SCIENCE CHINA
Life Sciences

THEMATIC ISSUE: Frontiers in rare diseases
• REVIEW •

July 2017 Vol.60 No.7: 686–691
doi: 10.1007/s11427-017-9099-3

Towards efficiency in rare disease research: what is distinctive and important?

Jinmeng Jia & Tieliu Shi*

The Center for Bioinformatics and Computational Biology, Shanghai Key Laboratory of Regulatory Biology, the Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, Shanghai 200241, China

Received June 4, 2017; accepted June 8, 2017; published online June 16, 2017

Characterized by their low prevalence, rare diseases are often chronically debilitating or life threatening. Despite their low prevalence, the aggregate number of individuals suffering from a rare disease is estimated to be nearly 400 million worldwide. Over the past decades, efforts from researchers, clinicians, and pharmaceutical industries have been focused on both the diagnosis and therapy of rare diseases. However, because of the lack of data and medical records for individual rare diseases and the high cost of orphan drug development, only limited progress has been achieved. In recent years, the rapid development of next-generation sequencing (NGS)-based technologies, as well as the popularity of precision medicine has facilitated a better understanding of rare diseases and their molecular etiology. As a result, molecular subclassification can be identified within each disease more clearly, significantly improving diagnostic accuracy. However, providing appropriate care for patients with rare diseases is still an enormous challenge. In this review, we provide a brief introduction to the challenges of rare disease research and make suggestions on where and how our efforts should be focused.

rare disease, rare disease diagnosis and treatment, data standard, data sharing, orphan drugs

Citation: Jia, J., and Shi, T. (2017). Towards efficiency in rare disease research: what is distinctive and important? Sci China Life Sci 60, 686–691. doi: 10.1007/s11427-017-9099-3

RARE DISEASE: WHAT'S DIFFERENT?

Compared with other disease categories (e.g. genetic disease, mental disease), rare disease is an independent classification of diseases grouped by their prevalence in a stable population. Generally speaking, there is currently no unified, widely accepted definition for rare disease. Some definitions rely solely on the number of people living with a disease, while others take factors such as the existence of adequate treatments into consideration. For example, the United States Rare Diseases Act of 2002(Wellman-Labadie and Zhou, 2010) defines a rare disease as "any disease or condition that affects fewer than 200,000 people (or about 1 in 1,500 people) in the United States" (Hampton, 2006; Reinecke et al., 2011). However, the European Commission on Public Health (ECPH) defines rare diseases as "life-threatening or chronically debilitating diseases which are of such low prevalence (fewer than 1 in 2,000 people) that special combined efforts are needed to address them" (Rodwell and Ayme, 2015; Baldovino et al., 2016). Under this definition, diseases that are not life-threatening or chronic are excluded, no matter how many people they affect. Furthermore, even for definitions defined solely by prevalence, differences still exist. Unlike the United States, the legal definition of a rare disease in Japan is one that affects fewer than 50,000 patients, or about 1 in 2,500 people (Migita et al., 2016). In China, there is currently no clear

*Corresponding author (email: tlshi@bio.ecnu.edu.cn)

definition for rare diseases. Therefore, rare diseases can vary in prevalence throughout different populations, and a disease that is considered rare in some populations may be considered common in others.

To facilitate increased communication, knowledge sharing and coordinated orphan drug development across national borders, the World Health Organization (WHO) defines rare disease based on a higher prevalence: less than 6.5–10 in 10,000 (Franco, 2013; Gong et al., 2016).

RARE DISEASE: WHAT'S IMPORTANT?

As an important public health issue and challenge to medical care, the diagnosis and treatment of rare diseases has attracted enormous efforts from researchers, clinicians, and companies worldwide over the past decades. However, research on both the diagnosis and treatment of rare diseases reveals an extreme imbalance between these efforts and their returns (Potter et al., 2016). This phenomenon is mainly attributed to the high research cost, extreme rarity, and obscure pathogenesis of these diseases. In this review, we address these important issues, and identify which areas require the most attention.

Reducing the high cost of research

High costs are a common obstacle in rare disease research, and are a continual source of frustration for governments and researchers. It is estimated that the cost of research and development efforts over 10 years will be nearly one billion dollars in the United States alone (Collins, 2011). This problem has seriously impeded the progress of obtaining new medical treatments for most patients suffering from a rare disease. There are more than 7,000 rare diseases identified by Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), but only 355 of them are known to have efficient therapies (Boycott et al., 2013).

