



The use of databases in primary immunodeficiencies

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Purpose of review

We provide an overview on the latest developments in primary immunodeficiency registries worldwide, on the basis of the recent literature amended by some older references to achieve completeness.

Recent findings

New primary immunodeficiency registries are emerging worldwide, although existing databases continue to thrive and provide valuable insights for clinicians and researchers.

Summary

In the area of rare disease research, data on a meaningful number of patients can only be achieved via collaboration. Registries for primary immunodeficiency are organized on different geographic levels and appear in various technical forms. Some registries are operated within single departments or hospitals, whereas others collect data from a country in the form of a national registry. With modern information technology and networks, it has become feasible to easily extend documentation to the transnational level. Most patient registries cover similar but not identical sets of data, whereas some have a special focus on, for example, genetics or incorporate only data from patients who have undergone a specific form of treatment. This review shows the usefulness and power of international immunodeficiency registries, as well as possible hurdles and limitations.

Keywords

database, primary immunodeficiency diseases, primary immunodeficiency, registry

INTRODUCTION

Patient registries are powerful tools that are suited to fulfil a range of purposes, such as describing the prevalence and natural history of disease, determining clinical and/or cost effectiveness of specific management decisions, assessing their safety or harm, and measuring quality of care and quality of life. They play an important role in comparing different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. They facilitate planning of randomized controlled trials, for example, for the comparison of different treatment strategies in registered patients. Especially in the area of rare diseases, patient registries represent a unique tool to capture data on a sufficient number of patients. Some registries provide up-to-date information on their status not only in publications, but also on their websites. We include information from these Internet sources, mainly on ongoing work and future plans.

Since our last review on primary immunodeficiency (PID)-registries in 2007 [1], a wealth of additional data has been reported. Comprehensive analyses have been published on the epidemiology, clinical course, and treatment of PID, and new

initiatives have emerged. An important 'extended feature' of wide-ranging registries is their capability to easily track down patients with a defined disease or complication, for example, for dedicated studies/research or in order to put attending physicians into contact. Apart from clinical patient registries, databases in PID are also used as tools in other contexts, for example, in mutation databases, transplant registries, or medical expert systems [2]. In this review, we focus on clinical PID patient registries and touch on databases closely related to them. There is consensus in the literature that patient registries are a valuable instrument in PID research and should be supported.

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KEY POINTS

- Resources for registries are limited, thus focusing on parameters necessary to answer the most burning research questions is recommended.
- Uniform and consistent clinical diagnostic criteria are still needed and should be elaborated on by a collective endeavor by disease experts worldwide.
- Sustainable long-term funding remains a central issue in the operation of registries.
- Joining forces and international collaboration are an important way forward to share the financial burden and also the available data on PID.

SECTION I: OVERVIEW OF PRIMARY IMMUNODEFICIENCY REGISTRIES

This section provides an overview of the scenery of PID registries worldwide. The registries are divided according to their organizational structure, starting with single-center registries and continuing with multiple-center collaborations (some of them already representing 'de-facto' national initiatives) to dedicated national registries and eventually transnational collaborations. Data on the properties and descriptive epidemiology of the respective registries can be found in Table 1.

India

Two recent publications report on data collected at the local level from 47 [3] and 159 [4] PID patients in India. The authors agree that there is a need for the installation of more advanced facilities for diagnosis and management of PID in India and also for the implementation of a national PID registry [5].

Oman

Sultan Qaboos University Hospital is the national referral center for PID in Oman. In 2010, a total of 90 patients were registered. The authors concluded that the estimated minimum prevalence of PID in Oman is 4.5 cases per 100 000 inhabitants. As outlined in other publications, the authors call for strategies to improve the care for PID patients and to increase the awareness among parents and physicians [6].

China

The Asian Primary Immunodeficiency Network has been established in 2009 with its genetic diagnostic laboratory unit based at Hong Kong University leading to 455 genetically confirmed PID diagnoses by July 2013 [7].

Egypt

A total of 160 children from two documenting centers (Ain Shams University and Cairo University) have been registered in the European Society for Immunodeficiencies (ESID) registry [8].

