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Health Policy Analysis

Value of the Rare Disease Registry of the Italian Region Friuli Venezia Giulia

Francesca Valent, MD,[1,*] Laura Deroma, MD,[2] Alessandro Moro, MD,[2] Giovanni Ciana, MD,[2] Paolo Martina, MSc,[3] Fabio De Martin, MSc,[3] Elisa Michelesio, MSc,[3] Maria Rosalia Da Riol, MD,[2] Daniela Macor, RN,[2] Bruno Bembi, MD,[2] the Rare Disease Network of the Friuli Venezia Giulia Region

[1]*Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine, Udine, Italy;* [2]*Regional Coordinating Center for Rare Diseases, University Hospital of Udine, Udine, Italy;* [3]*Insiel SpA, Udine, Italy*

ABSTRACT

Background: The lack of epidemiological and clinical data is a major obstacle in health service planning for rare diseases. Patient registries are examples of real-world data that may fill the information gap.

Objective: We describe the Rare Disease Registry of the Friuli Venezia Giulia region of Italy and its potential for research and health planning.

Methods: The Rare Disease Registry data were linked with information on mortality, hospital discharges, ambulatory care, and drug prescriptions contained in administrative databases. All information is anonymous, and data linkage was based on a stochastic key univocal for each patient. Average annual costs owing to hospitalizations, outpatient care, and medications were estimated.

Results: Implementation of the Registry started in 2010, and 4250 participants were registered up to 2017. A total of 2696 patients were living in the region as of January 1, 2017. The overall raw prevalence of rare diseases was 22 per 10,000 inhabitants, with higher prevalence in the pediatric population. The most common disease groups were congenital malformations, chromosomal and genetic syndromes, and circulatory and nervous diseases. In 2017, 30 patients died, 648 were hospitalized, and 2355 received some type of ambulatory care. The total annual estimated cost was approximately €6.5 million, with great variability in the average patient cost across diseases.

Conclusions: The possibility of following the detailed real-world care experience of patients with each specific rare disease and assessing the costs related to each step in their care path represents a unique opportunity to identify inefficiencies, optimize care, and reduce waste of resources.

Keywords: administrative health data, data linkage, disease registry, Italy, rare diseases.

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Introduction

The importance of real-world data for health surveillance purposes and for informing decision making is well recognized.[1] Evidence provided by randomized clinical trials may not fit the real-world characteristics of patients, have low external validity, and require long time and high costs to be produced. Nevertheless, the use of real-world data, favored by technological progress, can strongly contribute to generate clinical evidence, when supported by adequate study design.[2] Population-based registries are one of the potential solutions for obtaining evidence representative of the clinical real world of patients.[3] They consist of the organized collection of data on all new patients or outcomes of patients with a particular disease in a defined geographic area and can be effectively used for both epidemiological research and support to health policymaking, with the ultimate goal of improving the quality of patient care.[1]

In the field of rare diseases (RDs), a group of heterogeneous conditions that, in the European Union are defined as each having a prevalence ≤5 individuals per 10 000,[4] absence of reliable and consistent data and poor quality of epidemiological studies are important issues.[5] Some diseases are so rare that patients are never included in trials.[6] For other diseases, trials are conducted but active participation in research may entail such a great burden for patients that feasibility may be jeopardized.[7] To fill the information gaps and support epidemiological research in RDs, the

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* Address correspondence to: Francesca Valent, MD, SOC Istituto di Igiene ed Epidemiologia Clinica, Azienda Sanitaria Universitaria Integrata di Udine, Via Colugna 50, 33100 Udine, Italy. Email: francesca.valent@asuiud.sanita.fvg.it

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European Union has recommended that member states support information networks and disease registries.[8]

In the field of RDs, however, the development of registries may also be challenging because RDs are affected by unique issues, such as broad knowledge gaps, paucity of clinicians providing care to each type of patient, possible lack of treatment guidelines, many diverse stakeholders, and a large number of differences, making specific registries not feasible for every single one of them.[6] In addition, the setup and maintenance of RD registries may be hindered by practical, methodological, and cultural issues just like any other registry: insufficient funding, unclear protocol definition, lack of involvement of all relevant stakeholders, absence of data sharing or feedback, poor data quality, no representativeness, and patient privacy regulations.[1]

Despite these difficulties, observational data collection is fundamental for building the knowledge base for RDs. In 2013, the European Union Committee of Experts on Rare Diseases issued recommendations[9] to guide member states in this process.

