RARE X

THE POWER OF BEING COUNTED

A more accurate count of rare diseases and steps to getting counted.

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EXECUTIVE SUMMARY

Governments, nonprofits, and industry organizations involved in rare disease research often state that there are 7,000 rare diseases. Or they estimate the number to be between 5,000 to 8,000. The sources of these estimates are challenging to identify, given the circular nature of citations among the groups repeating these figures. What's more, these estimates have remained static for more than a decade even though nearly 300 new rare genetic disease descriptions are added to principal knowledge bases each year. It defies reason that so many new rare diseases are discovered from year to year while the estimate used to characterize the realm of rare diseases remains unchanged.

Getting a true count of rare diseases is complicated for several reasons. Among those are the inconsistent ways that rare diseases are defined around the globe and the differing standards and measures various knowledge bases apply before identifying a rare disease. Recent efforts by the Monarch Initiative to count rare diseases using a computational approach to harmonize major knowledge bases found that the count may exceed 10,000 conditions. Still, many academics and advocacy groups seem hesitant to embrace this updated figure.

This reluctance to use a more accurate number has cascading effects. This artificially low estimate fails to represent the full spectrum of the rare disease community. It also fails to describe the true socioeconomic impact on the lives of patients, families, and society. Policymakers using incomplete or inaccurate information will allocate limited resources in ways that disadvantage these invisible communities of patients. An artificially low estimate also undermines advocates seeking regulatory changes needed to address the special needs of rare disease communities.

RARE-X set out to get a more accurate count of the actual number of rare diseases. Its analysis, which is laid out in this paper, found that there are as many as **10,867** rare diseases, including genetic and non-genetic diseases. For the study, the authors divided the world of rare diseases into four distinct buckets: conditions for which treatment is available, conditions that are considered diagnosable because there are genotypic and phenotypic descriptions (even if more research is needed), conditions that are poorly defined, and conditions that are not currently recognized in major databases. Of those buckets, 8,640 (80%) are theoretically diagnosable, and 2,227 (20%) are so poorly defined that they may not be clinically actionable. We identified just over 500 counted disorders for which a treatment option is available. Treatments may include a dietary change, medical device, surgery or therapy. While the majority of the conditions for which treatments are available are for conditions considered diagnosable, there were some outliers for rare cancers and infectious diseases that are poorly described in our primary sources, OMIM and Orphanet, yet a treatment was identified.

Thousands of conditions already included in rare disease knowledge bases are excluded when we repeat the 7,000 estimate. Countless conditions have yet to be included in these disease compendiums due to their novelty, inadequate disease description, or resource constraints of expert panels who curate these knowledge bases. Unless a disease is included and described in a principal rare disease knowledge base, it is unlikely to be diagnosed, even by the best specialist. That can have life-threatening consequences as rare diseases are frequently progressive and disabling. Rare diseases that aren't adequately accounted for are unlikely to attract research interest and funding to understand a disease's etiology, new approaches to medical management, and possible treatments.

The purpose of this report is to present a more accurate rare disease count that is easily understood and resonates with patient communities. Our methodology was developed to ensure that everyone is counted, while also attempting to avoid double counting diseases that may be known by different names in different knowledge bases. We've also attempted to characterize rare diseases based on the robustness of the disease descriptions.

There is a path that most rare diseases follow that take them from obscurity to a condition that is well understood, readily diagnosed, and treated. Inclusion in the knowledge bases of rare diseases is the first milestone on this path. If it can't be named and adequately described, it is unlikely to be studied by researchers, attract necessary funding, or enable the formation of a patient community.

Far too many patients and their families suffer because they are lost in a system that doesn't recognize their condition. Their disease may be so novel that it has never been seen before, or it may affect a small handful of patients around the globe. For these patients and their families, inclusion of their disease in the medical knowledge bases brings with it the hope that others who similarly suffer, now or in the future, may at last be diagnosed, connected to a community, receive the appropriate care, and one day find a cure.

In performing this count, we have identified steps that patients and families can take to ensure that their conditions of interest are not only included in the primary knowledge bases but are well- defined, clinically actionable, and attractive to researchers.