Malaysia

A study [9] on 52 PID patients seen over 20 years at four Malaysian hospitals was recently published.

France

Centre de Référence Déficits Immunitaires Héritaires (CEREDIH) is the French national reference center for PID and collects data from all PID centers participating in a nationwide network of university medical centers. The data are collected by a group of dedicated and trained data entry clerks, using the ESID registry as the user interface for data collection. CEREDIH published a first overview of the results of the national registry in 2010 [10]. By that time, the registry comprised a total of 3083 patients (mainly children), with an overall documented prevalence of 4.4 cases per 100 000 inhabitants. As of June 2014, the number of registered patients has increased to 5426, according to the statistics provided by the ESID website, thus currently representing the world's largest national registry of PID [11].

Germany

PID-NET is a collaborative effort of immunodeficiency researchers in Germany organized in several conjoined projects. The PID-NET registry constitutes a key element of this consortium and is the central German registry for PID. Similarly to France, the registry uses the ESID registry as its technical platform for documentation. It also employs a data entry clerk who travels throughout Germany in order to support the centers at data entry and also helps with all administrative issues, for example, data protection or ethical approvals. According to the first report published in 2013 [12], the documentation rate in Germany significantly increased with the instantiation of this national registry and led to a boost in participation. Familial cases were reported in 20.6% of the patients. Currently, 30 centers with 1981 registered patients are participating in the PID-NET registry [13].

Iran

The Iranian National PID Registry published its third report on its activities just recently. The data can be entered either via an online system

Table 1. Disease distribution according to International Union of Immunological Societies groups

	France	Germany	Iran	Korea	Kuwait	Malaysia	Morocco	Oman	Qatar	Spain	Turkey	UK	ASCIA	LASID	USIDNET	ESID
Total patient number (male/female)	3083	1368 (783 male, 585 female)	1661 (1028 male, 633 female)	152	176 (98 male, 78 female)	52	421	90	131	2211	1435	2229 (1162 male, 1067 female)	1209	3321	3459 (62.6% male, 37.4% female)	19355
Reporting year	2010	2012	2013	2005	2012	2006	2012	2010	2012	2014	2010	2012	2007	2007	2013	2014
Parental consanguinity		86.0%			78.0%		43.2%	81.0%			14.3%	2.9%				
HCT		58.0%			15.3%		2.4%	11.0%				18.4%				
Percentage of minors		44.8%		100% < 19 years								22% < 17 years			25% < 18 years	
Presenting infections				Pneumonia most common		Rec. pneumonia (54%), abscess (27.5%), diarrhea (23.5%), sepsis (16.6%), otitis media (13.7%)	Lower respiratory tract infections (60.8%), skin infections (33.5%), candidiasis (26.1%)	Pneumonia 42%, deep abscess 27%, BCGosis 12%	Pneumonia (48.9%), failure to thrive (34.4%), otitis media (26%), sepsis (23.7%), chronic diarrhea (21.4%)							
Disease distribution																
Predominantly antibody deficiencies thereof, CVID	42.8%	62.7%	35.7%	53.5%	19.9%	40.4%	22.7%	18.0%	23.7%	73.0%	73.5%	61.0%	19.9%	53.2%	33% (CVID) 10.8% (XLA)	56.7%
Combined ID	14.0%	7.4%					10.3%			32.0%		36.3%				
Phagocytic	17.4%	4.4%	16.0%	13.2%	30.1%	15.4%	20.6%	12.0%	19.1%	2%	2.0%	9.9%	30.1%	9.5%	6.9% (SCID) 12.5% (CGD/LAD)	7.5%
Immune dysregulation	18.7%	8.1%	23.5%	28.9%	6.3%	17.3%	17.5%	42.0%		2%	3.5%	4.8%	6.3%	8.6%		8.8%
Complement deficiencies	6.6%	3.4%	2.4%		14.8%					1%	0.7%	1.4%		3.3%		3.9%
Other well defined	0.5%	1.0%	1.9%	4.6%	4.0%	11.5%	27.4%	13.0%	22.9%	13%		9.2%		2.8%		4.9%
	14.1%	12.5%	17.5%		25.0%					6%	5.5%	13.9%		22.6%	11.4% (DiGeorge)	13.9%
Autoinflammatory		3.1%	2.3%							1%	13.3%	1.0%				2.0%
Innate immunity		NA	0.7%							1%	1.0%	0.1%				1.0%
Unclassified Ids		4.0%								1%						1.4%
Sum	100.0%	99.1%	100.0%	100.2%	100.1%	84.6%	88.2%	85.0%	65.7%	100%	99.5%	101.3%	56.3%	100.0%	74.6%	100.1%