In Italy, a national RD network was created in 2001, when the government enacted a specific law to provide the right to gratuity of care for citizens suffering from RDs.[10] The law also provided for the creation of regional networks of centers of reference and RD registries. Furthermore, it established the Italian National Registry for Rare Diseases at the Istituto Superiore di Sanità. The new regional registries could be very different from each other in organization, information collected, and main purpose.[11] Nonetheless, as soon as they were implemented, they all started feeding into the National Registry, which combines information from each of the regional registries with a pre-agreed common minimum dataset (including patient's demographic data, name and group of disease, use of drugs, dates of first symptom occurrence, diagnosis, registration, and vital status).[12] Some regions started to implement RD registries as early as 2002,[13] although the whole system at the national level was completed more than 10 years later.

Veneto was the first Italian region that established an RD registry,[14] and its experience has been described after 10 years of activity.[13] The Registry of the Veneto region is based on an information system connecting all the regional centers of expertise with the local public health authorities and pharmacies through a protected network (intranet). Within the network, all the relevant clinical information on RD patients is entered into a specific form.[13]

Friuli Venezia Giulia (FVG), a 1 200 000-inhabitant region in the northeast of Italy, neighboring Veneto and including 5 local health agencies, started to implement its current Rare Disease Registry (RDR) in 2010 under the guidance of the Regional Coordinating Centre for Rare Diseases. Since 2010, the FVG region has contributed to the National Registry of Rare Diseases by annually sending its RDR data, although some of the variables required by the National Registry (dates of first symptom occurrence and of diagnosis) were not collected in the FVG region.[15]

The strategy for feeding data into the RDR in the FVG region is different from the one used in Veneto: information is not specifically entered by centers of expertise; it is retrieved from the generic patient management software used in all the regional public hospitals. In addition, in the FVG region, an anonymous version of the RDR is integrated into a Regional Health Information System (RHIS), a data warehouse including many health-related administrative databases that are completely anonymous but nonetheless can be deterministically linked with each other at the individual patient level through a univocal stochastic key.

Here we describe the data collected in the RDR of the FVG region from its implementation and, for all the patients living in FVG, additional information that can be obtained through linkage with other RHIS anonymous databases, including an estimate of direct medical costs, with the aim of showing the potential of these data for both research and health policy purposes.

Ethics Approval and Consent to Participate

The authors assert that all of the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and the Declaration of Helsinki of 1975 as revised in 2008. This article does not contain any studies with human or animal participants performed by any of the authors. Because this analysis was based on anonymous administrative data, patient informed consent and ethical committee approval were not required in Italy.

Methods

The analyses described in this article were based on the data contained in the RDR of the FVG region, whose implementation started in 2010. At that time, all physicians working in regional public hospitals were instructed to flag patients with RDs who were attending their ambulatories or hospital wards for the first time with the generic clinical management software that was used in the everyday practice by all clinicians in FVG hospitals (the "G2-Clinico" software developed by Insiel SpA, the in-house information and communication technology company of the FVG region). When a patient with an RD is flagged through a simple click on a designated item "MalattieRare" in the G2-Clinico patient management software, information on the patient, the diagnosed disease, the physician, the reference center, and the date of registration automatically feed the RDR, with no extra data entry required by the clinician. The G2-Clinico case report form is provided (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1917).

Patients living in the FVG region and in other Italian regions or countries can be flagged. Annually, the FVG Health Authority through Insiel SpA transfers information on patients with RDs, retrieved from the G2-Clinico software, to the Italian National Registry for Rare Diseases, including personal identifiers to avoid patients who attend clinics in different regions being duplicated in the National Registry.

For newly diagnosed patients living in the FVG region, registration in the RDR is necessary for obtaining an exemption from medical copayment of all healthcare services connected with the disease, as regulated by the Italian Ministry of Health.[16] Thus, the criterion for inclusion of a patient in the RDR of the FVG region is that the person has either a clinical or a laboratory diagnosis of a disease included in the list issued and periodically updated by the Ministry of Health. In 2017, the original national list of RDs entitling completely free medical care[10] was updated by the Ministry of Health, and a new list has been effective since September 2017.[16]

In the new list, RDs have been divided into 16 specialty-specific groups: (1) infectious and parasitic diseases, (2) neoplasms, (3) diseases of endocrine glands, (4) metabolic diseases, (5) immunity diseases, (6) diseases of blood and hematopoietic organs, (7) diseases of nervous system, (8) diseases of vision, (9) diseases of circulatory system, (10) diseases of respiratory system, (11) diseases of digestive system, (12) diseases of genitourinary system, (13) skin diseases, (14) diseases of bone and muscles, (15) congenital malformations and chromosomal and genetic syndromes, and (16) perinatal conditions. Some previously rare conditions (celiac disease, Reifenstein syndrome, Kawasaki disease, dermatitis herpetiformis, undifferentiated connectivitis, Down syndrome, and Klinefelter syndrome) were moved to the list of chronic disorders.[16]