- Seek others with the same symptoms, genetic variants or diagnosis. There is power in numbers, especially when advocating for a disease that has yet to be formally recognized. For many patients and families, this process is an essential part of the diagnostic odyssey, especially for those with ultra-rare conditions.
- Create a community of patients and advocates if one doesn't already exist. A community is the greatest catalyst for advancing awareness and understanding of your rare disease. The task may seem daunting, and you may feel you are on your own, but many patients and families have gone before you and are willing to share their experiences of raising awareness among physicians and the general public.
- Look for all available research on your condition and note the researchers publishing on it.
- Engage researchers who have published on your condition. Researchers are constrained by the limited number of patients available for study. It can take several years after the publication of the first case report for researchers to identify others who may have the same condition. Make yourself known to those who have previously published. By engaging researchers, you may make studies possible and elevate your condition to those who curate knowledge bases.
- Consider getting genetic sequencing. This is especially important if your condition is suspected of having a genetic basis, but the specific disease-causing gene has yet to be identified. More than half of the genes underlying rare disease have yet to be discovered. Even if your diagnostic journey has already involved some type of genetic testing, you may benefit from whole genome sequencing.
- Prioritize genetic sequencing if you are of non-European ancestry. There is a lack of literature on phenotypic differences in the presentation of rare pediatric disease in people of non-European ancestries, which imperils the promise of precision medicine. For this reason, there is a need for rare disease patients of non-European descent to contribute their genetic data so that genetic databases reflect the full spectrum of DNA.
- Repeat genetic sequencing periodically if you've already been sequenced and received a non-diagnostic result. Previously categorized variants of unknown significance may now be categorized as pathogenic or disease-causing.

- Contribute your samples and data to a disease registry, or create one. The scarcity of information on rare diseases creates an urgent need for patients to share demographic, phenotypic, genetic, and experiential data. In some instances, a registry may be associated with a biobank that also collects and stores biological samples like blood or tissue for research studies. Many organizations establish and maintain disease-specific registries, including patients and their families, advocacy groups, clinicians, and life sciences companies.
- Develop a research publication strategy to systematically assess and address knowledge gaps around your condition. The publication of rare disease research in peer-reviewed journals is vital to enhancing awareness and disease understanding. However, publication in and of itself does not guarantee impact.
- Recognize the power of expert-based evidence when it comes to medical management of a rare condition. Communities that can unite clinicians interested in their rare condition and encourage co-authorship of publications are more likely to succeed.
- Ensure publications are open access and not hidden behind paywalls where patients and some clinicians cannot easily read them.
- Understand the level of disease awareness required to attract research attention and investment from life sciences companies. Patient communities should be focused on ensuring their diseases are fully described in major knowledge bases and other sources. Without this comprehensive description, the risks of investing in more research are too high.
- Patient communities should engage industry and partners where possible. Some pharmaceutical companies have patient advocacy leaders who are willing to engage communities in the disease areas aligned with their research and development pipeline.
- Be clinical trial-ready. Rare disease drug development is an expensive and risky endeavor. Yet, research is vital as most rare diseases do not have an approved treatment. Clinical trials are essential to establishing the effectiveness and safety of a therapy. For pharmaceutical companies, organized communities with active biomarker development programs and patient registries help reduce the risk of clinical trial programs by providing needed information on the etiology and progression of disease, which is useful in trial design. These communities can also validate population size and create a channel for patient recruitment into clinical trials.
- Support the development of standards that ensure data is computable and interoperable. Although the statutory requirements for marketing approval for drugs are the same for both rare and common diseases, researchers can hit snags in the context of a rare disease for which there is often limited medical and scientific knowledge, natural history data, and drug development experience.
- Provide physicians with better tools to diagnose, treat, and manage patients with a rare disease. Patients and advocacy groups are a powerful force for change. One of the areas where they can advocate is for the development and dissemination of better decision-support tools.
- Provide physicians with better tools to diagnose, treat, and manage patients with a rare disease. Patients and advocacy groups are a powerful force for change. You can advocate for the development and dissemination of better decision-support tools.

As a result of this analysis and that of the Monarch Initiative, it is time for the rare disease community to recognize the significant undercounting in oft-quoted numbers and adopt a more accurate description of the actual number of rare diseases that exist. It is time for all rare disease patients to demand they be counted. Doing so is the first step along the path from diagnosis to a cure.

