Rare diseases, or orphan diseases, are a group of disorders that, despite affecting relatively few patients at the individual disease level, collectively affect many worldwide. The World Health Organization (WHO) defines a rare disease as one that affects fewer than 65 per 100,000 people; however, when combined, would represent approximately 4–6% of the total worldwide population.

Due to the rarity of the individual diseases, their complex presentation, and lack of clinician awareness, these conditions are often misdiagnosed or underdiagnosed. Rare disease treatment and research, such as clinical trial recruitment, is further complicated by small patient populations and underfunding, and as a result, research does not advance as quickly relative to common diseases. The term “orphan disease” stems from this unmet need and the perception that rare diseases have been left “orphaned” by the pharmaceutical industry, with access to specialized healthcare and support made difficult for people living with such conditions.

In recent years, awareness of rare diseases has grown, and there have been increased efforts in research to address unmet needs in the field. Most rare diseases are genetic in etiology; consequently, research to identify genetic variants should provide the first steps toward a better understanding of the causes of these conditions. For example, advances in genomic sequencing and precision medicine could improve the diagnosis and targeted treatment of patients with rare diseases. Initiatives and incentives such as the orphan drug legislation have also encouraged pharmaceutical companies to invest more resources in rare disease research. This is important because research investment in rare diseases can have positive impacts beyond their small patient populations. Research in rare diseases can lead to breakthroughs in the understanding of more common diseases, such as uncovering shared mechanisms in disease pathophysiology and opening up new treatment pathways for patients. An example of this is research around progerin in Hutchinson-Gilford Progeria syndrome (HGPS). HGPS is a rare disease that causes premature aging, and HGPS research may offer insights into common cardiovascular diseases such as heart attacks and strokes.

This CAS Insights™ report describes how the CAS Content Collection™, the largest human-curated collection of published scientific information, was instrumental in capturing an overview of the changing landscape of rare diseases. Through analysis of the research and publications landscape, we have captured insights into the progress of rare disease medicine, including challenges and potential opportunities for growth.
Publication and patent landscape: what is on the horizon for rare diseases?

Capturing the field

The CAS Content collection currently houses over 530,000 publications about rare diseases, comprised of both journal articles and patents. Analysis of this collection helped identify key trends around prominent research institutions, leading journals, and rare diseases currently of high commercial interest. This report will focus on three rare diseases: amyotrophic lateral sclerosis (ALS), Huntington’s disease (HD), and myasthenia gravis (MG).

Over the last decade, both journal and patent publications have been on the rise (Figure 1), with rapid growth in the number of journal publications, particularly between 2019–2021, whereas the increase in patent publications has been steadier.

![Figure 1. Numbers of publications relating to rare diseases from the CAS Content Collection for the period 2003–2023.](image)

To identify leading research organizations actively publishing rare disease scientific content, institutions were ranked by publication volume and impact, which was calculated using the average number of citations per publication. Of the leading 15 institutions, 67% originated from the United States (including Harvard Medical School), 20% from Canada (including the University of British Columbia), and 13% from Great Britain (including the University of Oxford).

Leading scientific journals for rare diseases were identified using similar methodology, including the New England Journal of Medicine (New Engl J Med), Journal of Clinical Oncology (J Clin Oncol), and Proceedings of the National Academy of Sciences (Proc Natl Acad Sci USA). Analysis of rare diseases revealed that the highest interest in journal articles was found in HD, MG, ALS, rare tumors and cancers, and systemic lupus erythematosus (SLE). The continual scientific interest stemming from rare diseases means research can lead to high-impact publications, such as “Targeting huntingtin expression in patients with Huntington’s disease”, published in 2019 by researchers in the UK in the New England Journal of Medicine. The article described the results of a Phase I/IIa trial for an oligonucleotide designed by Ionis Pharmaceuticals and F. Hoffmann-La Roche to inhibit messenger ribonucleic acid (mRNA) of HTT, the main gene responsible for HD, and has since been cited over 400 times.
Patent publication trends also indicate areas of research interest and were analyzed by country/region. The results showed that the list of top ten patent assignee countries/regions included seven common to both commercial and non-commercial entities (Figure 2). The US is the highest by countries/regions, contributing 31% and 40% to non-commercial and commercial patents, respectively.

Figure 2. Leading organizations in the field of rare diseases from assessment of patent publication data from the CAS Content Collection for the period 2003 to 2023. (A) Donut and (B) bar charts showing geographical distribution and leading organizations, respectively. Regions and institutions were separated into non-commercial and commercial categories. Bar colors in the bar charts correspond to countries or regions shown in the donut charts. Countries or regions represented by their standard three-letter codes – United States (USA), China (CHN), South Korea (KOR), France (FRA), Germany (DEU), Japan (JPN), Spain (ESP), Denmark (DEN), Italy (ITA), Belgium (BEL), Switzerland (CHE), Israel (ISR), and United Kingdom (GBR).
Commercial interest in rare diseases

Patent filing can be a key indicator of the commercialization of promising research. The University of California is the top non-commercial patent assignee in the rare diseases space and, since 2015, has filed patents for treatments in ALS (WO2023086603, WO2022104148, HD (WO2022165538A1), and MG (WO2018236955, WO2018049053).

Analysis of the patents from the top six commercial companies helped shed further light on the spread of commercial interest across rare diseases. The following diseases were subsequently found to be of high commercial interest to the top six companies: multiple sclerosis, SLE, scleroderma, and HD, as seen by the higher publication volume versus other diseases. Additionally, kidney cancer, thyroid cancer, melanoma and multiple myeloma, all had relevant patents filed by all six commercial companies.

However, the number of patent publications indicates that not all rare diseases are being explored to the same extent. Examples of rare diseases with apparent low commercial interest include iridocyclitis, familial Mediterranean fever, Rett syndrome and pseudoaldosteronism. Commercially underexplored rare cancers include nasopharyngeal carcinoma, blastic plasmacytoid dendritic cell cancer and B-cell prolymphocytic leukemia.

To identify the leading rare diseases in terms of published research, analysis of the CAS Content Collection dataset investigated trends in both journal articles and patents categorized by condition. ALS, HD, and MG publication volumes identified them as leading research areas. The evolution of interest in these and other rare diseases over the last five years is shown below (Figure 3); HD, ALS, and MG show a clear, steady, and consistent increase in publications. This increase is most evident for MG, with publications nearly doubling in this 5-year period.