In addition, since September 2017, a new organizational model for the Rare Disease Network has been implemented in the FVG region. In the new organization, the Network has been redesigned into *subnetworks*, each referring to a specific disease group among those classified by the Ministry of Health. For each disease group, only a few centers (usually <5), selected based on objective excellence criteria (eg, the highest number of patients attending the center, impact of scientific publications, initiatives with patient associations, as suggested by the European Network for Rare Diseases) are entitled to register new cases. (see evaluation grid in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1917).

For all persons flagged as patients with an RD in the G2-Clinico, the core data of the RDR are also automatically transferred, with no personal identifiers, into the regional data warehouse RHIS. As stated above, the RHIS includes data from other anonymous administrative health databases that can be linked with each other at the individual patient level, through a univocal stochastic key (for the complete list of currently available databases, see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.04.1917). The RDR, integrated within the RHIS, is made available for regional-level epidemiological analyses. For patients residing in the FVG region, the RHIS contains complete information. But for patients residing outside the region, only hospitalizations and ambulatory care accesses occurring in the regional centers are recorded.

In this article, we present all annual registrations from 2010 to 2017 in the RDR of the FVG region, including those of patients living out of the region. Nevertheless, because only partial information on health resource use is available for participants not living in the FVG region, they were excluded from further analyses.

Patients living in the FVG region, however, were included in additional analyses. To assess the prevalence of RDs in the FVG region, the number of patients registered in the RDR, living in the region as of January 1, 2017, was divided by the regional total resident population in 2017.[17]

Also, for patients with RDs living in the FVG region as of January 1, 2017, we integrated the RDR with the following RHIS databases: mortality, hospital discharges, ambulatory care, drug prescriptions, and medications directly dispensed by the hospital pharmacies to outpatients. For those participants, we provide an overview of demographic characteristics; mortality (number of deaths and the most frequent group of *International Classification of Diseases, Ninth Revision* causes); hospitalizations (average annual number of admissions, and the most frequent main discharge diagnosis); ambulatory care visits, exams, and procedures (average annual number, and the most frequent procedure; for laboratory tests performed on blood, the procedure "blood withdraw" was not counted to avoid duplications); and drug prescriptions (average annual number, and the most prescribed medication). These analyses referred to 2017 because it was the most recent year with complete information in all RHIS databases.

An estimate of direct medical costs was also obtained. For hospitalizations, diagnosis-related group tariffs were used as proxies of the hospitalization costs, although the actual production costs may differ according to hospital characteristics.[18] For ambulatory care, regional tariffs (per unit of service) adopted in the FVG region to fund healthcare providers were used.[19] For drug prescriptions, the cost estimate was different depending on the type of medicine and mode of distribution: for drugs retrieved by patients at community pharmacies, the cost is the drug public price with the application of discounts set by the law[20,21]; for drugs directly bought by the Regional Health System and either distributed by hospitals upon a patient's discharge or by community pharmacies on behalf of the Regional Health System, the cost depends on negotiations between manufacturers and the Regional Health System and also, when community pharmacies are involved, on agreements stipulated with wholesalers and pharmacies associations.[22]

To provide an example of the potential use of the RDR for specific rare diseases, we estimated the direct medical costs of patients with some lysosomal storage diseases that are usually associated with high medical costs[23] (Fabry disease, Gaucher disease, Niemann-Pick disease) in 2017.

To assess whether there was some temporal trend in the average estimated cost for patients with an RD, we applied the aforementioned calculations to the cohorts of participants living in the FVG region at the beginning of each previous year.

All the analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Overall, 4250 participants were included in the RDR of the FVG region from 2010 to 2017; of them, 3439 (80.9%) lived in the region and 811 came from outside. Figure 1 shows the distribution of registrations of patients by calendar year. The RDR included patients from all the other Italian regions (except the northwestern Valle d'Aosta region), with those from the neighboring Veneto region being the most frequent (445 patients, 55%). Thirty-six patients (4.4% of nonresidents) came from countries other than Italy. Half of the patients from outside the FVG region were registered for malformations, chromosomal and genetic diseases (N = 190), and metabolic diseases (N = 189). Fifty-five percent had ambulatory visits (447 patients, totaling 2302 visits, ie, 5.1 per patient on average), and 45% had hospitalizations (367 patients, totaling 1189 hospitalizations, ie, 3.2 per patient on average, and 4498 days in hospital) in the FVG region after the initial registration, with variability across disease groups. Patients with malformations and chromosomal and genetic diseases required the highest number of visits (N =786), with those with metabolic diseases having the highest number of hospitalizations (N = 524).