Establishing a national center with centralized resources and a centralized knowledge base has been proposed as one approach towards reducing costs (Ekins, 2017). It is anticipated that coordinating commercial efforts will generate new therapies by focusing efforts on the investigation of a single rare disease. Furthermore, generalizing the approach to therapeutic development across all rare disease treatment types will enhance productivity, and all rare diseases would benefit. Of course, sharing rare disease information through a well-structured knowledge base will significantly reduce research costs.

Sharing information across national borders

To facilitate better communication, data sharing and diagnosis of rare diseases, a request for collaboration across national borders has long been proposed (Mascalzoni et al., 2013). The first step towards this goal should be the development of a well-integrated knowledge base with enhanced data standards, which can provide comprehensive information about rare diseases worldwide. When building this international knowledge base, the following issues should be considered closely: reducing the redundancy of diseases listed in different registries, adding annotations for rare diseases and linking data from different levels with well-defined standards for each data category.

Because different populations have different rare diseases prevalent, it is unsurprising that existing rare disease registries/databases are often independent between nations or communities, making their representation of disease names inconsistent. Unifying disease name representation and reducing this redundancy should receive close attention. In addition, researchers increasingly recognize the importance of the coordination, sharing and exchange of rare disease information scattered around the world (Nambot et al., 2017; Ramoni et al., 2017; Trama et al., 2017). Therefore, the standardized annotation and categorization of rare diseases is urgently needed to improve recommendations for clinical management, and to advance research into disease mechanisms.

Recently, the concept of precision medicine has opened a new door in rare disease diagnosis and treatment (Collins and Varmus, 2015). The practices of precision medicine mainly rely on two factors: precisely personalized medical treatment and close tracking of clinical manifestations (including symptoms and phenotypes) (Mirnezami et al., 2012; Arnedos et al., 2015), which is used in the phenotypic annotation of rare diseases. Along with increasing public awareness of rare diseases, much effort has been devoted to relevant preclinical and clinical research. For example, next-generation sequencing (NGS) technology has been gradually adopted to identify genes that cause rare diseases (including some novel phenotypes), which is accompanied by a parallel need for large-scale phenotypic annotations (Boycott et al., 2013). In other words, when applying NGS to identify rare disease causing genes, precise and comprehensive phenotypic annotations should be enforced. Otherwise, large investments of manpower and financial resources will result in only very limited returns, and sequencing data will have limited value in subsequent integrative analyses. Because phenotypic annotations for rare diseases are limited, greater efforts should be made to systematically mine and integrate related data from existing databases, electronic medical records, and published literature.

Systematic investigations into a specific disease always involve both molecular and clinical data (Lu et al., 2016; Yang et al., 2016). Likewise, to thoroughly interpret rare diseases, different levels of data, including clinical records and molecular data are necessary. To more comprehensively integrate these data, linkages between data from different resources should be provided. Currently, genotypic data generated from biological experiments is always integrated and stored based

on the project. These genotype datasets mostly provide information regarding genotypes and genes without phenotypic or clinical information. In addition, the significant gap between rare disease treatment outcomes generated from highly controlled trials and real world outcomes could greatly benefit from a standardized health-system which can store, integrate and exchange clinical rare disease patient records (Westfall et al., 2007; Manuti et al., 2010; Potter et al., 2016).

Paying closer attention to pediatric rare diseases

Pediatric rare diseases mainly consist of two parts: rare pediatric diseases and childhood cancer. Rare pediatric disease is defined by the FDA as a disease that affects fewer than 200,000 individuals in the U.S., and primarily affects those aged from birth to 18 years (Bavisetty et al., 2013). Childhood cancer, which as a whole is classified as a rare disease, is defined by the National Center for Health Statistics in the United States (Howlader et al., 2017) as cancers with complete prevalence counts in children under 15 years of age (about 130 in 10,000 of all children). In contrast to adult cancers, rare pediatric cancer is classified according to morphology, rather than the primary site of origin (Steliarova-Foucher et al., 2005).