Not all publications provide a complete summary of all disease groups, some only report on the most prevalent. Thus, the values do not always add up to 100%. Some values add up to slightly more than 100%. This is caused by rounding differences. Please note the different reporting dates.

ASCIA, Australasian Society of Clinical Immunology and Allergy; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; ESID, European Society for Immunodeficiencies; ID, immunodeficiency; LASID, Latin American Society for Immunodeficiencies; UK, United Kingdom.

(<http://rcid.tums.ac.ir/>) or on paper. By March 2013, a total number of 1661 PID patients were registered in the Iranian National PID Registry [14[¶]].

Italy

The Italian PID network ipinet operates the national Italian Registry for PID within the Italian Association of Pediatric Hematology and Oncology [15]. Several studies [16–18,19[¶],20,21] have been published focusing on a dedicated disease group or a specific treatment question or in cases in which the registry has been instrumental in tracking down patients for further analyses. However, there are no publications available describing the overall demographic characteristics of this registry. Ipinet has been cooperating with ESID for many years and transfers data on a yearly basis to the ESID registry. Italy currently contributes 1275 patients to the ESID registry [11].

Korea

The first results of the Korean national survey on PID were published in 2012 [22]. Data were collected from 23 major hospitals throughout Korea and a total of 152 PID patients were reported.

Kuwait

Since the first report on 76 patients registered in the Kuwait National Primary Immunodeficiency Registry in 2008 [23], several studies have been published illustrating the advances of this project. In 2011, a study on 128 patients focused on parental consanguinity [24], whereas in 2012, the risk factors for death were analyzed in 176 PID patients [25].

Morocco

The first comprehensive report described 421 patients registered in the national registry established in 2008 by the Moroccan Society for PID [26[¶]]. A considerable underdiagnosis and a need to increase awareness of these conditions in Morocco is emphasized.

Qatar

A report on the PID registry that was established in Qatar analyzed 131 pediatric patients diagnosed between 1998 and 2012 [27].

Spain

The Spanish Register for PID (REDIP) was set up in 1993. A total of 2211 PID patients are currently

registered according to the REDIP website [28]. The REDIP registry collaborates with the ESID registry and data are transferred to ESID on a regular basis. According to the ESID website [11], Spain at the moment operates in a hybrid mode in which centers can register patients either through REDIP or directly into the ESID system. It is envisioned to adopt the new ESID registry as the technical platform for REDIP (N Matamoros, personal communication).

Turkey

The ESID online registry is used as a platform for the documentation of data on Turkish PID patients. A recent study [29] summarizes the clinical features of 1435 patients with PID registered at Uludag University (Bursa-Görükle) and Ege University (Bornova-Izmir), which were the main Turkish contributors to the ESID registry between 2004 and 2010.

United Kingdom

The UK Primary Immune Deficiency registry integrates all immunodeficiency centers in the United Kingdom. The technical platform is based on the system operated by ESID. According to the first report [30[¶]], 2229 patients have been enrolled in the project by 27 centers. A total of 24% of the patients were described as familial cases. Involvement of centers continues to increase across the United Kingdom with 35 centers involved and 3204 patients registered as of July 2014 [31].

Australasian Society of Clinical Immunology and Allergy

The Australasian Society of Clinical Immunology and Allergy PID register Australia and New Zealand consolidates data from the Australian PID registry established in 1994 with information from the Australian Pediatric Surveillance Unit [32]. In 2007, a report on 1209 patients from 88 centers was published [33]. The overall prevalence of reported PID cases was given as 5.6 in 100 000, which is significantly more than calculated earlier [34]. The authors identify underreporting as a key problem for the evaluation of the true disease prevalence. By comparing national data on Intravenous immunoglobulins (IVIG) distributed for PID with data from the register, they estimate having captured approximately 35% of patients within the relevant target group. In 2010, a study [35] on 1132 patients was published linking registry data to data from national death and cancer registries, indicating a slight increase in the number of registered patients.