Among patients living in the FVG region, the most frequent RD groups included the nervous system, congenital malformations, chromosomal and genetic syndromes, and the circulatory system (immune-rheumatologic diseases) (Table 1). Overall, women represented 60.1% of all patients, with variability depending on the disease group. Age at registration was also highly variable.

Of those participants, 2696 were living in the FVG region as of January 1, 2017. The distribution of prevalent cases across disease groups is shown in Table 2. The overall raw prevalence of RD was 22.13 cases per 10,000 inhabitants (95% CI: 21.30-22.97), that is, approximately 1 in 450 inhabitants. Age-specific prevalence was 37.25 (34.45-40.05) in the age group 0 to 17 (N = 676), 19.41 (18.39-20.42) in the age group 18 to 64 (N = 1403), and 19.68 (18.14-21.23) in the age group ≥65 years (N = 617). The raw prevalence of each group was 0.82 per 10 000 for infectious and parasitic diseases; 1.20 for neoplasms; 0.71 for diseases of endocrine glands; 1.33 for metabolic diseases; 0.97 for immunity diseases; 0.34 for diseases of blood and hematopoietic organs; 2.31 for diseases of nervous system; 1.26 for diseases of vision; 2.61 for diseases of circulatory system; 0.01 for diseases of respiratory system; 0.39 for diseases of digestive system; 0.64 for diseases of genitourinary system; 1.39 for skin diseases; 0.61 for diseases of bone and muscles; 3.45 for congenital malformations, chromosomal, and genetic syndromes; and 0.04 for perinatal conditions.

Among prevalent patients, 648 were hospitalized and 2355 received ambulatory care in 2017 (Table 2); the median

Figure 1. Annual registrations of subjects in the Rare Disease Registry of Friuli Venezia Giulia, Italy, by year and residence, 2010 to 2017.

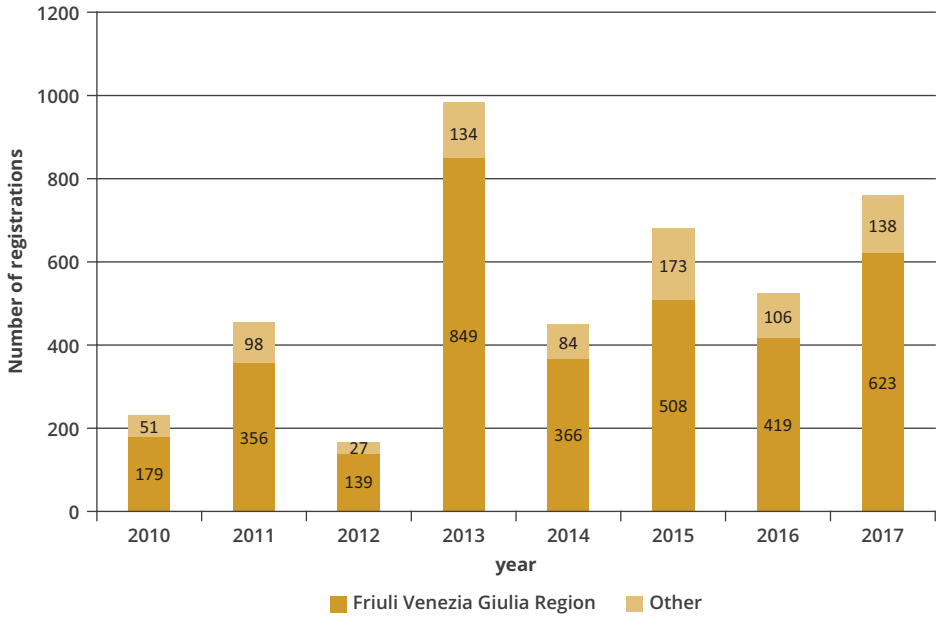


Table 1. Demographic characteristics of patients with rare diseases living in Friuli Venezia Giulia, Italy, 2010-2017.