Over the past years, pediatric rare disease research has been limited, and few studies have addressed the needs of pediatric rare disease patients separately from those of adults. However, 80% of rare diseases have a genetic component and 75% of rare diseases affect children (Bavisetty et al., 2013). There is a disparity between the large proportion of rare disease cases that are pediatric, and the corresponding research efforts, making pediatric rare diseases an important medical, social, and economic issue.

In addition, many pediatric rare diseases or conditions are more difficult to diagnose and manage than adult rare diseases, because early stage symptoms may be absent, masked, misunderstood, or confused with the symptoms of other diseases. This clear sense of urgency demands innovation and acceleration in diagnosis and drug development for pediatric rare diseases (Bhattacharya et al., 2016).

RARE DISEASE: WHAT DO WE ALREADY HAVE?

To find solutions to the challenges and problems listed above, various strategies have been developed, including data resources and tools. Here, we summarize those resources and tools, and give a brief introduction to their content and usage. Hence, we categorize these resources and tools into three groups.

Registries and databases with essential information about rare diseases

Centralizing resources and knowledge for rare diseases around the world is an efficient way of managing and sharing related information. The incorporated data should include clinical records, phenotypic and genetic annotations (gene and genotype) and suggested treatment strategies, etc.

To promote the sharing and exchange of information, a standardized registry system for rare diseases must be established. A rare disease registry (RDS) usually consists of anonymous, patient-reported information collected at baseline annually and information from medical record reviews (Solomon et al., 2017). Currently, some popular RDS include the ALS registry Swabia (Nagel et al., 2013), the Belgian Neuromuscular Disease Registry (Roy et al., 2015), the National Registry of Myotonic Dystrophy (DM) (Hilbert et al., 2012), and the Global Rare Diseases Patient Registry Data Repository (GRDR) (Rubinstein and McInnes, 2015).

By extracting disease-phenotype associations from disease descriptions in Online Mendelian Inheritance in Man (OMIM) (http://www.omim.org/), the Human Phenotype Ontology (HPO) intends to realize large-scale computational analysis of the human phenome (a set of all phenotypes expressed by a species) and currently contains around 116,000 terms to describe individual phenotypic anomalies (Groza et al., 2015). HPO provides an easy way for people to find rare disease-phenotype associations and integrate phenotypic annotations for rare diseases. In addition, text mining is a popular method to comprehensively collect phenotypic information and disease-phenotype associations. One of the most used approaches for disease-phenotype text mining is a pattern -based strategy (Xu et al., 2013).

By integrating gene and genotype, genetic data can greatly help to improve understanding of molecular disease etiologies, find rare cancers through cancer subclassification and facilitate new rare disease treatments (Kraja et al., 2011; Sykes et al., 2011; Veldhuijzen van Zanten 2017). As the molecular fundament of phenotype, genotype identification also plays a very important role in rare disease research (Bogdanova-Mihaylova et al., 2017; Waisbourd-Zinman et al., 2017). Close attention has been paid in detecting associations between rare mutations and rare diseases (including rare cancer) in recent years. When collecting genotypic information, both the individual mutations/variants and the genotype-phenotype correlation should be recorded. Current popular rare disease-specific databases with genotype-based data included are Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), Monarch Initiative knowledge base (https://monarchinitiative.org/) and DECIPHER (https://decipher.sanger.ac.uk/), but the lack of standardized genotype and phenotype data representation limits their usage in related fields. Application of NGS in disease research has identified many novel associations between genes and phenotypes, which necessitate the re-annotation of human disease-causing genes, especially for rare diseases. Community based efforts such as ClinVar (https://www.ncbi.nlm.nih.gov/clin-

var/) are being made to collect gene information, including both disease-gene and phenotype-gene correlations. The major databases hosting this information include HPO (http://human-phenotype-ontology.github.io/), OMIM (http://www.omim.org/), UniProt (http://www.uniprot.org/), GWAS (http://www.gwascentral.org/) and CTD_HUMAN (http://ctdbase.org/). A summary of these resources, with relevant information and listing their advantages and disadvantages can be found in Table 1.

Standards for multilevel data related to rare diseases

The significant characteristics of rare diseases are their extremely small population and dispersed distribution. Sharing and exchanging clinical and related data can greatly facilitate the effective diagnosis of rare diseases. To reach the goal of building a systematic knowledge base for commutating, exchanging, and sharing disease information, disease nomenclature and classification standards, together with synonym mappings across different databases are required.

