Rare diseases: the paradox of an emerging challenge

Rare (often called "orphan") diseases are conventionally defined as those affecting a very low number of individuals, but which can be associated with inappropriate management, chronic debilitation and adverse health outcome, up to death. This problematic definition is, quite understandably, a major drawback that many scientists, clinicians and laboratory professionals recognize while facing very uncommon pathologies. A disease is conventionally defined "rare" when the number of affected subjects is <1:2,000 (i.e., <0.05%) in the European Union and <1:200,000 (i.e., <0.0005%) in the US, thus making the list of these conditions quite large, encompassing up to 8,000 pathologies, for some of which molecular or biochemical underlying abnormalities have not been completely unraveled so far (1). Translating this figure into the real world, it is quite surprising that orphan diseases, cumulatively, are not as rare as universally perceived, since a vast number of subjects may be suffering from such "rare" conditions around the globe. In fact, assuming a mean prevalence of 1:100,000 for each single condition, and multiplying this figure for the nearly 8,000 rare disorders that have been identified and classified so far (1), the cumulative prevalence of these pathologies will increase to approximately 1:12.5 worldwide, thus reflecting the well-known concept that "little drops of water will make the mighty ocean" (*Figure 1*).

The reliable representation of a willful and diffuse indifference for orphan diseases is mirrored by an electronic search in Google Trends, i.e., a reliable instrument for investigating digital epidemiology or popularity of a given medical search term (2). The output of a research using the keywords "orphan diseases", "cancer" and "diabetes" clearly shows that the number of Google searches for cancer and diabetes is several orders of magnitude higher than that for "orphan diseases" (*Figure 2*).

The worldwide epidemiology and immigration are other important drawbacks, because a given disease can be defined as certainly rare in one geographical area, whilst its prevalence may be much higher in another, due to the impact of specific demographic, genetic and environmental factors. Thalassemias are a paradigmatic example, since the prevalence of these hemoglobin disorders is higher in some Mediterranean and Asian regions, whilst its burden remains still limited in other worldwide areas (3). Then, the classification of rare diseases is also strongly dependent on diagnostic efficiency (4), since many subjects with rare disorders will remain frequently underdiagnosed, depending on the availability of diagnostic tools and local (human and/or economic) resources, as well as for the concerning gap of knowledge that many healthcare providers have about some of these orphan conditions. Finally, the global epidemiology of rare diseases is also influenced by an alarming (though somehow understandable) lack of commercial interest from many diagnostic and pharmaceutic companies, which tend to focalize their research on more frequent—and thereby more economically secure and profitable—conditions, thus leaving many patients without appropriate diagnosis, support and treatment (this is where the term "orphan" comes from) (5).

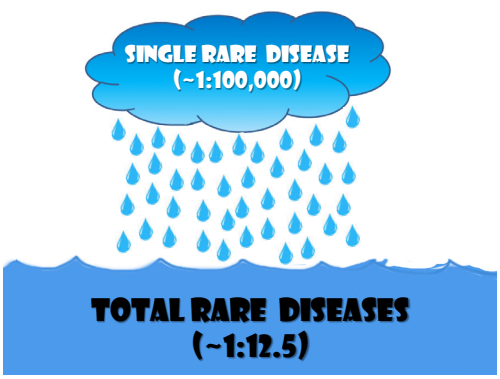

Figure 1 Cumulative prevalence of "rare diseases".

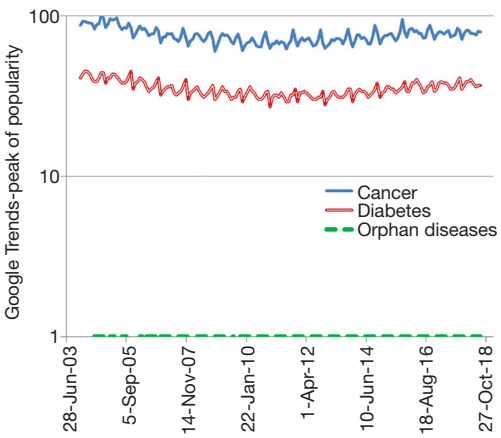

Figure 2 Peak of popularity of Google searches for "orphan diseases", "cancer" and diabetes".

Table 1 Drawbacks in the definition of rare diseases

Overall, the combined prevalence of rare diseases is not really rare
Prevalence of rare diseases is often heterogeneous and variable around the world
Underdiagnosis is frequent due to the lack of efficient diagnostic tools
Understatement may occur as a result of low interest from diagnostic and pharmaceutic industry

Regardless of these important caveats, which embody the still questionable definition of "rare (human) diseases" (*Table 1*), science and medicine should now be embarked on a landmark effort to provide more reliable answers for improving diagnosis and treatment of these conditions, thus enhancing both the amount and quality of life of "orphan" patients. It is exactly for this reasons that this special issue of *Annals of Translational Medicine*, entitled "Rare and orphan disorders: an emerging challenge?", will include a compilation of articles aimed at providing updated evidence on some "rare" human pathologies, thus including biliary tract cancers, cystic fibrosis, sclerosing mesenteritis, insulin autoimmune syndrome, chronic-inflammatory demyelinating polyneuropathies, neurodegenerative dementia, rare neonatal disorders, sleep apnea in childhood, acute intestinal ischemia, cardiac arrhythmias in sarcoidosis, Kounis syndrome, along with rare thrombophilic conditions, computer-related thrombosis, rare bleeding disorders, rare forms of von Willebrand disease (VWD) and hereditary spherocytosis.

It is our hope that the current gap of clinical knowledge could be at least partially filled, and that both diagnosis and treatment of patients with rare (orphan) diseases may be improved. We also wish to express our sincere gratitude to the authors of this special issue of the journal, trusting that these articles may be of interest for our readership.

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Elisa Danese

Giuseppe Lippi

Elisa Danese
(*Email: elisa.danese@univr.it*)
Giuseppe Lippi
(*Email: giuseppe.lippi@univr.it*)
Section of Clinical Biochemistry, *University of Verona*, *Verona*, *Italy*.
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