The patent-to-journal ratio of rare diseases was analyzed; 7 out of 14 scored >1, indicating greater commercial than general research interest. Of the leading rare diseases covered in this report, HD and MG had a patent-to-journal ratio of >1, whereas ALS had a patent-to-journal ratio of 0.7, indicating greater interest from the noncommercial community. The increased interest in ALS could be attributable to the viral “ice bucket” phenomenon, which may translate to greater commercial interest a few years down the line.

Similarly, interest in rare cancers is generally rising, with a broad increase in publications and all selected rare cancers showing clear, consistent, and rapid increases in publication numbers. Of special note are Kaposi’s sarcoma (cancer affecting the lining of blood vessels and lymph nodes), glioblastoma (cancer of the brain and/or spinal cord), and thyroid cancer with publications more than doubling between 2019 and 2022. Rare cancers generally are of high commercial interest, with >70% having patent-to-journal ratios >1.
Our analysis of the metrics of rare disease publications has shown that despite small patient populations, the research community has not forgotten the impact of rare diseases and continues to focus on these conditions.

The trends identified in this report suggest that interest in rare diseases is increasing and will offer more opportunities in the future.
Behind the scenes: from genetics to the pathogenesis of rare diseases

Research efforts continue to improve our understanding of rare diseases, from their root causes and mechanisms, to their application in novel treatment pathways.

Myasthenia gravis

MG is a rare, chronic, autoimmune neuromuscular disorder characterized by weakness and rapid fatigue of voluntary muscles. In MG, self-production of antibodies against acetylcholine (ACh) receptor (AChR) or muscle-specific kinase are believed to be the main causes of this condition, triggering the immune system to mistakenly attack receptors on muscle cells, particularly at the neuromuscular junction, and subsequently hindering muscle contraction (Figure 4).

Figure 4. Pathogenesis of MG schematic, detailing the three effects of antibodies at the neuromuscular junction and their consequent damaging effects. ACh, acetylcholine; AChR, acetylcholine receptor; NMJ, neuromuscular junction.
Autoantibodies are thought to be produced by the thymus, which may also contribute to the maturation of autoreactive T cells involved in the autoimmune response in MG. Symptoms caused by the autoimmune effects of MG can vary widely and complicate diagnosis over time. However, the hallmark symptom of MG is muscle weakness, typically worsening with activity and improving with rest.

Despite not being considered a purely genetic disorder, MG has a complex genetic background. As such, MG is regarded as an autoimmune disease with genetic predispositions. Certain genetic variations or polymorphisms may predispose an individual to develop MG. Often, these variations are observed in immune system function genes, such as those encoding human leukocyte antigens (HLAs), specifically the HLA-B8 and HLA-DR3 alleles, and HLA alleles within the major histocompatibility complex (MHC) region. Environmental triggers likely interact with genetic susceptibility factors to influence individual development of MG. Through the analysis of the CAS Content Collection, we have collated four genes that are associated with MG (Figure 5).

![Figure 5. Genes associated with MG based on data from the CAS Content Collection. Only genes with an association score of greater than 0.4 and at least ten records are shown. The majority of records were obtained from text mining.](image-url)

Treatments for MG, such as acetylcholinesterase inhibitors, immunosuppressants, and corticosteroids, aim to manage symptoms and improve quality of life. However, no cure is currently available.
Amyotrophic lateral sclerosis

ALS (also known as motor neuron disease or Lou Gehrig’s disease) is a rare, progressive, neurodegenerative disorder. ALS affects motor neurons in the brain and spinal cord that control voluntary muscle movement, and the resulting dysfunction leads to muscle weakness, atrophy, and paralysis (Figure 6).82–87

In Figure 6. Pathogenesis of ALS schematic, detailing the effects of the condition on motor neurons and their cellular structure. Glutamate,88–90 protein aggregation,91–94 mitochondrial dysfunction,95–97 and non neuronal cells all play key roles in ALS pathology.98–103
Illustration courtesy of https://smart.servier.com/

1 Excessive levels of glutamate are observed in the synaptic cleft. This can damage motor neurons, contributing to their degeneration and death.

2 Mutations in SOD1, TARDBP (encoding TDP-43), FUS, and C9orF72 may lead proteins to aggregate and accumulate within motor neurons and surrounding cells.

3 In the mitochondria, impaired energy metabolism and increased production of reactive oxygen species impacts motor neuron degeneration.

4 Non-neuronal cells such as astrocytes, microglia, and oligodendrocytes play important roles in ALS pathogenesis.
ALS, like MG, also has roots in genetics; however, the condition has been hypothesized not to be a single-gene disease but a plethora of overlapping conditions with common characteristics and genetic factors. As a result, diagnosis is complex, and treating physicians need to consider each individual’s medical history, neurological examinations, imaging, electromyography, and nerve conduction study results, as well as the possibility of a differential diagnosis against other plausible causes of muscle weakness and motor dysfunction. The genetic background of ALS is multifaceted, involving both familial and sporadic forms. While most ALS cases occur without a clear family history, possibly due to a combination of genetic susceptibility and environmental factors, approximately 5–10% of cases have a known genetic component (Figure 7). Significant genetic heterogeneity of ALS leads to distinct clinical phenotypes that are associated with disease progression.