NO DISEASE SHOULD GO UNCOUNTED

Governments, nonprofits, and industry organizations involved in rare disease research often state that there are 7,000 rare diseases. Or they estimate the number to be between 5,000 to 8,000.[1] The sources of these estimates are challenging to identify given the circular nature of citations among groups repeating these figures. What's more, these estimates have remained static for ten years, despite the significant scientific progress over the last decade to identify new rare diseases. Each year more than 10,000 articles are published detailing disease-gene associations.[2] Additionally, nearly 300 new rare genetic disease descriptions are added to principal knowledge bases every year.[1,3,4] Thousands of disease entries are updated annually in these knowledge bases to reflect advancements in our understanding. In some instances, larger conditions are found to be distinct rare diseases or a subtype of a condition. In other cases, rare diseases once thought of as unique conditions may represent the heterogeneity of a single condition.

Recent efforts by the Monarch Initiative to count rare diseases used a computational approach to harmonize major knowledge bases and found that the count may exceed 10,000 conditions.[3] Still, many academics and advocacy groups seem hesitant to embrace this updated figure. The reluctance to use a number that more accurately reflects all known rare diseases has cascading effects. This inaccurate estimate fails to represent the full spectrum of the rare disease community. It also fails to describe the socioeconomic impact on the lives of patients, families, and society. Policymakers using incomplete or inaccurate information will allocate limited resources in ways that disadvantage these invisible communities of patients. An artificially low estimate also undermines advocates seeking regulatory changes that are needed to address the special needs of rare disease communities.

Thousands of conditions already included in rare disease knowledge bases are excluded when we repeat the 7,000 estimate. Further, we know countless conditions have yet to be included in these disease compendiums due to their novelty, inadequate disease description, or resource constraints of expert panels who curate these knowledge bases.

Unless a disease is included and described in a principal rare disease knowledge base, it is unlikely to be diagnosed, even by the best specialist. That can have life-threatening consequences as rare diseases are frequently progressive and disabling.[5] Rare diseases that aren't included in rare disease knowledge bases are unlikely to attract research interest and funding that will help clinicians understand a disease's etiology, find new approaches to medical management, and develop possible treatments.

While some conditions are ultra-rare and individually uncommon, collectively nearly 400 million people are affected by rare disease globally. In the United States, approximately 33 million people live with a rare disease.[6] That number exceeds the entire population of Australia. Rare diseases affect more patients than cancer and Alzheimer's combined. Still, a "war on rare diseases" has yet to be called. Fortunately, there is a growing recognition that rare diseases are a public health priority. These conditions are frequently genetic, progressive, chronic, and irreversible. Half of all rare diseases affect infants and children, 30 percent of whom will die by the age of five.[7] Currently, more than 90 percent of rare diseases have no approved therapy. The multi-year diagnostic odyssey experienced by many rare disease patients imposes a significant psychological, physical, and socioeconomic burden that affects patients and their families and caregivers.[8,9] In the United States, four studies have recently been released that have attempted to calculate the economic burden of rare disease.[6,10–13] The EveryLife Foundation published

The National Economic Burden of Rare Disease Study in 2021 that examined 379 rare diseases with an economic impact of almost $1 trillion. Approximately $418 billion were direct medical costs. Indirect medical costs that include loss of productivity and non-medical out-of- pocket costs such as transportation to specialists and home modifications approached $548 billion.[10] Left uncounted are the stories of patients and families of the thousands of unstudied rare diseases and the toll of these conditions. In the three studies that looked specifically at direct medical costs associated with rare disease, estimates ranged from $400 to $823 billion.[6,10,12,13]

One of the primary challenges these researchers encountered was the inability to identify patients with rare diseases using electronic health records. Currently, only a small fraction of rare diseases have a specific diagnostic code, known as an International Classification of Disease (ICD) code. If there is no ICD code, clinicians may use other codes that describe symptoms rather than the underlying condition, or they might use a general code that fails to accurately reflect the many subtypes of a disorder. As a result, these patients and their disease become invisible within health information systems. Hospitals, epidemiologists, researchers, and pharmaceutical companies don't understand how many patients have a disease. They don't have a full picture of its characteristics, the health outcomes of new treatments, or even the cost of care.[14] Beginning in 2022, countries may begin to adopt updated ICD-11 codes that will include nearly 5,400 rare diseases—a ten-fold increase in the number of rare diseases represented over ICD-10.[15]