European Society for Immunodeficiencies

The ESID registry is the European registry for PID. It was established in 2004 and currently holds clinical and laboratory data of 19 355 patients from 126 centers (including national centers) in 30 countries [11]. A total of 45.6% of the registered living patients receive IG-replacement therapy (thereof 1/3 Subcutaneous immunoglobulins and 2/3 IVIG). Publications in the early phase of the project focused mainly on the system architecture [36] and general descriptive epidemiology [37]. Many national registries are engaged in the ESID registry and have published the respective results from their national cohorts, as outlined in the chapters above. Focusing on one disease entity – common variable immunodeficiency (CVID) – a comprehensive study [38^{***}] on 2212 CVID patients has been published recently, thus covering data from many European countries. A regularly updated list of publications related to the ESID registry is provided on the societies' website (website: <http://esid.org/Working-Parties/Registry/Resources/Publications>). Moreover, the ESID registry has been instrumental in answering research inquiries, for example, tracking down patients to form cohorts for dedicated studies or providing data for grant applications. Altogether, the registry has processed 121 such inquiries over the past 5 years. The registry has been transferred to a new technical platform (Grails; <http://www.grails.org/>) with improved data quality control and diagnosis verification tools in June 2014. Data will be organized in three levels of data depth, starting with a mandatory core dataset at level 1, which is complemented by category-specific datasets at level 2. Dedicated studies with a fixed time frame and specific questions form level 3 (website: <http://esid.org/Working-Parties/Registry/New-ESID-Registry/The-redesign-of-the-ESID-Registry>).

IDbases and MUTbase

The last report on the IDbases, a publicly available collection of currently 131 locus-specific databases holding data on immunodeficiency-causing variations from 7292 patients was published in 2006 [39]. The system has recently been moved from Tampere in Finland to Lund University, Sweden, apparently otherwise operating under the same conditions (website: <http://structure.bmc.lu.se/idbase/>). IDbases contain data on gene variation alongside information about clinical presentation that has been extracted from the literature as well as received directly from researchers. IDbases run with the proprietary MUTbase software suite [40].

Immunodeficiency resource

ImmunoDeficiency Resource (IDR) is a web accessible compendium of information on the immunodeficiencies initiated by the same curators who provide the IDbases. This resource includes tools for clinical, biochemical, genetic, structural, and computational analyses, as well as links to related information maintained by others. Currently, the IDR service includes 167 IDR factfiles, 222 IDdiagnostics gene tests for 44 diseases offered by 24 centers, 31 IDdiagnostics clinical tests, and 131 IDbases (see previous section). It covers 6038 patients/entries (website: <http://structure.bmc.lu.se/idbase/IDRefSeq/idr/index.shtml>).

Latin American Society for Immunodeficiencies

In 1993, a group of immunologists established the Latin American Group for Primary Immunodeficiency Diseases (LAGID). The second LAGID report was published in 2007 and describes the progress of the data collection on PID [41]. In 2009, LAGID evolved into Latin American Society for Immunodeficiencies (LASID), now representing a total of 14 countries. The online PID registry program for Latin America (LASID registry) was officially launched in 2009 in Sao Paulo (Brazil). The registry was adapted from the ESID registry using a similar technical framework. A recent review lists a variety of activities of LASID in Latin America, with the Online Registry being an essential tool with important impact, for example, on healthcare providers [42]. Several collaborative clinical epidemiological studies have been launched, focusing initially on chronic granulomatous disease, agammaglobulinemia, and Hyper-IgM syndrome [43^{***}]. A recent study [44] summarizes the general healthcare situation in Latin America and outlines the usefulness of a registry for the whole area of PID research. Information on the progress of the LASID registry is regularly provided on the project homepage. The latest available report, dated May 2014, shows 5059 patients registered in 91 centers from 13 countries (website: http://imuno.unicamp.br:8080/estatistica_mensal.html).