Rare Disease Group*	N	Percent of patients	Percent female	Age at registration			
				Mean	SD	Median	Range
1. Infectious and parasitic diseases	114	3.3	61.4	52.4	16.1	54	8-82
2. Neoplasms	170	4.9	50.6	28.3	21.9	22.5	0-73
3. Diseases of endocrine glands	109	3.2	68.8	32.1	23.3	31	0-82
4. Metabolic diseases	205	6.0	43.4	38.0	24.3	37	0-91
5. Immunity diseases	122	3.5	59.8	39.2	19.5	42	0-85
6. Diseases of blood and hematopoietic organs	74	2.2	48.6	35.1	25.6	33	0-87
7. Diseases of nervous system	468	13.6	45.5	50.1	23.2	55.5	0-89
8. Diseases of vision	220	6.4	46.8	43.7	20.0	42.5	0-84
9. Diseases of circulatory system	389	11.3	67.4	59.8	18.9	64	5-91
10. Diseases of respiratory system	46	1.3	52.2	53.9	11.5	50.5	37-81
11. Diseases of digestive system	86	2.5	37.2	41.6	24.2	39.5	0-95
12. Diseases of genitourinary system	100	2.9	91.0	55.0	18.5	56.5	10-89
13. Skin diseases	221	6.4	65.6	61.6	23.7	68	0-95
14. Diseases of bone and muscles	100	2.9	79.0	57.0	16.3	58.5	4-85
15. Congenital malformations, chromosomal, and genetic syndromes	448	13.0	60.7	16.4	16.8	11	0-83
16. Perinatal conditions	7	0.2	0.0	7.6	5.0	8	2-16
99. Diseases no longer included among rare diseases†	560	16.3	77.7	36.9	24.8	41	0-92
Total	3439	100.0	60.6	42.1	25.5	46	0-95

*List of diseases included in each group is available from the Italian Ministry of Health.[16]
†As of September 15, 2017; includes Reifenstein syndrome, Kawasaki disease, dermatitis herpetiformis, undifferentiated connectivitis, Down syndrome, and Klinefelter syndrome.

Table 2. Distribution of rare disease patients who were living in Friuli Venezia Giulia, Italy, as of January 1, 2017 (prevalent cases), and use of health resources.

Rare Disease Group*	N	Median age	% female	N deaths	Hospitalizations				Ambulatory care		Total cost of prescribed medications	Total cost of medications directly provided
					N of patients	N events	Total LOS	Total cost	N of patients	Total cost		
1. Infectious and parasitic diseases	100	56.5	66.0	0	11	17	376	€142 044	89	€35 389	€18 450	€5034
2. Neoplasms	146	21.5	45.9	1	27	40	198	€100 335	119	€65 160	€14 437	€7218
3. Diseases of endocrine glands	87	23	66.7	1	14	17	89	€42 668	80	€31 146	€17 203	€1563
4. Metabolic diseases	162	36	43.8	2	56	87	672	€370 815	140	€77 032	€297 369	€366 044
5. Immunity diseases	118	48	61.9	1	48	92	1127	€496 148	98	€79 808	€53 982	€19 628
6. Diseases of blood and hematopoietic organs	42	33	50.0	0	11	28	251	€135 022	32	€20 779	€7316	€6308
7. Diseases of nervous system	282	50	45.4	15	90	150	1169	€543 725	247	€95 707	€66 969	€19 654
8. Diseases of vision	153	42	48.4	0	17	25	158	€87 912	130	€45 264	€18 056	€2493
9. Diseases of circulatory system	318	65	66.0	5	80	131	1260	€704 607	298	€185 588	€113 830	€55 758
10. Diseases of respiratory system	1	68	100.0	0	1	3	21	€9487	1	€2866	€230	€0
11. Diseases of digestive system	48	24	25.0	0	7	7	24	€23 542	42	€14 286	€12 311	€262
12. Diseases of genitourinary system	78	59	89.7	0	19	26	153	€75 293	72	€28 879	€18 708	€4251
13. Skin diseases	170	68.5	65.3	0	43	66	487	€248 068	153	€63 648	€50 196	€2054
14. Diseases of bone and muscles	74	61.5	81.1	1	26	49	564	€216 788	64	€48 902	€32 324	€16 585
15. Congenital malformations, chromosomal, and genetic syndromes	420	14	61.0	1	130	212	931	€435 052	347	€167 749	€58 778	€15 150
16. Perinatal conditions	5	11	0.0	0	0	0	0	€0	4	€2129	€2503	€0
99. Diseases no longer included among rare diseases†	492	44	79.1	3	68	92	589	€308 991	439	€183 424	€114 769	€35 412
Total	2696	44	61.8	30	648	1042	8069	€3 940 496	2355	€1 147 756	€897 430	€557 414

LOS indicates length of stay.
*List of diseases included in each group is available from the Italian Ministry of Health.[16]
†As of September 15, 2017; includes Reifenstein syndrome, Kawasaki disease, dermatitis herpetiformis, undifferentiated connectivitis, Down syndrome, and Klinefelter syndrome.

number of health agencies where patients received outpatient care was 2. The most commonly prescribed medications were cholecalciferol (1212 prescriptions), pantoprazole (N = 775), acetylsalicylic acid (N = 688), amoxicillin, and beta-lactamase inhibitor (N = 652). During the year, 30 patients died. The initial cause of death was related to the underlying RD in most cases (Table 3).