### Table of Genes and Proteins Involved in ALS

<table>
<thead>
<tr>
<th>Role</th>
<th>Gene</th>
<th>Protein</th>
<th>Protein Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations in SOD1</td>
<td>SOD1 1.0</td>
<td>Superoxide dismutase 1</td>
<td>Mutations in SOD1 are believed to induce protein misfolding, leading to ALS.</td>
</tr>
<tr>
<td>Mutations in Senataxin</td>
<td>SETC 1.0</td>
<td>Senataxin</td>
<td>Mutations in Senataxin are thought to affect its function, leading to juvenile ALS-4, which develops in patients before the age of 25 years.</td>
</tr>
<tr>
<td>Mutations in TDP-43</td>
<td>TARDBP 0.9</td>
<td>TDP-43</td>
<td>Mutations in TDP-43 may affect gene expression, resulting in some pathologies seen in ALS, such as fibril formation and RNA regulation.</td>
</tr>
<tr>
<td>Mutations in Optineurin</td>
<td>OPTN 0.9</td>
<td>Optineurin</td>
<td>Mutations may alter optineurin’s ability to interact with and consequently remove damaged mitochondria.</td>
</tr>
<tr>
<td>Mutations in Sequestosome 1</td>
<td>SQSTM1 0.9</td>
<td>p62 protein/Sequestosome 1</td>
<td>Mutations in Sequestosome 1 may impair removal of misfolded or aggregated protein, and reduce autophagy.</td>
</tr>
<tr>
<td>Mutations in FUS</td>
<td>FUS 0.9</td>
<td>Fused in sarcoma (FUS) RNA binding protein</td>
<td>Mutations in FUS have reduced ability to bind to a nuclear import receptor, resulting in accumulation of mutant FUS in the cytoplasm.</td>
</tr>
<tr>
<td>Mutations in PRN1</td>
<td>PRN1 0.9</td>
<td>Profilin 1</td>
<td>Mutations in profilin 1 may result in its aggregation alongside TDP-43, which may contribute to ALS-related dysfunctions.</td>
</tr>
<tr>
<td>Mutations in MATR3</td>
<td>MATR3 0.9</td>
<td>Matrin 3</td>
<td>Matrin 3 interacts with TDP-43 and FUS, and may have a role in ALS.</td>
</tr>
<tr>
<td>Mutations in UBQLN2</td>
<td>UBQLN2 0.9</td>
<td>Ubiquilin 2</td>
<td>Mutant ubiquilin may have reduced capacity for protein degradation through affected interactions with binding partners and other proteins.</td>
</tr>
<tr>
<td>ALS2</td>
<td>ALS2 0.8</td>
<td>Alsine</td>
<td>Some alsin mutations associated with ALS result in expression of forms without crucial domains, reducing the functionality of alsin as a guanine nucleotide exchange factor.</td>
</tr>
</tbody>
</table>

### Figure 7

Figure 7 shows a schematic representation of the role of various proteins and genes in the development of ALS. The figure highlights the interaction between different proteins, such as TDP-43, FUS, and Optineurin, and their involvement in the disease process. It also emphasizes the importance of autophagy in the clearance of toxic proteins and the role of Sequestosome 1 in this process. The figure underscores the multifactorial nature of ALS, with contributions from genetic mutations, environmental factors, and cellular homeostasis.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>angiogenin</td>
<td>VAPB</td>
<td>interacts with a number of partners; one extensively studied mutation has several proposed mechanisms in ALS.</td>
</tr>
<tr>
<td>Peripherin</td>
<td>Coiled-coil-helix-coiled-coil-helix domain containing protein 10</td>
<td></td>
</tr>
<tr>
<td>FIG4</td>
<td>Polyphosphoinositide phosphatase</td>
<td>Investigated. There is evidence FIG4 mutations could disrupt intracellular trafficking due to excessive vacuoles, though this mutation is still being investigated.</td>
</tr>
<tr>
<td>KIF5A</td>
<td>Kinesin family member 5A</td>
<td>It has been demonstrated that a KIF5A mutation disrupts the autoinhibition of kinesin family member 5A, leading to increased mitochondrial transport.</td>
</tr>
<tr>
<td>ERBB4</td>
<td>Erb-b2 receptor tyrosine kinase 4 (ErbB4)</td>
<td>ErbB4 interacts with a number of partners; one reported ALS mutation results in reduced autophosphorylation.</td>
</tr>
<tr>
<td>CCNF</td>
<td>Cyclin F</td>
<td>Mutant CCNF causes abnormal ubiquitination and is believed to contribute to ALS.</td>
</tr>
<tr>
<td>ANXA11</td>
<td>Annexin A11</td>
<td>Mutant annexin A11 has been reported to increase formation of insoluble aggregates, disrupt Ca2+ homeostasis, and interfere with RNA transport.</td>
</tr>
<tr>
<td>NEK1</td>
<td>NIMA-related kinase 1</td>
<td>NIMA-related kinase 1 has a large role in cellular processes, and two main mutations (a loss of function and missense variant) are thought to be associated with ALS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD1</td>
<td>Leading to ALS.</td>
<td>Protein misfolding, FUS accumulation of mutant receptor, resulting in reduced ability to bind RNA binding protein in the cytoplasm.</td>
</tr>
<tr>
<td>TDP-43</td>
<td>Matrin 3 is a DNA/RNA-binding nuclear protein that interacts with and affects other proteins.</td>
<td></td>
</tr>
<tr>
<td>ALS2</td>
<td>Ubiquilin 2</td>
<td>Mutant ubiquilin may impair removal of misfolded or aggregated protein, and reduce autophagy.</td>
</tr>
<tr>
<td>TBK1</td>
<td>Sequestosome 1</td>
<td>May impair removal of aggregated protein, and reduce autophagy.</td>
</tr>
</tbody>
</table>

Figure 7. Genes associated with ALS based on data from the CAS Content Collection. Only genes with an association score greater than 0.6 and at least 10 records are shown here. Color corresponds to association score: yellow (1.0), light green (0.9), orange (0.8), purple (0.7) and aqua (0.6). The nature of the line indicates the association source, with dashed lines indicating a majority of records resulting from text mining.
Huntington’s disease

HD is a rare, hereditary, neurodegenerative disorder causing progressive motor impairment, cognitive decline, and psychiatric symptoms. The associated motor symptoms include jerky and unpredictable movements in the face, arms, and legs.116–118

The pathogenesis of HD involves a complex interplay of genetic, molecular, and cellular mechanisms that ultimately lead to neurodegeneration in specific regions of the brain (Figure 8).119–122 HD is caused by a mutation in the HTT gene, which encodes for a mutant huntingtin protein (mHTT). The mHTT causes disturbances to normal cellular and neuronal functions and exacerbates neurodegeneration, including altered gene expression patterns and impaired neuronal function, survival, and plasticity.123–125 eventually leading to cell death.126–129 Synaptic dysfunction is also an early feature of HD that contributes to cognitive and motor impairments.130,131

Huntington’s disease pathogenesis

1 mHTT causes misfolding and aggregation of the protein, creating the so-called inclusion bodies and accumulating within neurons.

