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Drug repositioning trends in rare and intractable diseases

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Drug repositioning (DR) is an effective way for developing drugs for rare and intractable diseases (RIDs). Preparation of the ontology is essential for drug development in RIDs, in which disease names have been inconsistently used worldwide. Ontology-based analysis of clinical trial data revealed that DR occurs actively in RIDs. Drugs and their target genes are keys to explore repositionable drugs, because shared target genes between diseases indicate a common mechanism of drug action. This approach visualizes a DR landscape that facilitates drug development. Here, we review the current situation of ontology in RIDs, the trends in drug development, and an efficient strategy for DR based on drug target gene information.

Keywords: Rare and intractable diseases; Ontology; Clinical trials; Drug target genes; Drug repositioning; Drug repurposing

Introduction

Approximately 7000 RIDs have been identified to date, affecting an estimated 300 million individuals worldwide.[1–3] These diseases can cause potentially life-threatening conditions throughout patients' lives and severely reduce their quality of life. Despite strong unmet medical needs, new drugs are developed and marketed at a much slower pace for RIDs than for diseases affecting large numbers of patients.[4,5] Smaller patient populations yield a smaller amount of disease-related information. Moreover, the same RID can present a complex set of symptoms. Precise clinical diagnostic criteria have not been established for many RIDs. Often, different clinical names are used to describe the same entity. For example, whereas 'rare diseases' is a common term worldwide, 'intractable diseases' ('Nanbyo' in Japanese) is the term officially used in Japan.[6] Thus, we used the term 'RID' in this review. To effectively address the range of known RIDs, it is necessary to establish a systematic approach based on knowledge of current trends in RID drug development.

Abbreviations: DR, Drug repositioning; RID, Rare and intractable disease; DID, Designated intractable disease in Japan; SPCD, Specific pediatric chronic disease in Japan; SLE, Systemic lupus erythematosus; ALS, Amyotrophic lateral sclerosis.

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DR, or drug repurposing, is a strategy to identify new indications for approved medications.[7,8] DR can also serve as a powerful method for discovering new RID therapies.[9] Interest in DR has been growing because it can help reduce the time, cost, and risk involved in new drug discoveries. DR opportunities lie in identifying promising pairings of drugs and new therapeutic target diseases. A systematic method for identifying these pairings will help facilitate and accelerate the marketing authorization of new RID drugs.[10–13]

For this purpose, a systematic, international clinical RID database should be created.[14] Specifically, RIDs should be logically grouped and classified, and clinical and other data related to these diseases should be documented using this framework. Omics-based drug discovery, whereby omics data are used to establish the linkage between drugs and disease-related genes, can be a viable approach. A cornerstone to develop the DR strategy for RIDs is to characterize current trends of drug development in this area. Analyses of recent drug development activities will help maximize the utility of the data available on these diseases.

In this review, we discuss the DR strategies for RIDs based on clinical trial data. First, we describe the current status of RID nomenclature in Japan, Europe, and the USA, and the need for a new, systematic ontology: in other words, a formal and explicit specification of a shared conceptualization.[15,16] The systematic ontology will be used to link RIDs with clinical and other data. Second, trends in developing RID drugs and DR are described, identified using the ontology-based methodology mentioned above. Finally, a score to reflect and predict DR for RIDs is explained.

Development of an effective ontology for RIDs in Japan

Research on RIDs is conducted by academic and clinical institutions around the world. The first step in DR analyses for RIDs is to systematically organize and classify the diagnostic names of these diseases. In the field of RIDs, the classifications of diseases are often variable, diagnoses remain challenging, and even disease names are used inconsistently. These features of RIDs make the integration of information particularly difficult.

To link and analyze data available worldwide, an effective ontology needs to be introduced to define ideas and classify data components in a hierarchical order. This need reflects the fact that many international databases on RIDs often use different names for the same disease entity. In addition, different databases use different ontologies to describe diseases, drugs, genes, and phenotypes, indicating the need for a standardized ontology for data integration.