To standardize disease names, an ontology/controlled vocabulary is thought to be an ideal solution, because it can not only provide standard representation of each concept (i.e. disease), but also provide essential information for data sharing and exchange (e.g. synonyms, cross reference linkages) (Schriml and Mitraka, 2015). Current ontologies/CVs that can be used as documents to develop standards for rare disease nomenclature include Disease Ontology (DO), the Orphanet Rare Disease Ontology (ORDO), the Unified Medical Language System (UMLS), Medical Subject Headings, and SNOMED. For the same reasons, ontologies/CVs are also needed to standardize rare disease classification. These ontologies include International Classification of Diseases (ICD, the most popular versions in use are ICD-9 and ICD-10) and Disease Ontology. Although integrating existing standards can improve the nomenclature and classification of rare diseases, updating ontologies/CVs and adding more disease terms are still necessary, because each system has its own internal limitations. A defect common to these systems (excluding ORDO) is that they are not specific to rare disease, and only a limited selection of rare disease names is listed. Although ORDO is developed especially for rare diseases, it only includes rare diseases in Orphanet. As a classification system mainly focusing on common diseases, different versions of ICD use different codes for the same diseases, which makes it hard to map and standardize corresponding diseases with ICD systems.

The acceleration of data accumulation requires a pub-

Table 1 Comparison of selected databases with a focus on genetic (including gene, genotype, and genotype-phenotype relationships) information in human diseases[a)]

	Name	Scope and Scale	Standards	Advantage (√)/Disadvantage (×)
DB	DECIPHER	Genetic information and phenotypic descriptions from NGS studies ~ 43,000 cases	HGVS, HGNC, HPO	√ Genetic information is derived from both genomic screening and exome sequencing × Genetic and phenotypic data are represented as free text in descriptions/ summaries, hard to integrate and analyze
	HPO	Gene-disease correlations and phenotypic curated data from OMIM. ~ 12,000 Phenotypes	HPO, NCBI	√ Gene(s) and phenotype(s) with their associated diseases are represented as well-structured disease-gene or disease-phenotype pairs, which make it easier to integrate and analyze × Rare diseases are limited, and disease names are non-standardized
KDB	Orphanet	Phenotypic descriptions and genes 5,833 disease entries	HGNC, ICD, MedDRA, MeSH, OMIM, UMLS, UniProt	√ Rare disease-specific knowledge × Genetic and phenotypic data are represented as free text in descriptions/summaries, hard to integrate and analyze
	OMIM	Phenotypic descriptions and genes 22,644 entries (disease or gene)	HGNC, HPO, ICD, OMIM, PhenoDB, SNOMED, UMLS	√ Entries include both disease and gene, which makes information easier to retrieve. Disease names are standardized × Rare diseases are limited.
	MIkb	Human and model organism genetics and phenotypes 36K diseases, 33K phenotypes, 500K genotypes, 30K genes, 2M curated phenotype associations, >100 species.	HPO, MPO	√ Provides information for multi-species × Rare diseases are limited, and disease names are non-standardized

a) DB, database; KDB, knowledge base; MIkb, Monarch Initiative knowledge base; HGVS, Human Genome Variation Society; HGNC, HUGO gene Nomenclature Committee; HPO, Human Phenotype Ontology; NCBI, National Center for Biotechnology Information; ICD, International Classification of Diseases; MedDRA, Medical Dictionary of Regulatory Activities; MeSH, Medical Subject Headings; UMLS, Unified Medical Language System; SNOMED, Systematized Nomenclature of Medical Terms.

lic-oriented database, with a well-structured framework and proper linkages between multilevel information about rare diseases. To meet this demand, we are working with Beijing Children's Hospital to develop a standards-based annotation system for rare disease called eRAM (www.pediascape.org/eram), which contains multilevel information including symptom, phenotype, genotype, gene and genotype-phenotype relationships for about 16,800 rare diseases. Our system provides an initial step for the share and exchange of data with the public, which can help clinical professionals, patients and their families to learn more about rare diseases. We welcome people around the world to share their experiences and clinical information through our system, which will greatly benefit rare disease diagnosis, treatment, and research.