Resource of Asian Primary Immunodeficiency Diseases (Japan)

The RIKEN Jeffrey Modell Immunodeficiency Research Center, located in Tsurumi, Yokohama, has built the PID clinical archive Primary Immunodeficiencies Database Japan that was opened in 2008 with the support of scientists and clinicians. The database currently contains more than 1500

clinical datasets collected from all over Japan and also integrates the basic analytical data including immunological and DNA/RNA analyses performed by the RIKEN JMF Research Center [45]. In 2009, the Resource of Asian Primary Immunodeficiency Diseases, a web-based compendium of molecular alterations in patients with PID was opened. Currently, the site lists 248 PID genes and diseases and 5012 unique mutations [46].

SCETIDE

Stem Cell Transplant for ImmunoDeficiencies in Europe (SCETIDE) is a registry encompassing a large number of European centers with a longstanding expertise in the field of hematopoietic stem cell transplantation for patients with PID, members of the Inborn Errors Working party-European Group for Blood and Marrow Transplantation-ESID and managed by the CEREDIH team, Necker, Paris, France [47]. An analysis of 1482 PID patients documented in the SCETIDE database during the years 1968–2005 has been published recently [48].

USIDNET

The first PID registry in the United States was established in 1993 in order to collect data on chronic granulomatous disease [49]. A total of 368 patients had been included by the time of publication in 2000. The results from this registry showed that this disease was more common and sequelae more severe than previously expected. This registry was incorporated into the United States Immunodeficiency Network (USIDNET) registry in 1997. A comprehensive report on the activities of USIDNET describes the USIDNET registry as a key instrument in the endeavor to improve knowledge and care for PID patients and their families [50^{***}]. The registry was established in the current electronic version in 2008 and currently contains data of 3459 patients from 42 sites, including one hospital in Montreal, Canada. Similarly to other registries, data are entered by physicians or USIDNET staff who visit the respective centers. A unique way of registering data is the 'patient self-entry mode'. Here, the patients request their data from the attending center and provide the documents to USIDNET staff. This mode has increasingly been used during the last years: 31% of all entries made in 2013 were reported this way. Two analyses (termed 'pilot studies') on age at diagnosis and Ig replacement doses have been performed, which were limited by typical weaknesses of registry data such as missing values. Apart from this, the authors see the registry as a valuable instrument for users to compile general information, for example,

in order to prepare grant proposals or guiding patient care. Since 2011, the registry has been involved in 82 such queries.

SECTION II: CHALLENGES AND APPROACHES

The challenges outlined in the following chapter describe problems commonly faced by all (PID) registries, as well as ways to tackle them.

Data coverage and data quality

In general, data entry poses a large burden to all medical centers, even if this process is facilitated to some extent by the means of electronic online documentation as provided by modern registries. In contrast to registries in which reporting is mandatory or even enforced by law, participation in the aforementioned PID registries is completely voluntary. Expectations on the completeness of number of patients in the registry should be adjusted for this fact.

A complete automated transfer of data from electronic patient charts in all (participating) centers is desirable, but often not feasible because of the huge variety of data structures in each information system.

The issue of limited man power for the documentation process can be addressed by sharply focusing on the number of parameters required for the documentation. If needed, additional forms can be provided for a given purpose or time frame.

As there is no obligation to register all PID patients who have been diagnosed, a reporting or recruiting bias possibly plays a role in the varying disease distribution observed (see Table 1), for example, by an overrepresentation of pediatric centers or severe cases with more prominent symptoms. Another issue that will contribute to the differences in the disease frequency is the lack of precise clinical PID diagnostic criteria.

Curators of a patient registry in general have to rely on the accuracy of data entered to the registry. Many gross errors can be revealed by built-in quality assurance measures. However, some mistakes, such as transposed digits, cannot be detected via those mechanisms. Extensive source data verification is unrealistic to be performed on a regular basis in a registry with thousands of patients.