We developed an ontology for RIDs that are officially designated in Japan. At the time of writing, 333 diseases were designated as intractable by the Japanese Government (the designated intractable diseases in Japan: DIDs). These are classified into 15 disease groups, covering all disease groups, such as neuromuscular diseases and metabolic disorders.[17] Many of the 333 disease names are umbrella ones that include subcategorized disease names related to them. For example, Gaucher disease is categorized as a lysosomal disease. If subcategorized diseases were counted separately, there would be 787 (more than twice the original count of 333). We translated the Japanese terms for these 787 diseases into English and added associated synonyms and abbreviations. Consequently, a list of 1294 RIDs was created (see Table S1 in the supplemental information online).

We compared the list with major rare disease databases: Orphanet in Europe[18] and the Genetic and Rare Diseases Information Center (GARD) in the USA.[19] We also compared them with MalaCards, a database of all human diseases,[20] and the chronic pediatric diseases designated in Japan (specific pediatric chronic diseases; SPCDs)[21] (Fig. 1a). Of the 333 diseases, the numbers of diseases registered in Orphanet and GARD were 260 and 256, respectively, with 235 diseases (70.6%) in common among Japan, Europe, and the USA. By contrast, 19 of the 333 DIDs (5.7%) were not included in any other databases. Comparison of the databases demonstrated a greater variability of RIDs included in each database. Even among these databases, different disease names and subcategorical structures were often used for an identical disease (Fig. 1b). For example, 'Lupus' is used as a representative name for systemic lupus erythematosus (SLE) in GARD, whereas the category of amyotrophic lateral sclerosis (ALS) is absent and subcategories, such as 'Amyotrophic lateral sclerosis 1', are registered parallelly in MalaCards.

The differences in the definition of RIDs among major databases reflect regional differences in epidemiology and regulatory definition. In Japan, diseases are designated when a diagnosis is established and fewer than 1 in 1000 people are affected. In the USA, a rare disease is defined by the Orphan Drug Act as a condition that affects fewer than 200 000 people,[19] whereas legislation in the European Union (EU) defines a rare disease when it affects fewer than 1 in 2000 people.[18] Given these differences in definition, the disease list does not overlap completely among databases. For example, multiple sclerosis, which affects ~ 20,000 patients in Japan, is designated in Japan, but not in the EU and USA.

These preliminary findings underscore the importance of a medically accurate and complete ontology in RID research. Using our standardized ontologies for RIDs in Japan, we extracted drugs from global clinical trial data and connected them to drug target genes and molecular pathways.[22]

Trend analysis of DR based on clinical trials for RIDs

When drug manufacturers or physicians plan to conduct a clinical trial, they must register relevant information, such as the target disease(s), the drug(s) to be tested, and outcome variables, in the clinical trial registries. Currently, the major registries are ClinicalTrials.gov in the USA,[23] the European Clinical Trials Registry (EUCTR) in Europe,[24] Chinese Clinical Trial Register (ChiCTR) in China,[25] and the Japan Primary Registries Network (JPRN) in Japan.[26,27]

We analyzed these four registries using our RID ontology.[28] We obtained clinical trial data of the four registries from the WHO ICTRP website[29] and found that 15, 194 RID clinical trials were registered by November 2019, involving 1,666 drugs (DrugBank).[30] Given that antibody and several other types of drug are associated with specific target genes or their products, we queried the Kyoto Encyclopedia of Genes and Genomes (KEGG) database[31] using each of the 1,666 drugs as the search

