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# The Italian National Rare Disease Registry: epidemiology of rare diseases in Italy and European Reference Networks (ERNS)

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## Introduction

The National Registry of Rare Diseases (RNMR) is a network of Regional Registries (RR), established by law in 2001, rooted in the public health system. In view of the establishment of European Reference Networks, RNMR provided information on the activity of Centres to be endorsed by the Italian government. Till 2012, RR were established in all Italian Regions and a minimum set of data was agreed. Data are collected at the time of diagnosis certification. RNMR monitors an updateable list of 283 individual and 47 groups of rare diseases (RD). In particular RNMR can be considered now a population-based registry with a well-defined population amounting to about 61 million residents.

## Method

The RNMR is structured into three levels of data flow, reflecting the Italian Healthcare System: local, regional and national. The local level refers to the clinical centers identified by each Region, which are the primary sources of data flow . The intermediate level is made by regional registries. The central database is located at the National Center for Rare Diseases, Istituto Superiore di Sanità. Data are collected at the time of "certification", which is a document given to RD patients in order to get the first access to specialized care. Regional Registries (RR) are fed by clinicians working at the CCEs (Figure 1). The data collected were submitted to a control procedure involving the collaboration of RNMR, RR and primary source experts, to highlight and correct formal errors, inaccuracies and incoherencies among data and to manage duplicate records. The internal validity of the database has been checked comparing the time-course of incident cases and the dispersions of the RD profiles across all regions. By far most regions show data with a reasonable degree of coherence with each other and throughout the last years, suggesting that the registration process has come to a sufficient maturity and reliability.



Figure 1. Flow chart of RNMR
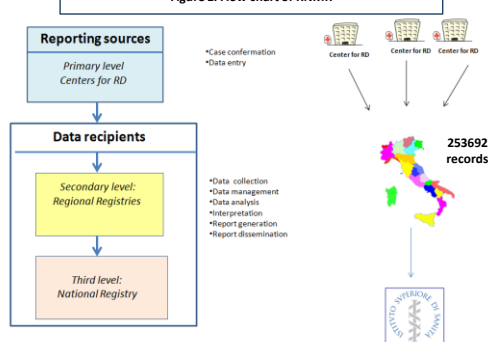
## Results

Since 2012 RR cover the whole national territory, and therefore the RNMR can be considered as a population-based registry with a well-defined population. On 31/12/2016 RNMR provides information on 239388 RD cases, 245986 RD occurrences and on 253692 certifications.
Records related to RD diagnosed or certified in the 2-year period 2015-2016 amount to 43270, of which : 21112 females, 20781 males. Of these the 47.9% have a group exemption code for their healthcare and the 52.1% are diseases with individual exemption code. The most frequent rare diseases related to two years-period shown in (Fig 2).



Figure 2. Shows the distribution of most frequent RD.
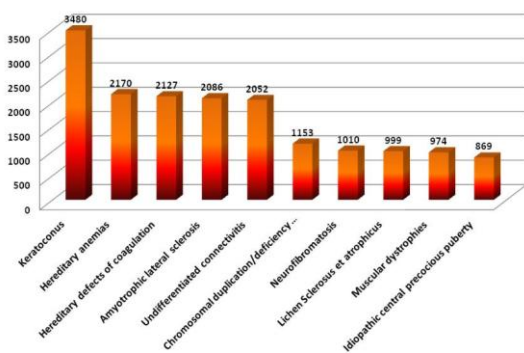
The most reported ICD-9 CM chapters in the RNMR are, in descending order of frequency, the diseases of the nervous system and of the sense organs; congenital malformations; diseases of the endocrine glands, nutrition, metabolism and immune disorders; and diseases of the blood and hematopoietic organs. These groups of diseases represent a total of 76% of the occurrences reported to the RNMR.



Figure 3. Shows the distribution, across the ICD 9-CM Chapters, of the diagnoses notified to the RNMR from 2001 to 2016
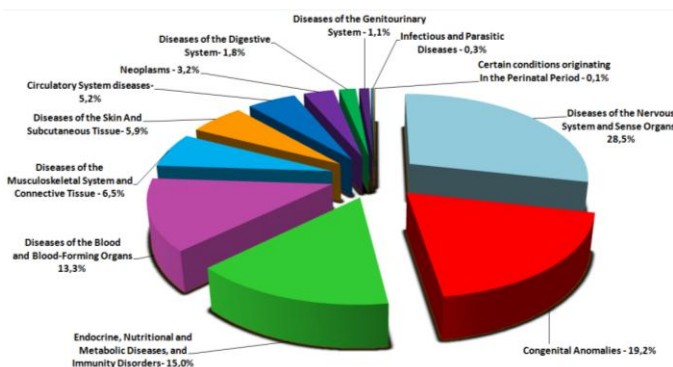
Data collected by RNMR provides also systematic information on the activity of the Italian RD Centres, which was one of the criteria for the identification of the Centres of Expertise for the European Reference Networks (ERNs) and will be important for the monitoring process. This information includes their volume of activity, variety of treated RD, contribution to diagnosis and pediatric or adult care.

To each ERN group is associated the percentage of pathologies calculated on the total of monitored pathologies.



Figure 4. Shows the distribution of RD surveilled by RNMR in the 18 ERN group.
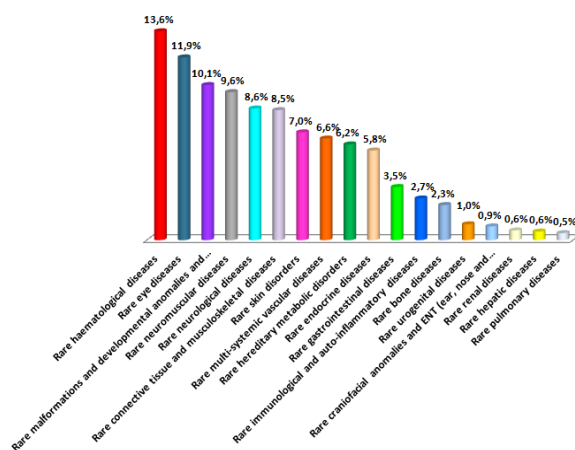
## Conclusions

RNMR data  allow a simple but sound epidemiological description of a rather substantial number of RDs in the Italian population. Similarly, it provides  information on the operation of the Italian Network of RD Centres and is supporting an evidence-based selection of Italian CCEs to be considered for the implementation of ERNs. Nonetheless, now that the system has been established and is operative, a process of improvement should be planned in order to give full execution to DM 279/2001 and to exploit most efficiently this undertaking. Indeed, this unique structure and population dimension, could contribute significantly to global research on RD, especially if the set of data collected could be extended and made interoperable with other databases.