2 Mitochondrial function is affected, impairing energy production, increasing oxidative stress, and mitochondrial fragmentation.

3 Dysregulation of glutamate signaling and excitotoxicity from astrocyte dysfunction may occur.

4 Axonal transport and synaptic processes are affected, with mHTT impairing the delivery of essential proteins and organelles to synapses.

5 Neuroinflammation contributes to HD pathogenesis.

Figure 8. Potential pathogenesis of HD schematic. The CAG repeat in HTT encodes for mHTT, causing aggregation and inclusion bodies. mHTT causes mitochondrial dysfunction, excitotoxicity, dysregulation of axonal transport and synaptic processes, and neuroinflammation.132–134
Illustration courtesy of https://smart.servier.com
Currently, no cure is available for HD, with treatments focusing on managing symptoms and improving quality of life. Disease-modifying treatments are the goal of ongoing research efforts, and an increased understanding of the underlying mechanisms of HD is important to achieve this. Current clinical trials focus on therapies that target the mutant huntingtin protein, neuroinflammation, and other factors of HD pathogenesis.\textsuperscript{144,145}

HD is an “autosomal dominant” disease, meaning affected individuals may have only inherited one expanded CAG repeat from one of their parents. The age of onset and severity of symptoms can vary widely among individuals.\textsuperscript{146} but often, the longer the CAG repeats, the earlier the onset and the higher the severity of the disease.\textsuperscript{119,126,147,148} Other genetic factors may also influence the onset and progression pattern of HD, and predictive genetic testing is available to help inform individuals at risk of HD. Those invited for testing are advised to attend genetic counseling to discuss their results with a genetic counselor and any potential repercussions.\textsuperscript{149,150}

Despite the established role of HTT in HD pathogenesis,\textsuperscript{151} this analysis also investigated other potential genetic contributors to the development of HD, with additional genes identified (Figure 9).

![Figure 9](image)

**Figure 9.** Genes associated with HD, based on data from the CAS Content Collection. Only genes with an association score greater than 0.8 and at least ten records are included. Color corresponds to association score: yellow (1.0), green (0.9) and orange (0.8). The majority of records were gathered from text mining.
Landscape analysis

Publication growth and geographical trends

Patent and journal publications in ALS have steadily increased over the last two decades, with a similar trend for MG which has had a steeper rise since 2018. Patents in HD have also been growing consistently since 2018, and journal publications also displayed an upward trend (Figure 10). All three rare diseases have a greater journal-to-patent publication ratio throughout the window of analysis. Although growth is evident in all three diseases, MG exhibited the fastest growth in the years 2003–2006, following which ALS took the lead since 2014, with nearly 8% relative growth between 2003–2023.

Figure 10. Publications for specific rare diseases: (A) ALS, (B) HD and (C) MG. Data includes journal and patent publications sourced from the CAS Content Collection for 2003–2023.
Comorbidities

Reports of comorbidities were assessed in publications available from the CAS Content Collection. In ALS, hypertension and dyslipidemia are the most commonly reported comorbidities. This is notable, as there are ongoing debates about the potential protective role of hypertension and other cardiovascular disorders towards the prognosis and survival of patients with ALS. As well as cardiovascular-related disease, autoimmune diseases are frequently reported in this patient population, although little is known about the related clinical presentation. Finally, despite research in this area, the association of ALS with the risk of cancer (both generally and for specific cancers) is ambiguous and inconsistent.

HD has frequently been associated with depression, affecting nearly 43% of all patients, the majority of whom are female. Individuals with HD have also been known to have a higher prevalence of comorbidities (musculoskeletal, cardiovascular, and psychiatric) than healthy individuals. Conditions more commonly observed in patients with adult-onset HD versus healthy individuals include obsessive-compulsive disorder, psychosis, communication disorders, depression, anxiety, dementia, and others.

Both autoimmune and non-autoimmune comorbidities are observed in patients with MG, with autoimmune thyroiditis, SLE, and rheumatoid arthritis being the most frequent. Comorbidity onset may be related to MG disease onset, as patients with early-onset MG are more likely to develop an autoimmune disease than their late-onset counterparts. A known non-autoimmune comorbidity of MG is cardiovascular disease.

Using the CAS Content Collection, we examined the co-occurrences of ALS, HD, and MG with other rare and non-rare diseases (Figure 11).
Figure 11. Co-occurrences of ALS, HD, and MG with medical topics such as (A) other rare and non-rare diseases, (B) types of therapy and drugs used to treat symptoms and (C) cells and proteins. Data include patent and journal publications sourced from the CAS Content Collection for the period 2003–2023 in the field of rare diseases.
Types of therapy

Combination therapies are the most common type of treatment for all three rare diseases. This is perhaps no surprise given that ALS and HD are multifactorial diseases, meaning single-target drugs are likely to be insufficient when compared with combination drug therapy, which involves multifunctional and biologically diverse agents.\(^\text{165}\)

Certain topic combinations are more likely to occur than other combinations in rare disease publications. MG occurs most frequently with combination therapy and secondly with the topic of immunotherapy, whereas ALS and HD often co-occur with gene therapy. Over 50 gene mutations have been identified with a potential causative role in ALS, and efforts are being made to understand the role of these genes in ALS pathogenesis.

Due to the potential of gene therapy, suppressing the toxic impact of etiologic genes has been widely investigated. Major strategies include: removal or inhibition of abnormally transcribed ribonucleic acid (RNA) using micro RNA or antisense oligonucleotides (ASOs); degradation of normal messenger RNA using RNA interference; a decrease in or inhibition of mutant proteins by using, for example, antibodies against misfolded proteins; and/or deoxyribonucleic acid (DNA) genome editing with methods such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) or CRISPR/Cas.\(^\text{166}\) As some studies have shown positive results, ALS clinical trials have incorporated these strategies for C9orf72 and SOD1.\(^\text{166–169}\)

HD is a good candidate for gene therapy as a monogenic disease with mHTT as a known cause. Genetic therapies may, therefore, help to enhance the function of affected genes throughout the disease course and slow progression.\(^\text{170}\) Removing, known as “knocking out” the HTT gene has recently been tested, with promising results.\(^\text{171}\)

Immunotherapeutic biologics also show some promise as therapeutic agents for MG, including two monoclonal antibodies known as eculizumab and rituximab. Eculizumab has been approved by the US Food and Drug Administration for the treatment of MG that does not respond to other therapies,\(^\text{172}\) and rituximab is in the advanced stages of clinical trials. As new biologics become available, targeted immunotherapies with higher specificity for MG may be developed.