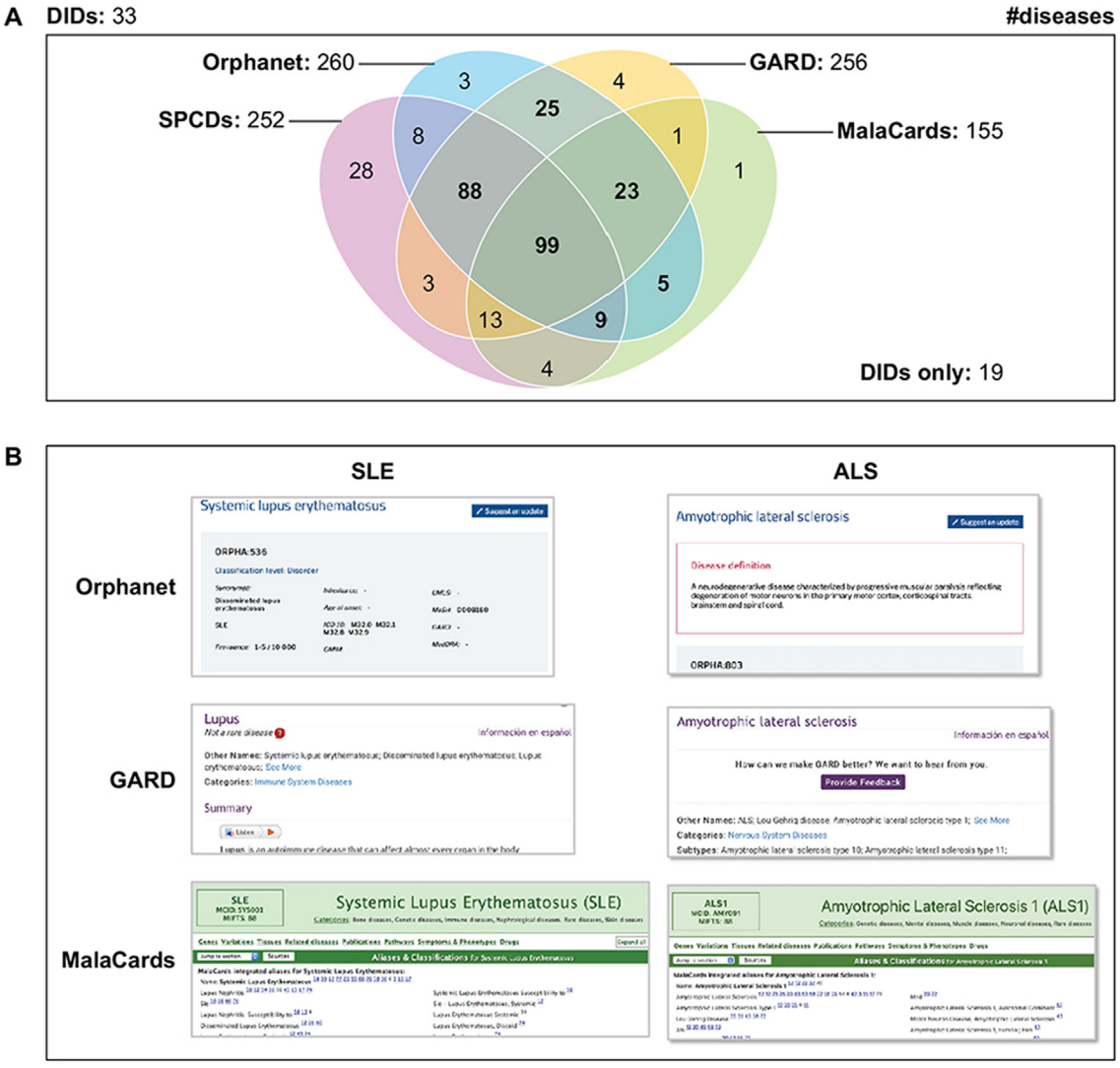

FIGURE 1

Comparison of rare and intractable disease (RID) entries among the major disease databases. (A) Venn diagram of disease entries among the five databases. Of the 333 designated intractable diseases (DIDs) in Japan, 260 (78.1%) and 256 (76.9%) diseases were registered in Orphanet and Genetic and Rare Diseases Information Center (GARD), respectively, and 19 DIDs (5.7%) were registered only in Japan. By comparison, DIDs shared 75.7% (252/333) diseases with chronic pediatric diseases designated in Japan (specific pediatric chronic diseases; SPCDs). (B) Examples of diseases reported differently among databases. 'Lupus' is the representative disease name in GARD, whereas systemic lupus erythematosus (SLE) is used in other databases. For amyotrophic lateral sclerosis (ALS), subcategories of ALS, such as 'ALS1', are registered in MalaCards.

terms, and identified 551 target genes involved in 275 molecular pathways.