Choosing the right diagnosis

Most reports on registries state which disease classification was used when registering patients. As the

genetic cause remains unclear in many patients, the chosen diagnosis is based on clinical criteria. For diagnoses without genetic proof in the field of PID, it is not exactly clear how the diagnosis has been verified and if and which (set of) diagnostic criteria have been applied when assigning the diagnosis. Definition and adoption of unified diagnostic criteria is a plodding and ongoing process among international PID experts [51]. A recent publication provides a helping hand to pick the proper diagnosis on the basis of the International Union of Immunological Societies classification for the clinician in form of decision diagrams [52^{***}].

Funding and sustainability

A patient registry aiming at collecting long-term data, for example, on the (natural) history of chronic diseases is by nature set up with an open end. Any registry project that has such a 'longitudinal approach' requires several years of documentation before enough data have been collected to create a meaningful output. As outlined above, the sheer workload of documentation requires considerable time and preparatory effort in order to gather sufficient data for valid conclusions, for example, on the prevalence of PID. Thus, a constant challenge for these projects is to provide sustainable funding.

For all registries described here, the main pillars of support – apart from common honorary work – are public research grants and sponsorship by the industry that provides treatment for the respective disease, that is, in the field of PID, the plasma producing companies. However, sustainable long-term funding is very difficult to secure. Despite the long-term approach, most grants offer only sponsoring opportunities for some years at best and thus have to be continuously renewed. Companies that are only interested in a given disease group or market region are often not prepared to support activities outside of their focus.

Organization and collaboration

The operation of a registry should be supplemented by organizational provisions, such as a steering committee and transparent guidelines, regarding the use of data or material in order to minimize any preoccupation. This is especially important in larger projects and implemented, for example, by ESID and USIDNET [53–56].

Sharing resources and combining forces already works well in the field of PID research, as for example demonstrated by the international classification of PID [57^{***}].

CONCLUSION

Registries are an important tool to capture data on PID patients. All registries face a set of common challenges, such as ensuring data quality and sustainability of a registry project. Providing dedicated data entry personnel that travels to reporting centers in order to enter data is a common approach. New strategies, such as patient self-reporting, are a promising approach but used rarely so far.

There is consensus in the literature that patient registries are an essential instrument in PID research and should be supported.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Knerr V, Grimbacher B. Primary immunodeficiency registries [review]. *Curr Opin Allergy Clin Immunol* 2007; 7:475–480.
2. Samarghitean C, Vihinen M. Bioinformatics services related to diagnosis of primary immunodeficiencies. *Curr Opin Allergy Clin Immunol* 2009; 9:531–536.
3. Chinnabhandar V, Yadav SP, Kaul D, *et al.* Primary immunodeficiency disorders in the developing world: data from a hospital-based registry in India. *Pediatr Hematol Oncol* 2014; 31:207–211.
4. Madkaikar M, Mishra A, Desai M, *et al.* Comprehensive report of primary immunodeficiency disorders from a tertiary care center in India. *J Clin Immunol* 2013; 33:507–512.
5. Gupta S, Madkaikar M, Singh S, Sehgal S. Primary immunodeficiencies in India: a perspective. *Ann N Y Acad Sci* 2012; 1250:73–79.
6. Al-Tamemi S, Elnour I, Dennison D. Primary immunodeficiency diseases in Oman: five years' experience at Sultan Qaboos University Hospital. *World Allergy Organ J* 2012; 5:52–56.
7. Lee PP, Lau YL. Endemic infections in Southeast Asia provide new insights to the phenotypic spectrum of primary immunodeficiency disorders. *Asian Pac J Allergy Immunol* 2013; 31:217–260.
8. Reda SM, El-Ghoneimy DH, Afifi HM. Clinical predictors of primary immunodeficiency diseases in children. *Allergy Asthma Immunol Res* 2013; 5:88–95.
9. Noh LM, Nasuruddin BA, Abdul Latiff AH, *et al.* Clinical-epidemiological pattern of primary immunodeficiencies in Malaysia 1987–2006: a 20 year experience in four Malaysian hospitals. *Med J Malaysia* 2013; 68:13–17.
10. CEREDIH: The French PID study group. The French national registry of primary immunodeficiency diseases. *Clin Immunol* 2010; 135:264–272.
11. European Society for Immunodeficiencies. <http://www.esid.org/working-parties/registry/ESID-Database-Statistics>. [Accessed 28 August 2014]
12. Gathmann B, Goldacker S, Klima M, *et al.* The German national registry for ■ primary immunodeficiencies (PID). *Clin Exp Immunol* 2013; 173:372–380. This is the first comprehensive report on the advances of the German national PID register.
13. PID Registry. <http://www.pid-net.org/registry/>. [Accessed 09 July 2014]
14. Aghamohammadi A, Mohammadnejad P, Abolhassani H, *et al.* Primary ■ immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. *J Clin Immunol* 2014; 34:478–490. Update on the achievements of the Iranian national registry.