PERSPECTIVES

In this review, we provide a brief introduction to the challenges present in the field of rare disease research, and provide suggestions concerning where and how our efforts should be focused. Although providing appropriate care for patients with rare diseases is still challenging, efforts made by researchers to emphasize the importance of rare diseases have been successful in raising public awareness. In recent years, advances in NGS and 'Precision Medicine' have offered tremendous promise in the effective diagnosis of rare disease, providing hope for millions of affected patients. As a result, more recent discoveries regarding the molecular basis of rare diseases have enabled the identification of many potential therapies.

Although previous works on rare diseases have increased public awareness, the existing body of research is still not enough, and considerable efforts should be continually made from medical specialists to develop the knowledge base for clinicians with patients in their care (Potter et al., 2016). To reach the goal of improved and more efficient diagnosis, treatment, and novel drug development for rare diseases, the sharing and integration of multilevel data about rare diseases with international cooperation is one of the key factors for the success.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

Acknowledgements *This work was supported by the National High Technology Research and Development Program of China (2015AA020108, 2015AA020104), the National Science Foundation of China (31671377), and Shanghai 111 Project (B14019).*

Arnedos, M., Vicier, C., Loi, S., Lefebvre, C., Michiels, S., Bonnefoi, H., and Andre, F. (2015). Precision medicine for metastatic breast cancer—limitations and solutions. Nat Rev Clin Oncol 12, 693–704.

Baldovino, S., Montserrat, A., Taruscio, D., Daina, E., and Roccatello, D. (2016). Rare diseases in Europe: from a wide to a local perspective. Isr Med Assoc J 18, 359−363..

Bavisetty, S., Grody, W.W., and Yazdani, S. (2013). Emergence of pediatric rare diseases. Rare Diss 1, e23579.

Bhattacharya, I., Manukyan, Z., Chan, P., Harnisch, L., and Heatherington, A. (2016). Making every subject count: a case study of drug development path for medication in a pediatric rare disease. Clin Pharmacol Ther 100, 330–332.

Bogdanova-Mihaylova, P., Alexander, M.D., Murphy, R.P., and Murphy, S.M. (2017). Waardenburg syndrome: a rare cause of inherited neuropathy due to SOX10 mutation. J Peripher Nerv Syst, .

Boycott, K.M., Vanstone, M.R., Bulman, D.E., and MacKenzie, A.E. (2013). Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet 14, 681–691.

Boycott, K.M., Vanstone, M.R., Bulman, D.E., and MacKenzie, A.E. (2013). Rare-disease genetics in the era of next-generation sequencing: Discovery to translation. Nat Rev Genet 14, 681−691..

Collins, F. (2011). An audience with...francis collins. Interviewed by Asher Mullard. Nat Rev Drug Discov 10, 14..

Collins, F.S., and Varmus, H. (2015). A new initiative on precision medicine. N Engl J Med 372, 793–795.

Ekins, S. (2017). Industrializing rare disease therapy discovery and development. Nat Biotechnol 35, 117–118.

Franco, P. (2013). Orphan drugs: the regulatory environment. Drug Discovery Today 18, 163–172.

Gong, S., Wang, Y., Pan, X., Zhang, L., Huang, R., Chen, X., Hu, J., Xu, Y., and Jin, S. (2016). The availability and affordability of orphan drugs for rare diseases in China. Orphanet J Rare Dis 11, 20.

Groza, T., Köhler, S., Moldenhauer, D., Vasilevsky, N., Baynam, G., Zemojtel, T., Schriml, L.M., Kibbe, W.A., Schofield, P.N., Beck, T., Vasant, D., Brookes, A.J., Zankl, A., Washington, N.L., Mungall, C.J., Lewis, S.E., Haendel, M.A., Parkinson, H., and Robinson, P.N. (2015). The human phenotype ontology: semantic unification of common and rare disease. Am J Human Genets 97, 111–124.

Hampton, T. (2006). Rare disease research gets boost. JAMA 295, 2836−2838..

Hilbert, J.E., Kissel, J.T., Luebbe, E.A., Martens, W.B., McDermott, M.P., Sanders, D.B., Tawil, R., Thornton, C.A., and Moxley Iii, R.T. (2012). If you build a rare disease registry, will they enroll and will they use it? Methods and data from the National Registry of Myotonic Dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD). Contemporary Clinical Trials 33, 302–311.