We searched for DR-related clinical trials. We defined DR as an event in which a drug that had previously been tested in a clinical trial on disease A was tested in a later clinical trial on disease B. Here, disease A was designated as the DR donor, and disease B was designated as the DR acceptor (Fig. 2a). Our investigation showed that 12, 528 DR events had occurred over the past 20 years (Fig. 2b). Although this investigation included all clinical trials, a separate investigation that was restricted to Phase III and IV clinical trials showed that ~ 2,864 DR events took place during the same period. These findings indicate that DR events occur very frequently, given the large number of RIDs.

What types of RID are associated with the greatest potential for successful DR? Overall, RIDs belong to all major disease groups, including neuromuscular diseases and metabolic disorders. Our investigation showed that DR donor diseases and acceptor diseases often belong to different disease groups, indicating that DR events might occur in an interdisease group manner. For example, we identified several DR cases in which a drug previously tested for a neuromuscular disease was later tested for a digestive disorder. This finding indicates the limitations of seeking DR opportunities within a specific disease group. Rather, interdisease group DR opportunities should be investigated, covering the entire range of RIDs. Sildenafil (Viagra®) is a well-known example of successful DR. First approved for the treatment of erectile dysfunction, this drug was later designated as an orphan medicine for pulmonary arterial hypertension (Revatio®).