Repurposed drugs

As the pharmaceutical development process is both time-consuming and costly, drug repurposing provides a chance to accelerate therapy discovery and development. During drug repurposing, approved agents with established safety profiles, pharmacokinetics, formulations, dosages, and manufacturing procedures are explored as treatment options for new conditions.

Within the CAS Content Collection, ALS and HD most frequently co-occurred with mention of anti-Alzheimer and anti-Parkinson drugs. Ropinirole, a treatment for Parkinson’s disease, has been found to delay the progression of ALS,\(^\text{173}\) while allopurinol and carvedilol, treatments for gout and high blood pressure, respectively, show evidence of reducing the risk of developing ALS.\(^\text{174,175}\) The brain-permeable iron chelator M30 has also been associated with neuroprotection across neurodegenerative diseases.\(^\text{176,177}\)

Other drug classes have been explored for the treatment of ALS, such as anti-cancer, antiretroviral, anti-inflammatory, anticonvulsant, and antiestrogen drugs.\(^\text{178}\) Antipsychotic therapies have also been studied for use in ALS and HD.\(^\text{178–181}\) Other repurposed drugs used to treat HD include tetrabenazine (an antipsychotic also used for diseases involving abnormal, involuntary movements),\(^\text{179}\) tiapride,\(^\text{180}\) olanzapine,\(^\text{182}\) risperidone,\(^\text{181}\) and quetiapine.\(^\text{183}\)

Contrastingly, MG frequently co-occurred with immunosuppressive and anti-rheumatic drugs within the CAS Content Collection, as they may act by helping to dampen the immune system’s response and prevent it from attacking the NMJ. Such therapies include prednisone, azathioprine, cyclophosphamide, methotrexate, tacrolimus, mycophenolate, and mofetil.\(^\text{184–187}\) Two drugs used for treating rheumatoid arthritis, abatacept and rituximab, are also reported to help prevent MG and reduce the risk of deterioration, respectively.\(^\text{187,188}\)
Proteins

Patterns of co-occurrences of rare diseases with proteins were also analyzed; for example, transactive response DNA binding protein 43 (TDP-43) had the highest co-occurrence with ALS. In 97% of cases, ALS is characterized by loss of TDP-43 from the nucleus and abnormal accumulation in the cytoplasm of affected neurons,189–191 and has been related to disease severity and progression.192

While huntingtin is the key protein in HD etiology, recent research has revealed the presence of β-amyloid deposits and elevated levels of phosphorylated tau in the brains of patients despite these being typically associated with Alzheimer's disease.193–195

Cells

The CAS Content collection determined astrocytes and microglial cells as the most frequently co-occurring cells associated with ALS and HD publications, whereas

T- and B-cells are commonly associated with MG. Astrocytes have roles in ALS and HD throughout the disease course through various mechanisms.196 Microglia are immune cells initially recruited to respond to neuronal injury and promote tissue repair but may become chronically activated in ALS and HD, leading to further motor neuron degeneration.196–198 Other cell types including oligodendrocytes and NG2 glia, may also play a part in ALS and HD pathology.

Substance data

The CAS Registry contains over 250 million substances of diverse classes. Between 2012–2023, the number of patent publications related to small molecules, protein/peptide sequences, and nucleic acid sequences increased (Figure 12), with no similar trend observed in journal publications. This is indicative of a commercial interest in developing these therapeutics. For ALS, HD, and MG, small molecules represented the largest fraction of explored substances (Figure 12).
Huntington’s disease (HD)

Graphs showing the relative growth (%) in substances associated with journal and patent publications over the years 2012 to 2023. The categories include small molecules, protein/peptide sequences, nucleic acids sequences, and others.

Circle diagram indicating the percentage distribution of substances associated with HD publications.
Figure 12. Substance data from the CAS Registry is associated with (A) ALS, (B) HD and (C) MG. Data includes substances associated with patent and journal publications sourced from the CAS Registry and the CAS Content Collection for the period 2012–2023.
Rare diseases such as ALS, HD, and MG have been the subject of intense research and investment over the past decade, as confirmed by data from Pitchbook, an online platform for investment data. However, a mild decline has been observed in the amount of money invested in this field over the last three years (2021–2023), which could indicate a slight decrease in commercial interest (Figure 13). Between 2013–2023, the greatest amount of financial investment came from the US, followed by Belgium, the Netherlands, and the UK.

The top industry investors in rare diseases are life sciences based, followed by oncology and healthtech. Vaccinex, a US-based biotech company, has the highest number of deals in this field. Its lead drug candidate, pepinemab, has been identified as a potential disease-modifying treatment for HD, Alzheimer’s, and other neurodegenerative diseases and is currently being investigated in Phase II clinical trials. Another biotech company, Cytokinetics, is investing in diseases linked to the NMJ, such as ALS. These trends confirm a solid commercial interest in rare diseases, including ALS, HD, and MG.

What story does the financial data tell?

Figure 13. Commercial interest in rare diseases (data sourced from PitchBook, an online platform for investment data). Capital invested and deals related to rare diseases (HD, ALS, MG) for the past decade (2012–2023).
What is in the pipeline?

Drugs, trials, and candidates

Nearly 250 substances are being researched and in preclinical development for treating ALS, HD, and MG (Tables 1, 2, and 3). The vast majority (74%) of these substances are for the treatment of ALS, but therapies for the treatment of HD (18%) and MG (8%) are also in the development pipeline. Small molecule drugs dominate the total number of drug candidates, followed by gene, antibody, RNA, ASO, and stem cell therapies (Figure 14).

Rare disease therapeutic drug candidates in commercial preclinical development (Source: https://clinicalintelligence.citeline.com/).