15. Cineca. <http://www.cineca.it/en>. [Accessed 22 June 2014]
 16. Quinti I, Soresina A, Spadaro G, *et al*. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol* 2007; 27:308–316.
 17. Carsetti R, Rosado MM, Donnanno S, *et al*. The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J Allergy Clin Immunol* 2005; 115:412–417.
 18. Plebani A, Soresina A, Rondelli R, *et al*. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicentre study. *Clin Immunol* 2002; 104:221–230.
 19. Cancrini C, Puliafito P, Digilio MC, *et al*. Clinical features and follow-up in patients with 22q11.2 deletion syndrome. *J Pediatr* 2014; 164:1475–1480. The study describes how analyses from registry data can help to improve guidelines for diagnosis and eventually patient care.
 20. Moschese V, Martire B, Soresina A, *et al*. Anti-infective prophylaxis for primary immunodeficiencies: what is done in Italian Primary Immunodeficiency Network centers (IPINet) and review of the literature. *J Biol Regul Homeost Agents* 2013; 27:935–946.
 21. Quinti I, Soresina A, Guerra A, *et al*. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. *J Clin Immunol* 2011; 31:315–322.
 22. Rhim JW, Kim KH, Kim DS, *et al*. Prevalence of primary immunodeficiency in Korea. *J Korean Med Sci* 2012; 27:788–793.
 23. Al-Herz W. Primary immunodeficiency disorders in Kuwait: first report from Kuwait National Primary Immunodeficiency Registry (2004–2006). *J Clin Immunol* 2008; 28:186–193.
 24. Al-Herz W, Naguib KK, Notarangelo LD, *et al*. Parental consanguinity and the risk of primary immunodeficiency disorders: report from the Kuwait National Primary Immunodeficiency Disorders Registry. *Int Arch Allergy Immunol* 2011; 154:76–80.
 25. Al-Herz W, Moussa MA. Survival and predictors of death among primary immunodeficient patients: a registry-based study. *J Clin Immunol* 2012; 32:467–473.
 26. Bousfiha AA, Jeddane L, El Hafidi N, *et al*. First report on the Moroccan registry of primary immunodeficiencies: 15 years of experience (1998–2012). *J Clin Immunol* 2014; 34:459–468.
- Comprehensive report on the Moroccan national PID registry.
27. Ehlal MS, Bener A, Laban MA. Primary immunodeficiency diseases in children: 15 year experience in a tertiary care medical center in Qatar. *J Clin Immunol* 2013; 33:317–324.
 28. REDIP. <https://redip.org.es/redip/index.php?l=es&m=estadisticas>. [Accessed 21 July 2014]
 29. Kilic SS, Ozel M, Hafizoglu D, *et al*. The prevalences [correction] and patient characteristics of primary immunodeficiency diseases in Turkey: two centers study. *J Clin Immunol* 2013; 33:74–83.
 30. 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.
- First comprehensive report from the national UKPID registry.
31. UKPIN. <http://ukpin.org.uk/home/>. [Accessed 22 June 2014]
 32. ASCIA. http://www.immunodeficiency.org.au/about_register.html. [Accessed 22 June 2014]
 33. Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and New Zealand. *J Clin Immunol* 2007; 27:517–524.
 34. Baumgart KW, Britton W, Kemp A, *et al*. The spectrum of primary immunodeficiency disorders in Australia. *J Allergy Clin Immunol* 1997; 100:415–423.
 35. Vajdic CM, Mao L, van Leeuwen MT, *et al*. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? *Blood* 2010; 116:1228–1234.
 36. Guzman D, Veit D, Knerr V, *et al*. The ESID Online Database network. *Bioinformatics* 2007; 23:654–655.
 37. Eades-Perner AM, Gathmann B, Knerr V, *et al*. The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. *Clin Exp Immunol* 2007; 147:306–312.