We are encouraged by the tremendous advancements in genomics that aid in identifying novel rare diseases and deepening our understanding of long-standing ones. Rare diseases are the focus of more than 5,000 clinical trials. The emergence of gene therapies now holds the promise of curing diseases. While diseases with higher prevalence rates have benefited the most from these developments, therapies are being developed for nano-rare genetic diseases that may affect only a few individuals. For all rare disease patient communities to benefit, all must first be counted. The purpose of this report is to present a more accurate rare disease count that is easily understood and resonates with patient communities. Our methodology was developed to ensure that everyone is counted, while also attempting to avoid "double counting." We've also attempted to characterize rare diseases based on the robustness of the disease descriptions. Our findings inform our **Calls to Action** that are intended to guide rare disease communities in their efforts to ensure their disease is not only included, but well-defined, clinically actionable, and attractive to researchers.

Patient communities that would like to learn more about ensuring their condition is included in future releases may refer to the ICD Roadmap developed by the EveryLife Foundation
everylifefoundation.org/icd-code-roadmap

THE CHALLENGES OF COUNTING RARE DISEASES

Counting rare diseases is complicated by a fundamental lack of consistency in basic definitions. To all but academics, it is perplexing that the definitions of both "rare" and "disease" may vary depending on your location. A global study in 2015 found that there were 296 unique definitions of what constitutes a rare disease across 1,100 public and private-sector organizations in 32 international jurisdictions.[16]

Some of the contributing factors include:

- Definition of rare varies based on country, region, and even ethnicity
- Multiple approaches to defining a disease
- Disease information is spread across multiple knowledge bases
- Our understanding of disease is dynamic and always evolving

There are two major international databases that have taken on the daunting task of curating rare disease information, Orphanet and the Online Mendelian Inheritance in Man (OMIM). The analysis presented in this report was done using the information included in these two sources.

How rare is rare?

Typically, governments define prevalence or incidence thresholds through statute to encourage research and development into orphan conditions. In the United States, the Orphan Drug Act (ODA), passed in 1983, defines a rare disease as any condition affecting fewer than 200,000 people.[i] The equivalent number in Japan is fewer than 50,000. The use of an absolute number is an anomaly, as most other countries define a rare disease based on prevalence rates. For example, in the European Union, any condition that affects fewer than five in 10,000 is rare. To understand how the definition of a rare disease varies around the world, we normalized the rates to reflect cases per 100,000 in the general population and adjusted the U.S. definition to reflect growth in population since 1983. The range is anywhere from five to 65 per 100,000.

Table 1: Comparison of rare disease definitions[17,18]

Country or Region	Prevalence per 100,000 (fewer than)
Peru	1
South Korea	4-5
Taiwan	10
Russia	10
Japan	40
Argentina	50
Australia	50
Chile	50

Country or Region	Prevalence per 100,000 (fewer than)
Columbia	50
E.U.	50
Canada	50
Panama	50
Singapore	50
U.S.*	60
Brazil	65

* population-adjusted based on 2020 census

i The United States is an outlier in using a fixed number rather than a prevalence rate. The consequence is that as the population grows, it requires disease to be even less common to be considered rare. The United States should consider formalizing the definition of a rare disease in terms of prevalence.

People who trace their ancestry to certain geographic regions may have a higher likelihood of some genetic conditions.[19] Because genes are passed down from our ancestors, if one of the shared genes is a disease-causing variant, higher rates of a particular genetic disorder may be seen in those ethnic groups, highlighting that "rare" may vary by region or ethnicity. For example, the U.S. Centers for Disease Control (CDC) estimates the incidence for sickle cell trait is 73.1 cases per 1,000 black newborns, 3.0 cases per 1,000 white newborns, and 2.2 cases per 1,000 Asian or Pacific Islander newborns.[20]

How do you define disease?