### Amyotrophic lateral sclerosis (ALS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Effect</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foralumab</td>
<td>Monoclonal antibody, humanized</td>
<td>CD3 antagonist</td>
<td>Tiziana Life Sciences, UK</td>
</tr>
<tr>
<td>Mecobalamin</td>
<td>Neuroprotectant</td>
<td>Vitamin B12 agonist</td>
<td>Eisai, Japan</td>
</tr>
<tr>
<td>Mitometin</td>
<td>Cognition enhancer, neuroprotectant</td>
<td>Carnitine palmitoyltransferase 1 inhibitor</td>
<td>2N Pharma, Denmark</td>
</tr>
<tr>
<td>Pimicotinib</td>
<td>Neuroprotectant</td>
<td>Colony stimulating factor 1 receptor antagonist; immuno-oncology therapy</td>
<td>Sperogenix Therapeutics, China</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Cognition enhancer, neuroprotectant</td>
<td>DNA-directed RNA polymerase inhibitor</td>
<td>Medilabo RFP, Japan</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Neuroprotectant</td>
<td>Dopamine receptor agonist; glutamate antagonist; voltage-gated sodium channel antagonist</td>
<td>Brain Trust Bio, USA</td>
</tr>
</tbody>
</table>

Table 1. Examples of therapeutic drug candidates in ALS.

### Huntington’s disease (HD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Effect</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debametorcel</td>
<td>Stem cell therapy</td>
<td>Glial-cell-derived neurotrophic growth factor agonist</td>
<td>BrainStorm Cell Therapeutics, USA</td>
</tr>
<tr>
<td>HD therapy</td>
<td>PROTAC</td>
<td>HTT inhibitor; E3 ubiquitin ligase stimulant, protein degrader</td>
<td>Arvinas, USA</td>
</tr>
<tr>
<td>HD therapy</td>
<td>Cognition enhancer, neuroprotectant</td>
<td>Reverses mitochondrial dysfunction</td>
<td>MitoRx Therapeutics, UK</td>
</tr>
<tr>
<td>HD therapy</td>
<td>RNA interference</td>
<td>Utilizing a small hairpin RNA or short hairpin RNA for gene expression inhibition</td>
<td>Novartis, Switzerland; Voyager Therapeutics, USA</td>
</tr>
</tbody>
</table>

Table 2. Examples of therapeutic drug candidates in HD.

### Myasthenia gravis (MG)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Effect</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equecabtagene autoleucel</td>
<td>CAR T-cell therapy</td>
<td>Immuno-oncology therapy; T-cell stimulant</td>
<td>Nanjing IASO Biotechnology, China</td>
</tr>
<tr>
<td>Pozelimab</td>
<td>Monoclonal antibody, humanized</td>
<td>C5a inhibitor</td>
<td>Regeneron, USA</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Musculoskeletal therapy</td>
<td>Glucocorticoid agonist</td>
<td>Sarcomed AB</td>
</tr>
</tbody>
</table>

Table 3. Examples of therapeutic drug candidates in MG.
As part of the exploration of these new rare disease therapies, over 1 thousand clinical trials have been registered on the US National Institutes of Health clinical trial website over the last 20 years. ALS has the highest number of registered trials, followed by HD and MG (Figure 15).

Figure 14. Preclinical drug therapy candidates and their respective rare disease indications that are currently in the development pipeline.

Figure 15. Number of clinical trials by rare disease indications for the years 2003–2023.
Nearly half of all rare disease clinical trials are not phased; for those that are, Phase II and Phase III studies are the most common phase of trial for ALS/HD and MG, respectively. While almost half of all trials for these three diseases have a status of “completed”, “recruiting” is the second-most common status, suggesting a continued interest in this space.

In ALS, therapy types in clinical development include cell and gene therapies, and small-molecule drugs. RAPA Therapeutics is developing a candidate for autologous T-cell therapy, RAPA-501, to address the limited options for the treatment of neuroinflammation. They are currently recruiting for a Phase II/II clinical trial (NCT04220190) to assess its safety and efficacy in standard-risk patients.204 Additionally, a gene therapy agent, AMT-162 from UniQure Biopharma, will soon be evaluated in patients with SOD1 mutations and rapidly progressive disease (NCT06100276). Rare disease research is also no exception to the application of artificial intelligence (AI), which helped to discover the small molecule FB1006 for the potential treatment of ALS.205 Two more small molecules, ibudilast (CAS RN: 50847-11-5) and pridopidine (CAS RN: 346688-38-8), discovered by MediciNova and Prilenia respectively, are being investigated as part of the HEALEY ALS Platform trial (NCT04297683). The latter was granted orphan drug designation in 2021 from the US Food and Drug Administration (FDA).206

In HD, therapies under development include ASO, cell, and monoclonal antibody therapies, computer-based cognitive stimulation, and small-molecule agents. One such ASO is WVE-003 from Wave Life Sciences, a gene-silencing therapeutic. Further biological-based therapies include NestaCell, a stem cell therapy discovered by Cellavita, which is currently being evaluated in Phase I and Phase II/III clinical trials (NCT02728115 and NCT04219241). A pioneering study by Santa Cre Hospital (Spain) is investigating computer-based cognitive rehabilitation (NCT05769972) in patients with movement disorders. Sage Therapeutics is currently recruiting for Phase II/III clinical trials (NCT05107128, NCT05358821, and NCT05655520) for their small molecule drug SAGE 718 (CAS RN: 1629853-48-0). SAGE 718 was granted FDA Fast Track designation205 in 2022 and Orphan Drug Designation in 2023, an indication of its promise towards HD.208

Therapies under development for MG include biologics such as antigen, cell, and fusion proteins, as well as small molecule-based treatments. COUR Pharmaceutical is developing CNP-106, an antigen-specific therapeutic that prevents immune-mediated NMJ destruction and aims to reprogram the immune system to address the immunological root cause of MG (NCT06106672). An mRNA CAR-T cell therapy currently under investigation is Descartes 08, by Cartesian Therapeutics. Preliminary results for Descartes 08 indicate it is well tolerated, with meaningful improvement in MG disease scorings (NCT04146051),209 and the FDA has granted it Orphan Drug Designation in 2024.210 Another biological therapy is telitacicept, a fusion protein constructed of a domain of an extracellular protein from B cells and immunoglobulin G, from RemeGene.211 RemeGene is currently recruiting for a Phase III clinical trial (NCT05737610). Finally, Alexion Pharmaceuticals is currently investigating their candidate ALXN2050 (CAS RN: 2086178-00-7), a small molecule factor D inhibitor, in a Phase II clinical trial (NCT05218096).