Table 4 shows the overall estimated direct medical costs by disease group and the average cost per patient in 2017. The average cost per patient was approximately €2400, with variability across disease groups. Overall, 60% of the cost was due to hospitalizations, 18% to outpatient care, 14% to prescribed medications, and 8% to medications directly distributed by hospital pharmacies.

Table 3. Initial cause of death among 30 rare disease patients who were living in Friuli Venezia Giulia, Italy, as of January 1, 2017, and died in 2017.

Underlying Rare Disease Group*	*ICD-9* code	Description	N
2. Neoplasms	415.1	Pulmonary embolism	1
3. Diseases of endocrine glands	173.9	Unspecified malignant neoplasm of skin	1
4. Metabolic diseases	277.3	Amyloidosis	1
4. Metabolic diseases	519.8	Diseases of respiratory system not elsewhere classified	1
5. Immunity diseases	202.3	Malignant histiocytosis	1
7. Diseases of nervous system	335.2	Motor neuron disease	6
7. Diseases of nervous system	340	Multiple sclerosis	6
7. Diseases of nervous system	519.8	Diseases of respiratory system not elsewhere classified	3
9. Diseases of circulatory system	070.5	Viral hepatitis without mention of hepatic coma	1
9. Diseases of circulatory system	203	Multiple myeloma and immunoproliferative neoplasms	1
9. Diseases of circulatory system	205.0	Acute myeloid leukemia	1
9. Diseases of circulatory system	428.9	Unspecified heart failure	1
9. Diseases of circulatory system	486	Pneumonia	1
14. Diseases of bone and muscles	571.9	Unspecified chronic liver disease without mention of alcohol	1
15. Congenital malformations, chromosomal, and genetic syndromes	558	Unspecified noninfectious gastroenteritis and colitis	1
99. Diseases no longer included among rare diseases†	038.9	Unspecified septicemia	1
99. Diseases no longer included among rare diseases†	153.9	Malignant neoplasm of colon	1
99. Diseases no longer included among rare diseases†	431	Intracerebral hemorrhage	1

ICD-9 indicates *International Classification of Diseases, Ninth Revision*.
*List of diseases included in each group is available from the Italian Ministry of Health.[16]
†As of September 15, 2017; includes Reifenstein syndrome, Kawasaki disease, dermatitis herpetiformis, undifferentiated connectivitis, Down syndrome, and Klinefelter syndrome.

In 2017, there were 11 patients with Fabry disease, 11 with Gaucher disease, and 2 with Niemann-Pick disease in the FVG region. Overall, they had 19 hospitalizations for a total of 96 days. The average annual direct costs among these patients were much higher than the average cost per RD patient: €11 291, €9310, and €19 525 per patient, respectively. Among these patients, 70.6%, 85.6%, and 82.7%, respectively, of the direct medical costs were due to medications directly dispensed by hospital pharmacies (in particular, velaglucerase alfa, imiglucerase, agalsidase beta, miglustat, and migalastat).

In Figure 2, we compare the estimated costs in each year 2014 to 2017 (the years with the highest completeness of patient registration). The average cost of hospitalizations has progressively decreased, whereas the other cost components did not show a marked decreasing pattern. Case fatality was higher among patients in 2014 and 2015 than in 2016 and 2017.

Discussion

According to the classification of registries by Kodra et al,[24] the RDR of the FVG region is a public health registry. In fact, it focuses on disease occurrence and collects rather basic data. It is highly representative of the disease experience in the regional population, and it is used mainly for descriptive epidemiology, health planning, and healthcare path identification.

In this region, an added value is the possibility of linking RDR data with many other administrative health-related databases, such as hospital discharge or ambulatory or drug prescription data, in a completely anonymous manner. This allows health professionals to enrich the core data contained in the RDR with other information useful to assess, in a timely and efficient manner, the healthcare provided to RD patients. In this article, we only presented an overview of information that can be easily obtained through data linkage, but potentially all types of retrospective studies, both descriptive and etiological, can be designed and conducted using these databases: prevalence studies, cohort studies, case-control studies, and case-crossover studies, as already done for conditions other than RDs.[25–28]