Howlader, N., Noone, A.M., Krapcho, M., Miller, D., Bishop, K., Kosary, C.L., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, D.R., Chen, H.S., Feuer, E.J., and Cronin, K.A. (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

Kraja, A.T., Czajkowski, J., Feitosa, M.F., Borecki, I.B., and Province, M.A. (2011). Detecting disease rare alleles using single SNPs in families and haplotyping in unrelated subjects from the Genetic Analysis Workshop 17 data. BMC Proc 5 Suppl 9: S96..

Lu, P., Chen, X., Feng, Y., Zeng, Q., Jiang, C., Zhu, X., Fan, G., and Xue, Z. (2016). Integrated transcriptome analysis of human iPS cells derived from a fragile X syndrome patient during neuronal differentiation. Sci China Life Sci 59, 1093–1105.

Manuti, B., Rizza, P., Bianco, A., Nobile, C.G., and Pavia, M. (2010). The quality of preventive health care delivered to adults: results from a cross-sectional study in Southern Italy. BMC Public Health 10, 350.

Mascalzoni, D., Knoppers, B.M., Ayme, S., Macilotti, M., Dawkins, H., Woods, S., and Hansson, M.G. (2013). Rare diseases and now rare data? Nat Rev Genet 14, 372..

Migita, K., Izumi, Y., Jiuchi, Y., Iwanaga, N., Kawahara, C., Agematsu, K., Yachie, A., Masumoto, J., Fujikawa, K., Yamasaki, S., Nakamura, T., Ubara, Y., Koga, T., Nakashima, Y., Shimizu, T., Umeda, M., Nonaka, F., Yasunami, M., Eguchi, K., Yoshiura, K., and Kawakami, A. (2016).