**Telitacicept**

Targets B-cell development key molecules: **B-cell lymphocyte stimulator** and a proliferation-inducing ligand

B-cell mediated autoimmune responses

Anti-AChR antibodies

MG-related symptoms

Tolerable safety profile

Figure 16. Mode of action of telitacicept, a fusion protein-based therapy. Telitacicept interacts with B cells to decrease the resulting mediated immune response and anti-AChR antibodies, and thus, decreases MG symptoms.
Currently, there are no cures for ALS, HD, or MG, but there are treatments to slow disease progression and treat symptoms. There are 13 drugs currently approved by the FDA for treating these rare diseases, of which three have multiple approved formulations (Table 4). Several of the approved drugs for ALS and HD are small molecules. In contrast, biologic therapies such as monoclonal antibodies, antibody fragments, and peptide therapy make up most of the approved treatments for MG. Patents pertaining to ALS, HD, and MG were identified from the CAS Content Collection (Table 5).

### What could the future hold?

Currently, there are no cures for ALS, HD, or MG, but there are treatments to slow disease progression and treat symptoms. There are 13 drugs currently approved by the FDA for treating these rare diseases, of which three have multiple approved formulations (Table 4). Several of the approved drugs for ALS and HD are small molecules. In contrast, biologic therapies such as monoclonal antibodies, antibody fragments, and peptide therapy make up most of the approved treatments for MG. Patents pertaining to ALS, HD, and MG were identified from the CAS Content Collection (Table 5).

<table>
<thead>
<tr>
<th>FDA approved small molecule and biological drugs for rare diseases</th>
<th>Structure/therapy type</th>
<th>CAS Registry Number®</th>
<th>Mechanism and notes</th>
<th>Company, location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exservan (riluzole) for ALS</td>
<td></td>
<td>1744-22-5</td>
<td>Glutamate signaling blocker/oral film formulation</td>
<td>Mitsubishi Tanabe Pharma America, USA</td>
</tr>
<tr>
<td>Nuedexta (dextromethorphan hydrobromide and quinidien sulfate) for ALS</td>
<td></td>
<td>2445595-41-3</td>
<td>Sigma-1 receptor agonist, NMDA receptor antagonist</td>
<td>Otsukac America Pharmaceutical, USA</td>
</tr>
<tr>
<td>Radicava (edaravone) for ALS</td>
<td></td>
<td>89-25-8</td>
<td>Free radical scavenger</td>
<td>Mitsubishi Tanabe Pharma America, USA</td>
</tr>
<tr>
<td>Relyvrio (sodium phenylbutyrate and taurursodiol) for ALS</td>
<td></td>
<td>2436469-04-2</td>
<td>Small molecule chaperone and Bax inhibitor/withdrawn 2024</td>
<td>Amylyx, USA</td>
</tr>
<tr>
<td>Rilutek (riluzole) for ALS</td>
<td></td>
<td>1744-22-5</td>
<td>Glutamate signaling blocker/oral tablet formulation</td>
<td>Sanofi, USA</td>
</tr>
<tr>
<td>Name</td>
<td>Mechanism and notes</td>
<td>Company, location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiglutik (riluzole) for ALS</td>
<td>Glutamate signaling blocker/oral thickened suspension</td>
<td>ITF Pharma, USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austedo (deutetrabenazine) for HD</td>
<td>VMAT2 inhibitor</td>
<td>Teva Pharmaceutical, Israel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austedo XR (deutetrabenazine) for HD</td>
<td>VMAT2 inhibitor/extended-release formulation</td>
<td>Teva Pharmaceutical, Israel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingrezza (valbenazine) for HD</td>
<td>VMAT2 inhibitor</td>
<td>Neurocrine Biosciences, USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xenazine (tetrabenazine) for HD</td>
<td>VMAT2 inhibitor</td>
<td>Lundbeck Pharmaceuticals, Denmark</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structure/therapy type</td>
<td>CAS Registry Number®</td>
<td>Mechanism and notes</td>
<td>Company, location</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Qalsody</strong> <em>(tofersen)</em> for ALS</td>
<td>Gene therapy</td>
<td>2088232-70-4</td>
<td>Targets SOD1 mRNA to reduce SOD1 protein production</td>
<td>Biogen, USA</td>
</tr>
<tr>
<td><strong>Rystiggo</strong> <em>(rozanolixizumab-noli)</em> for MG</td>
<td>Monoclonal antibody</td>
<td>1584645-37-3</td>
<td>Targets FcRn to prevent IgG recycling</td>
<td>UCB, USA</td>
</tr>
<tr>
<td><strong>Soliris</strong> <em>(eculizumab)</em> for MG</td>
<td>Monoclonal antibody</td>
<td>219685-50-4</td>
<td>Complement factor C5 inhibitor</td>
<td>Alexion, UK</td>
</tr>
<tr>
<td><strong>Ultomiris</strong> <em>(ravulizumab-cwvz)</em> for MG</td>
<td>Monoclonal antibody</td>
<td>1803171-55-2</td>
<td>Complement factor C5 inhibitor</td>
<td>Alexion, UK</td>
</tr>
<tr>
<td><strong>Vyvgart</strong> <em>(efgartigimod alfa-fcab)</em> for MG</td>
<td>Antibody fragment</td>
<td>1821402-21-4</td>
<td>Fc receptor blocker, intravenous injection</td>
<td>Argenx, Netherlands</td>
</tr>
<tr>
<td><strong>Vyvgart Hytrulo</strong> <em>(efgartigimod alfa and hyaluronidase-qvfc)</em> for MG</td>
<td>Antibody fragment</td>
<td>1821402-21-4</td>
<td>Fc receptor blocker, subcutaneous injection</td>
<td>Argenx, Netherlands</td>
</tr>
<tr>
<td><strong>Zilbrysq</strong> <em>(zilucoplan)</em> for MG</td>
<td>Peptide therapy</td>
<td>1841136-73-9</td>
<td>Complement factor C5 inhibitor</td>
<td>UCB, USA</td>
</tr>
</tbody>
</table>

