Finland	2010	1411	http://www.fhrb.fi/front-page.html
French constitutive hematologic diseases	Service d'hématologie pédiatrique CHU Paris-GH-St-Louis Lariboisière F Widal Hôpital Saint-Louis, Paris, France	France			thierry.leblanc@aphp.fr
International Collaborative Gaucher Group (ICGG) Gaucher Registry	Genzyme (Sanofi)	International	1991	6000+ since 2015	[ref 33] https://clinicaltrials.gov/ct2/show/NCT00358943
Italian Registry for MYH9-related thrombocytopenia	Fondazione IRCCS Policlinico San Matteo, Pavia, Italy	Italy	2006	150+	http://www.registromyh9.org/English_version/
Registry for Vascular Anomalies Associated With Coagulopathy (VAC)	Medical College of Wisconsin	USA	2007	30	bdrolet@mcw.edu aschamerhorn@mcw.edu