Familial Mediterranean fever is no longer a rare disease in Japan. Arthritis Res Ther 18, 175.
Mirnezami, R., Nicholson, J., and Darzi, A. (2012). Preparing for precision medicine. N Engl J Med 366, 489–491.
Nagel, G., Ünal, H., Rosenbohm, A., Ludolph, A.C., and Rothenbacher, D. (2013). Implementation of a population-based epidemiological rare disease registry: study protocol of the amyotrophic lateral sclerosis (ALS) - registry Swabia. BMC Neurol 13, 22.
Nambot, S., Gavrilov, D., Thevenon, J., Bruel, A.L., Bainbridge, M., Rio, M., Goizet, C., Rotig, A., Jaeken, J., Niu, N., Xia, F., Vital, A., Houcinat, N., Mochel, F., Kuentz, P., Lehalle, D., Duffourd, Y., Riviere, J.B., Thauvin-Robinet, C., Beaudet, A.L., and Faivre, L. (2017). Further delineation of a rare recessive encephalomyopathy linked to mutations in GFER thanks to data sharing of whole exome sequencing data. Clin Genet, .
Potter, B.K., Khangura, S.D., Tingley, K., Chakraborty, P., and Little, J. (2016). Translating rare-disease therapies into improved care for patients and families: what are the right outcomes, designs, and engagement approaches in health-systems research? Genet Med 18, 117−123..
Ramoni, R.B., Mulvihill, J.J., Adams, D.R., Allard, P., Ashley, E.A., Bernstein, J.A., Gahl, W.A., Hamid, R., Loscalzo, J., McCray, A.T., Shashi, V., Tifft, C.J., and Wise, A.L. (2017). The undiagnosed diseases network: accelerating discovery about health and disease. Am J Human Genets 100, 185–192.
Reinecke, M., Rommel, K., and Schmidtke, J. (2011). Funding of rare disease research in Germany: a pilot study. J Community Genet 2, 101–105.
Rodwell, C. and Ayme, S. (2015). Rare disease policies to improve care for patients in Europe. Biochim Biophys Acta 1852(10 Pt B): 2329−2335..
Roy, A.J., Van den Bergh, P., Van Damme, P., Doggen, K., and Van Casteren, V. (2015). Early stages of building a rare disease registry, methods and 2010 data from the Belgian Neuromuscular Disease Registry (BNMDR). Acta Neurol Belg 115, 97–104.
Rubinstein, Y.R., and McInnes, P. (2015). NIH/NCATS/GRDR® Common Data Elements: A leading force for standardized data collection. Contemporary Clinical Trials 42, 78–80.
Schriml, L.M., and Mitraka, E. (2015). The Disease Ontology: fostering interoperability between biological and clinical human disease-related data. Mamm Genome 26, 584–589.
Solomon, D.H., Shadick, N.A., Weinblatt, M.E., Frits, M., Iannaccone, C., Zak, A., and Korzenik, J.R. (2017). Clinical patient registry recruitment and retention: a survey of patients in two chronic disease registries. BMC Med Res Methodol 17, 59.
Steliarova-Foucher, E., Stiller, C., Lacour, B., and Kaatsch, P. (2005). International classification of childhood cancer, third edition. Cancer 103, 1457–1467.
Sykes, J., Cheng, L., Xu, W., Tsao, M.S., Liu, G., and Pintilie, M. (2011). Addition of multiple rare SNPs to known common variants improves the association between disease and gene in the Genetic Analysis Workshop 17 data. BMC Proc 5 Suppl 9: S97..
Trama, A., Marcos-Gragera, R., Sánchez Pérez, M.J., van der Zwan, J.M., Ardanaz, E., Bouchardy, C., Melchor, J.M., Martinez, C., Capocaccia, R., Vicentini, M., Siesling, S., and Gatta, G. (2017). Data quality in rare cancers registration: the report of the RARECARE data quality study. TJ 103, 22–32.
Veldhuijzen van Zanten, S.E.M., Baugh, J., Chaney, B., De Jongh, D., Sanchez Aliaga, E., Barkhof, F., Noltes, J., De Wolf, R., Van Dijk, J., Cannarozzo, A., Damen-Korbijn, C.M., Lieverst, J.A., Colditz, N., Hoffmann, M., Warmuth-Metz, M., Bison, B., Jones, D.T.W., Sturm, D., Gielen, G.H., Jones, C., Hulleman, E., Calmon, R., Castel, D., Varlet, P., Giraud, G., Slavc, I., Van Gool, S., Jacobs, S., Jadrijevic-Cvrlje, F., Sumerauer, D., Nysom, K., Pentikainen, V., Kivivuori, S.M., Leblond, P., Entz-Werle, N., von Bueren, A.O., Kattamis, A., Hargrave, D.R., Hauser, P., Garami, M., Thorarinsdottir, H.K., Pears, J., Gandola, L., Rutkauskiene, G., Janssens, G.O., Torsvik, I.K., Perek-Polnik, M., Gil-da-Costa, M.J., Zheludkova, O., Shats, L., Deak, L., Kitanovski, L., Cruz, O., Morales La Madrid, A., Holm, S., Gerber, N., Kebudi, R., Grundy, R., Lopez-Aguilar, E., Zapata-Tarres, M., Emmerik, J., Hayden, T., Bailey, S., Biassoni, V., Massimino, M., Grill, J., Vandertop, W.P., Kaspers, G.J.L., Fouladi, M., Kramm, C.M., and van Vuurden, D.G. (2017). Development of the SIOPE DIPG network, registry and imaging repository: a collaborative effort to optimize research into a rare and lethal disease. J Neurooncol 132, 255–266.
Waisbourd-Zinman, O., Surrey, L.F., Schwartz, A.E., Russo, P.A., and Wen, J. (2017). A rare BSEP mutation associated with a mild form of progressive familial intrahepatic cholestasis type 2. Ann Hepatol 16, 465−468..
Wellman-Labadie, O., and Zhou, Y. (2010). The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? Health Policy 95, 216-228..
Westfall, J.M., Mold, J., and Fagnan, L. (2007). Practice-based research—"Blue Highways" on the NIH roadmap. JAMA 297, 403–406.
Xu, R., Li, L., and Wang, Q. (2013). Towards building a disease-phenotype knowledge base: extracting disease-manifestation relationship from literature. Bioinformatics 29, 2186–2194.
Yang, L., Mei, T., Lin, X., Tang, H., Wu, Y., Wang, R., Liu, J., Shah, Z., and Liu, X. (2016). Current approaches to reduce or eliminate mitochondrial DNA mutations. Sci China Life Sci 59, 532–535.