Table 4. FDA-approved drugs for the treatment of specified rare diseases (Source: The CAS Content Collection). Each drug is listed with the disease indication, therapy type, CAS identifier, mechanism, company, location, and any extra information. Tile colors are defined by therapy type: small molecule (yellow), gene therapy (orange), monoclonal antibody (blue), antibody fragment (light green), and peptide therapy (purple).
<table>
<thead>
<tr>
<th>Patent number</th>
<th>Year</th>
<th>Patent assignee, location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20200002723</td>
<td>2020</td>
<td>Deutsches Krebsforschungszentrum, Germany</td>
<td>Early markers for development: nucleotide sequences called Multiple Sclerosis Brain Isolate (MSBI), as well as probes, primers, and antibodies against polypeptides encoded by MSBI sequences</td>
</tr>
<tr>
<td>WO2020010049</td>
<td>2020</td>
<td>The General Hospital Corporation, AZTherapies, Inc., United States</td>
<td>Treatment: composition of micronized cromolyn sodium, α-lactose, and salt of fatty acid (preferably magnesium stearate)</td>
</tr>
<tr>
<td>CN117050134</td>
<td>2023</td>
<td>Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China</td>
<td>Treatment and prevention: novel oleamide derivative for activating a KEAP/NRF2/ARE signaling pathway</td>
</tr>
<tr>
<td>EP4255406A1</td>
<td>2020</td>
<td>Massey Ventures Ltd., United States</td>
<td>Treatment: (2S)-2-Aminopentanethioic S-acid or a pharmaceutically acceptable salt</td>
</tr>
<tr>
<td>WO2022138707</td>
<td>2022</td>
<td>Eisai R&amp;D Management Co., Ltd., Japan</td>
<td>Treatment: pharmaceutical composition of anti-EphA4 antibodies that promote the cleavage of EphA4</td>
</tr>
<tr>
<td>WO2023099648</td>
<td>2023</td>
<td>AstraZeneca AB, Sweden</td>
<td>Treatment: pyrazolo- and triazolo-azinone compounds that inhibit receptor-interacting protein kinase 1</td>
</tr>
<tr>
<td>US20240076310A1</td>
<td>2023</td>
<td>Sage Therapeutics Inc., United States</td>
<td>Treatment: neuroactive steroids (or their combinations), that target GABA receptor complex (GRC)</td>
</tr>
<tr>
<td>WO2022235329A1</td>
<td>2022</td>
<td>University of South Carolina, United States</td>
<td>Treatment: hydrophilic nanogels based on polyethylene glycol (PEG) copolymers to encapsulate an antibody for delivery to the brain. May include ligands for blood-brain barrier receptors</td>
</tr>
<tr>
<td>WO2022132894A1</td>
<td>2022</td>
<td>Rush University Medical Center, United States</td>
<td>Treatment: pharmaceutical composition of glycerol tribenzoate and glycerol phenylbutyrate</td>
</tr>
<tr>
<td>WO2020068913A1</td>
<td>2020</td>
<td>Chase Therapeutics Corporation, United States</td>
<td>Treatment: combination 5HT3 -antagonist and/or a NK-1 antagonist with 6- propylamino-4,5,6,7-tetrahydro-1,3-benzothiazole-2-amine and with fluoxetine, zonisamide, or a statin</td>
</tr>
<tr>
<td>WO2020014072A1</td>
<td>2020</td>
<td>GT Biopharma, Inc., United States</td>
<td>Treatment: NK1-antagonist (e.g., aprepitant) in combination with neostigmine.</td>
</tr>
<tr>
<td>WO2023236967A1</td>
<td>2023</td>
<td>RemeGene Co., Ltd., China</td>
<td>Treatment: development of the drug, a dosage regimen, an administration interval, and a mode for treating MG using TAC1-Fc fusion protein, showing good clinical efficacy and safety</td>
</tr>
<tr>
<td>WO2020086506A1</td>
<td>2020</td>
<td>Ra Pharmaceuticals, Inc., United States</td>
<td>Treatment: methods of treating MG with zilucoplan (complement inhibitor), including devices and kits available for administration</td>
</tr>
<tr>
<td>CN112048565A</td>
<td>2020</td>
<td>Shijiazhuang People's Hospital, China</td>
<td>Diagnosis: microbial marker (comprising Megamonas hypermegale and/or Fusobacterium mortiferum) with good specificity and high sensitivity</td>
</tr>
</tbody>
</table>

Table 5. List of notable patents pertaining to ALS, HD, and MG – identified from the CAS Content Collection.
In the vast landscape of medical conditions, rare diseases occupy a unique and often overlooked niche. Despite their low prevalence, these disorders collectively affect millions worldwide. Each rare disease represents a unique manifestation of genetic, environmental, and/or infectious factors, often with distinct clinical presentations. This variation means initial diagnosis and ongoing treatment may be challenging.

Research into rare diseases has uncovered many novel disease mechanisms, with advances in genomics, molecular biology, and precision medicine holding promise for improved diagnosis and targeted therapies. Insights gained from studying underlying mechanisms of rare diseases have broad implications for understanding more prevalent disorders, such as progerin in HGPS and possible links to cardiovascular disease. Future research into rare diseases will hopefully continue to identify druggable targets and novel therapeutic strategies. Despite these advances, significant roadblocks remain to progress in rare disease research and care. The small size of patient populations limits the potential for robust clinical trials, leading to fewer evidence-based treatment options. Even once research is underway, the confidentiality associated with scientific research (including rare diseases) can impede collaboration and knowledge sharing among the scientific community.

Historically, there has been a lack of commercial incentives for developing treatments for rare diseases, accounting for a lack of interest from the pharmaceutical industry. However, new incentives are beginning to change this. Collaborative and regulatory incentives and patient-centered trial designs are accelerating the translation of scientific discoveries into clinically meaningful interventions. Furthermore, sharing data and resources through collaborative platforms and consortia has become a cornerstone of rare disease research. Continued investment in rare disease research, infrastructure, and policy initiatives is critical for overcoming existing challenges and maximizing the potential of scientific advancements to improve the lives of people living with rare diseases.
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173. Youdim, M. B. H. Multi Target Neuroprotective and Neurorestorative Anti-Parkinson and 


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    tb03060.x.


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For more details on the research landscape of rare diseases, see our publication at http://link.cas.org/rarediseases
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