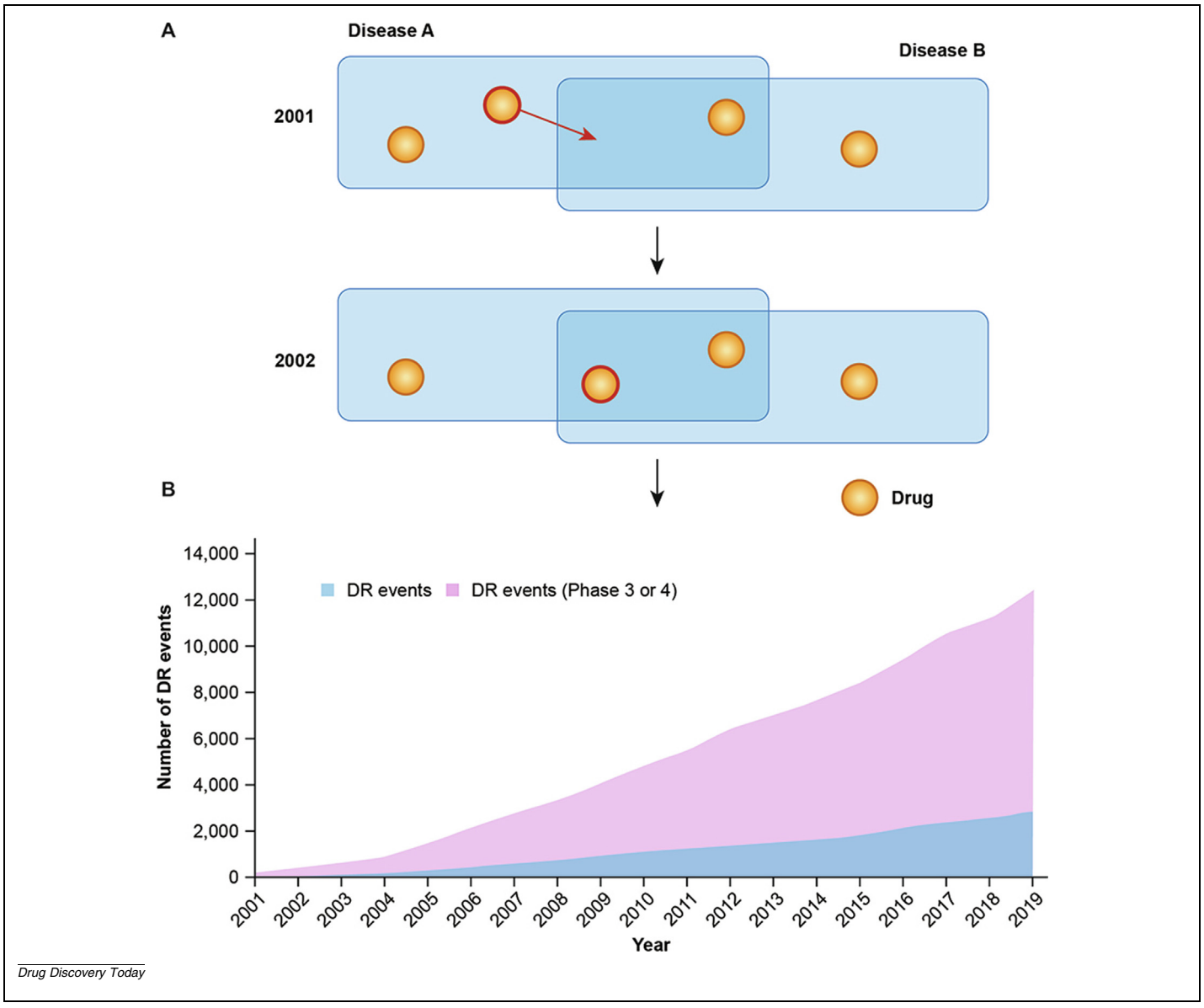

FIGURE 2

Drug repositioning (DR) for rare and intractable diseases. (A) Schema of DR. A drug for disease A is repositioned to disease B, shown as the move from 'exclusive region for disease A' to 'shared region of disease A and B'. Annual changes were counted for both directional cases (disease A to disease B, and vice versa). Reproduced, with modifications, from [28]. (B) Accumulated number of DR events from 2001 to 2019. More than 12 000 DR events, and 2864 DR events of Phase III and IV clinical trials, have occurred during this time.

Clinical trials are sponsored by pharmaceutical companies or physicians. Although the factors driving interdisease group DR have not yet been fully elucidated, identifying them will help formulate effective DR approaches. We speculate that past DR opportunities were often serendipitous, depending on hunches or observations by treating clinicians. For example, a physician administering a drug for a given neuromuscular condition might speculate that it could be used to treat patients with a specific digestive disorder presenting with similar symptoms. Effectively collecting input from clinicians is one possible approach to DR.

Creation of a DR score to represent drug repositionability between RIDs

How can DR opportunities be created for RIDs? Many RIDs are of genetic origin. The accumulated data on various genetic mutations and polymorphisms in patients with RIDs can inform the search for target genes and their products. Using genome-wide association study (GWAS) data, Fang and colleagues searched for therapeutic targets in 30 immunological diseases.[32] They also developed a method to identify drug targets for each disease by systematically developing an ontology-based disease nomenclature and linking the disease names with genetic and protein pathway data. Through GWAS and protein–protein network analysis, they developed a priority index to prioritize drug target genes. Thus, as their example shows, genetics-led approaches can serve as a powerful tool for identifying drug targets in RIDs.

When repositioning a drug, it is important to find a target disease that has a com-

mon mechanism of action for the drug.[33,34] Drugs were developed to target genes or their products by inhibiting their disease-related activities as enzymes or receptors, to produce pharmacological effect.[35,36] We considered that drug target genes are able to provide key information for the mechanism. Increasing volumes of drug target data have been stored and are available from KEGG and other online databases. Drugs are likely to work on the same genes or their products when administered to patients with different diseases. If the same genes are involved, for example, in the pathogenesis of a neuromuscular diseases and a digestive disorder, it follows that these diseases are etiologically related to each other and could be treated with the same drug.