In addition to being a resource for research purposes, the RDR is a valuable tool for quantifying the resources needed for the management of the different diseases by the regional centers; for local and regional health planning purposes; for funding allocation; and as a scientific basis for decisions on device supply, relations with patient organizations, and policies regarding patients with RDs. We showed that almost 20% of registered patients live outside the FVG region, suggesting that our region is capable of providing high-quality care and attracting patients living elsewhere, especially for some conditions. For example, the FVG Registry recorded hundreds of patients from Veneto (eg, 51 with metabolic diseases, 41 with interstitial cystitis, 17 with Williams' disease) despite that in that region there are various centers of expertise within the European Reference Networks for rare diseases.[29] The fact that many patients with RDs often seek care outside their own region and that some Italian regions have particularly attractive centers of expertise is not new.[15]

Table 4. Total estimated direct cost per rare disease group and average cost per patient in 2017, among rare disease patients who were living in Friuli Venezia Giulia, Italy, as of January 1, 2017, (prevalent cases).

Rare Disease Group*	Total cost	Average patient cost
1. Infectious and parasitic diseases	€200 918	€2009
2. Neoplasms	€187 149	€1282
3. Diseases of endocrine glands	€92 580	€1064
4. Metabolic diseases	€1 111 260	€6860
5. Immunity diseases	€649 565	€5505
6. Diseases of blood and hematopoietic organs	€169 425	€4034
7. Diseases of nervous system	€726 055	€2575
8. Diseases of vision	€153 725	€1005
9. Diseases of circulatory system	€1 059 783	€3333
10. Diseases of respiratory system	€12 583	€12 583
11. Diseases of digestive system	€50 401	€1050
12. Diseases of genitourinary system	€127 131	€1630
13. Skin diseases	€363 965	€2141
14. Diseases of bone and muscles	€314 598	€4251
15. Congenital malformations, chromosomal, and genetic syndromes	€676 729	€1611
16. Perinatal conditions	€4633	€927
99. Diseases no longer included among rare diseases†	€642 595	€1306
Total	€6 543 096	€2427

*List of diseases included in each group is available from the Italian Ministry of Health.[16]
†As of September 15, 2017; includes Reifenstein syndrome, Kawasaki disease, dermatitis herpetiformis, undifferentiated connectivitis, Down syndrome, and Klinefelter syndrome.

Our analyses also showed that some groups of diseases require more hospitalizations or medication prescriptions than others; that some disease groups involve mainly female patients, prompting healthcare professionals to pay attention to issues that typically involve women; and that at least half of patients are visited in more than one health district, indicating fragmentation of healthcare and the need to investigate the reasons that induce patients, including those from other regions,[15] to seek care at different places (eg, are patients with rare diseases also engaged in doctor shopping?).[30] We also observed that proton pump inhibitors and antibiotics are largely prescribed in patients with RDs, as they are in the general Italian population.[31]

The possibility of estimating at least some direct medical costs is very useful for resource allocation and priority setting. In fact, our analysis shows great heterogeneity in the average annual medical cost and in cost partitioning (hospitalizations vs drugs) across RD groups. The RDR of the FVG region has the advantage of being able to investigate the resource needs and use for each and every RD, whereas usually cost and burden evaluations focus on a very limited number of conditions.[32] The possibility of following the detailed real-world care experience of patients with each specific disease and assessing the costs related to each step in their care path represents a unique opportunity to identify inefficiencies, optimize care, and reduce any waste of resources.

The RDR also allowed us to estimate the RD prevalence in this region. The raw prevalence estimated in the FVG region was approximately 10 times greater than the prevalence estimated in Taiwan from National Health Insurance data (33/100,000 in 2014).[33] Nevertheless, analyses based on hospital records data in Australia[34] and Hong Kong[35] found a much higher cumulative prevalence: 2% and 1.5%, respectively. Based on those studies and on literature data periodically reviewed by Orphanet,[36] Ferreira hypothesizes a minimal cumulative prevalence of 1.5% to 6.2%,[37] that is, up to 1 person in 16, could be affected by an RD. The RDR of the FVG region, then, has probably captured only part of the patients with RDs living in the region. Our estimated prevalence (22/10,000) was also lower than prevalence estimated in the Italian neighboring Veneto region (33/10,000),[13] although both estimates had the same order of magnitude. Looking at age-specific prevalence estimates, the difference between the FVG region and Veneto (44/10 000 in the age group 0-17, 31 in the group 18-64, and 18 in the group ≥65 years[13]) is small. Thus, part of the difference in the crude overall prevalence between the 2 regions may depend on different population structures, with the FVG region being much older.[38] In addition, the registry of the FVG region is much younger than the one of the Veneto region, which was started in 2002, and this could also partly explain the difference between the 2 estimates. The prevalence in the FVG region is certainly underestimated, also owing to a lack of registration of patients diagnosed before 2010, especially in case of mild diseases not requiring frequent access to the public healthcare centers where registration can take place. If this hypothesis is true, at least part of the gap will be filled with time. At the moment, our estimate should be considered a minimum value.