 38. Gathmann B, Mahlaoui N, Gérard L, *et al*. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2014; 134:116–126.e11.
- The first comprehensive multinational analysis on CVID, the most prominent group of PID patients in the ESID registry.
39. Piriälä H, Väliäho J, Vihinen M. Immunodeficiency mutation databases (IDbases). *Hum Mutat* 2006; 27:1200–1208.
 40. Rikonen P, Vihinen M. MUTbase: maintenance and analysis of distributed mutation databases. *Bioinformatics* 1999; 15:852–859.
 41. Leiva LE, Zelazco M, Oleastro M, *et al*. Primary immunodeficiency diseases in Latin America: the second report of the LAGID registry. *J Clin Immunol* 2007; 27:101–108.
 42. Condino-Neto A, Franco JL, Espinosa-Rosales FJ, *et al*. Advancing the management of primary immunodeficiency diseases in Latin America: Latin American Society for Immunodeficiencies (LASID) initiatives. *Allergol Immunopathol (Madr)* 2012; 40:187–193.
 43. Cabral-Marques O, Klaver S, Schimke LF, *et al*. First report of the Hyper-IgM syndrome Registry of the Latin American Society for immunodeficiencies: novel mutations, unique infections, and outcomes. *J Clin Immunol* 2014; 34:146–156.
- The article impressively describes the usefulness of registries. In this study, the registry was instrumental in tracking down new mutations and revising the spectrum of infections seen in patients suffering from HIGM syndrome.
44. Errante PR, Franco JL, Espinosa-Rosales FJ, *et al*. Advances in primary immunodeficiency diseases in Latin America: epidemiology, research, and perspectives. *Ann N Y Acad Sci* 2012; 1250:62–72.
 45. IMS RIKEN Center for Integrative Medical Sciences. <http://www.ims.riken.jp/english/projects/pj01.php>. [Accessed 22 June 2014]
 46. RAPID. <http://web16.kazusa.or.jp/rapid/>. [Accessed 13 July 2014]
 47. SCETIDE. <https://www.scetide.org/>. [Accessed 22 June 2014]
 48. Gennery AR, Slatter MA, Grandin L, *et al*. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol* 2010; 126:602–610.
 49. Winkelstein JA, Marino MC, Johnston RB Jr, *et al*. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)* 2000; 79:155–169.
 50. Sullivan KE, Puck JM, Notarangelo LD, *et al*. USIDNET: a strategy to build a community of clinical immunologists. *J Clin Immunol* 2014; 34:428–435.
- A comprehensive report on the activities of the USIDNET including an extensive description of the USIDNET registry.
51. European Society for Immunodeficiencies. <http://esid.org/Working-Parties/Clinical>. [Accessed 27 June 2014]
 52. Bousfiha AA, Jeddane L, Ailal FA, *et al*. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. *J Clin Immunol* 2013; 33:1078–1087.
- Very innovative and vivid presentation of guidelines to PID diagnosis in the form of decision diagrams based on the International Union of Immunological Societies disease classification and ongoing work.
53. European Society for Immunodeficiencies. <http://esid.org/Working-Parties/Registry/Resources/Registry-Steering-Committee>. [Accessed 29 June 2014]
 54. European Society for Immunodeficiencies. <http://esid.org/Working-Parties/Registry/Resources/Publications>. [Accessed 29 June 2014]
 55. USIDNET. <http://usidnet.org/usidnet-registry/registry-data-query-form/>. [Accessed 29 June 2014]
 56. USIDNET. <http://usidnet.org/committees/steering-committee/>. [Accessed 29 June 2014]
 57. Al-Herz W, Bousfiha A, Casanova JL, *et al*. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol* 2014; 5:162.
- The regularly updated standard classification in the rapidly progressing field of PID research.