For each DR donor–acceptor pair, we determined the proportion of shared drug target genes and created the DR score (R_{gene}) to represent drug repositionability between diseases.[28] DR for RIDs had several noteworthy characteristics. We identified and examined the 100 pairs of DR donors and acceptors with the greatest R_{gene} scores (see Table S2 in the supplemental information online). These pairs were associated with 33 diseases, suggesting that DR events centered around a relatively small set of diseases (Fig. 3a). In particular, multiple sclerosis and Crohn's disease were paired with many diseases, suggesting that many DR events occurred. By contrast, a systematic approach to find the candidate drugs is still necessary in DR-inactive RIDs.

Using the clinical trial data on the drugs that targeted these shared genes, we traced the annual changes in R_{gene}. Consequently, we discovered that DR donor–acceptor pairs with high DR event frequencies showed a large increase in R_{gene} shortly before the occurrence of DR events. That is, the proportion of shared drug target genes showed a rapid rise before a DR event took place. We found that the increase in the proportion of shared drug target genes and subsequent occurrence of DR events repeated multiple times, like waves, for several disease pairs. Therefore, we termed the rise and fall in the R_{gene} score the 'DR wave'. The DR wave represented a bimodal pattern in which the rise in R_{gene} (ΔR_{gene}: standardized during the period) preceded the onset of a DR event ($\Delta Drug$: number of observed DR events standardized during the period) by 1 to 2 years (Fig. 3b). By logistic regression analyses, we confirmed the reliability of the R_{gene} in predicting upcoming DR events for the top 100 disease pairs.[28]

Future direction of DR in RIDs

The comprehensive interdisease (or interdisease group) approach to DR assessment is in its early stages. Analysis of clinical trial data provides powerful predictability potential. This approach will have wide applications for the future research and development of candidate drugs for RIDs. The methods described in this review can be applied not only to RIDs, but also to common diseases. Therefore, they will facilitate DR from common to rare diseases and from rare to common diseases. Disease proximity and drug and genetic commonalities are the major factors that characterize the multidimensional DR landscape for RIDs.

It is reported that a large subset (~80%) of RIDs is considered to have genetic origins.[37] Some drugs target disease-related genes directly and some target indirectly or unrelated (i.e., drugs for supportive care). R_{gene} can be used in any RID, regardless of whether there is a genetic origins, because R_{gene} is calculated based on drug-based analyses. Currently, it is often