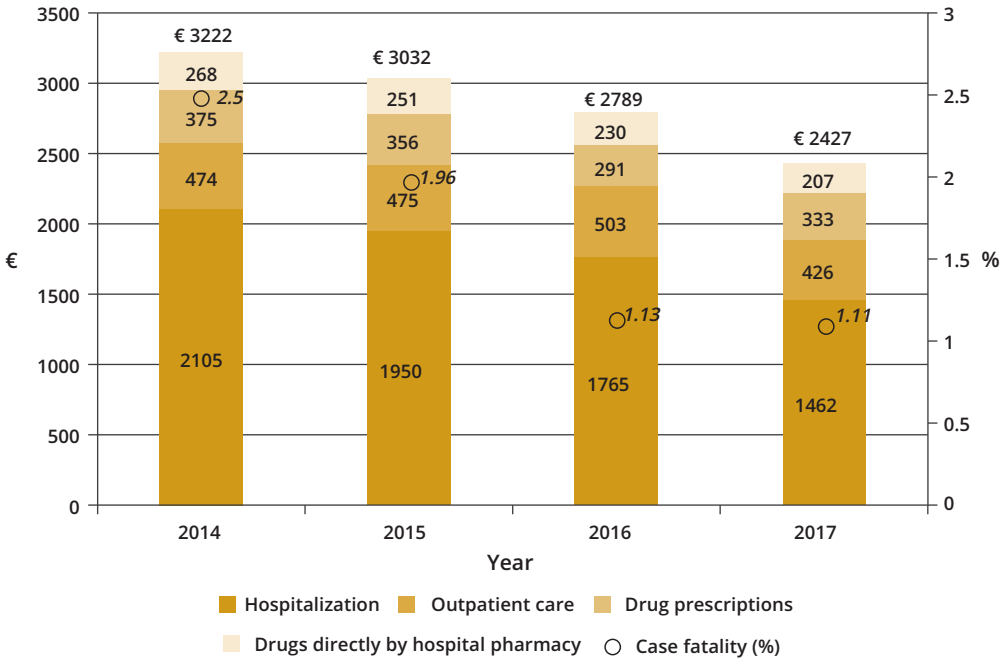
At the national level, Italian estimates of birth prevalence and incidence of selected diseases[15] differed from those estimated by Orphanet, which, however, considered studies employing heterogeneous methodologies and might overestimate prevalence since epidemiological studies are more likely to come from regions with higher prevalence.[36]

Despite the undeniable difficulties in assessing the real cumulative prevalence of RDs, studies consistently found that they are high in the pediatric population[13,33] and that remarkable proportions of all RD cases involve children.[34,35] This was also evident in the FVG region, indicating the need to address challenges faced by parents during their child's diagnosis and care experience,[39] access to social services, medical home and transition care, and psychological support.[40]

Despite the initial difficulties with data registration, we believe the RDR of the FVG region is a high-quality data collection. Case ascertainment is now good, although we lack a gold standard of comparison to measure completeness: the yearly distribution of registrations suggests that registration was partial during the first 4 years, followed by a peak in 2013 (when awareness was strongly raised among the clinicians by the Regional Coordinating Center), after which a sort of plateau was reached, indicating the achievement of a fairly complete registration of the new cases. To further foster the timely and accurate registration of all new cases by the physicians of the regional Rare Disease Network, all regional reference centers have the goal of recording 100% of cases they manage.[41]

One limitation of the registry is that is does not collect information on dates of diagnosis and of first occurrence of symptoms. Thus, we cannot estimate the incidence of diseases or assess the diagnostic delay. A newer version of the data collection form should include that information.

Figure 2. Estimated annual average of direct medical costs of patients in the Rare Disease Registry of Friuli Venezia Giulia, Italy, living in the region from January 1, 2014, to January 1, 2017.



Conclusions

Despite that some prevalent cases may still have to be captured in the RDR, the possibility to link it with other databases allows the evaluation of healthcare resource utilization and the conduction of most types of retrospective studies.

The potential is enormous. Maintaining accuracy of case registration will permit us to fill the suspected prevalence gap and to pursue complete case ascertainment. Enriching the registry minimum dataset with the dates of first symptom occurrence and diagnosis would allow estimating incidence and diagnostic delay.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.04.1917.

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