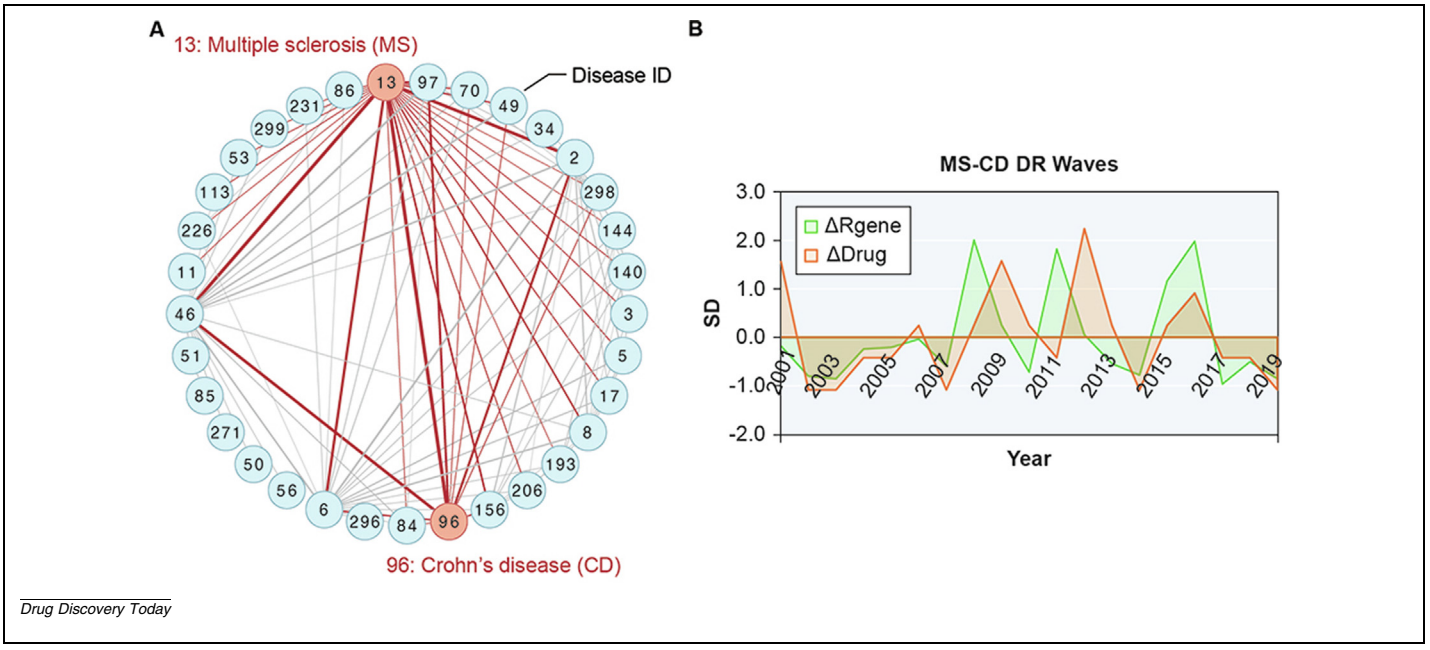

FIGURE 3

Estimation of drug repositionability for rare and intractable diseases (RIDs). (A) A network of disease pairs with the top 100 largest drug repositionability. This network comprised 33 diseases, and drug-repositionable disease pairs are connected by lines. Multiple sclerosis (MS) and Crohn's disease (CD) have a greater potential for drug repositionability (red circles and lines). (B) MS–CD drug-repositioning waves. For the MS–CD pair, the annual change in the score of drug repositionability (R_{gene}) and observed drug-repositioning events were standardized by SD. The three surges in R_{gene} (ΔR_{gene}) appeared to precede corresponding surges in drug repositioning ($\Delta Drug$) by about a year or two. Reproduced, with modifications, from.[28]

difficult to discriminate the directness of the drug mechanism of action. In diseases in which genetic origin is clear, R_{gene} has more potential to find more effective treatments.

Increasing numbers of clinical trials investigate multidrug regimens instead of monotherapies. The analysis of the pharmacodynamics of a drug, which is the basis of their repositionability, will also help identify optimal drug combinations. In addition to developing new therapeutic pipelines, pharmaceutical companies can benefit from drug combinations accelerated by DR in expanding their market shares.

R_{gene} scores can vary depending on clinical trial data. For example, analysis of successful versus failed trials can yield different R_{gene} scores. The higher R_{gene} scores in the analysis of early phases of clinical trials might suggest the higher potency of success in drug repositioning. Further detailed analyses will lead us to the more precise estimation of drug repositionability.

In addition to the R_{gene}, multimodal analytical approaches will find a more suitable score of drug repositionability. These approaches involve metabolomic, proteomic, and network pathway analyses. Future strategies should adopt a reverse translational approach that uses clinical presentation and other phenotypic data. Finally, the repositionability of a drug can be effectively estimated if its mechanism of action sheds light on the relatedness and proximity between one disease and another. Thus, the analysis of various aspects of disease–disease relationships will contribute to elucidate pharmacological and pathogenetic mechanisms.

Concluding remarks

In this review, we have discussed the ontologies and trend of DR for RIDs. Systematic ontologies can be used to link RIDs with drugs, target genes, and other omics information. DR events have occurred at high frequencies for RIDs, and drug target genes could inform a scoring of DR. These preliminary findings allow us to envision future opportunities for DR research.

Currently, effective medications are available only for a small set of RIDs. Given that numerous patients have a RIDs, systematic, interdisease approaches to DR should facilitate the development of new therapies. By utilizing clinical trial data of RIDs together with ontology preparation, and drug target gene-based DR analyses will open new doors for drug development.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.drudis.2022.01.013.

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