Although ubiquitous, the term "disease" does not have a clear, generally accepted definition.[21] Broadly speaking, a disease is any condition that impairs the body's normal functioning and is described by its individual signs and symptoms—the phenotypic features—that commonly occur in patients with this condition. Other dimensions of a disease description include:

- Age of onset
- Prevalence
- Etiology or cause
- Pathophysiology
- Diagnostic methods and tests, including associated biomarkers and genotypes
- Disease progression including natural history, disease stages, disease prognosis
- Clinical management, treatment guidelines, and response to treatment

For far too many rare diseases we lack these critical details.

Clinicians and even knowledgebases may use other terms to refer to conditions that are not ready to be fully classified as a disease.

> ***A syndrome*** is a recognizable set of medical signs and symptoms that are correlated with each other and often associated with a particular condition that may not have a clearly understood cause. Only after a causative agent or process is clearly identified does a syndrome become a disease. Mucocutaneous lymph node syndrome became Kawasaki syndrome which in turn became Kawasaki disease.[21]
>
> ***A condition*** is a broad, value-neutral term that indicates a state of health, whether well or ill. A condition associated with illness may be referred to as a disease or disorder.[22]
>
> ***A disorder*** might indicate that a specific disease is possible but there is not enough clinical evidence for diagnosis. It may be clear you have an autoimmune disorder of some sort, but it may take time to receive a specific diagnosis like rheumatoid arthritis.
>
> ***A disorder subtype*** is a subdivision of a disorder according to a positive criterion that makes up a patient population subgroup. It can be a clinical subtype, an etiological subtype, or a histopathological subtype.

OMIM

The Online Mendelian Inheritance in Man (OMIM.org) is a comprehensive, authoritative compendium of more than 16,000 human genes and genetic phenotypes freely available and updated daily. It includes information on known Mendelian disorders resulting from specific mutations in a single gene inherited from one's parents. OMIM is maintained and updated monthly by a team at Johns Hopkins.[23]

Orphanet

Orphanet (orpha.net) is a publicly available rare disease knowledge base that is intended to improve the diagnosis, care, and treatment of patients with rare disease. It includes information on all known rare diseases regardless of their genetic origins. Its information, including disease descriptions, orphan drugs, clinical trials, and expert networks, is free to the public and used by clinicians, researchers, and patients. INSERM (French Institute for Health and Medical Research) established Orphanet in 1997. It is now supported by the European Commission and a consortium of 40 countries, which use the ORPHA nomenclature for sharing data through their eHealth platform and for disease registries.[24,25]

GARD

The Genetic and Rare Disease (GARD) Information Center (rarediseases.info.nih.gov) is a program of the National Center for Advancing Translational Sciences (NCATS). It is funded by NCATS and the National Human Genome Research Institute (NHGRI). GARD provides the public with access to current, reliable, and easy-to-understand information about rare or genetic diseases.[26]

Who's counting?

There is no central, comprehensive repository of information on rare diseases. Clinical information is spread across disparate knowledge bases, each with their own organizing principles and functions. These knowledge bases play an essential role in a physician's ability to diagnose and manage a patient with a rare disease. They are integral to any count of rare diseases. Understanding the differences across these knowledge bases can benefit patient communities.

The two primary knowledge bases used in our analysis were the Online Mendelian Inheritance in Man (OMIM) and Orphanet. Both knowledge bases rely exclusively on the information contained in peer-reviewed medical studies. Expert panels manually curate the information and determine what is included. OMIM entries focus primarily on genes of known or suspected Mendelian disorders—conditions that result from specific mutations to a single gene inherited from one's parents. Orphanet includes information on both genetic and non-genetic rare diseases. Some rare infectious diseases, cancers, and conditions resulting from exposure to toxins are listed in Orphanet and OMIM and are included in our count and analysis. These conditions, however, may be better described in specialty-focused knowledge bases like the National Cancer Institute (NCI) Thesaurus, for example. Another reason for limiting our analysis to OMIM and Orphanet is the actively maintained mapping of conditions linking similar and related entries.

The Genetic and Rare Diseases Information Center (GARD) is another knowledge base that is often referenced. At the time of our analysis, GARD was undergoing a reorganization and therefore was not part of our analysis. It is, however, a valuable resource for patients, families, clinicians, and researchers. It includes rare disease descriptions in both English and Spanish.

Orphanet has developed and maintains the Orphanet nomenclature of rare diseases, which is a multilingual, standardized, controlled, medical terminology specific to rare diseases. It is organized hierarchically, and includes all disorders, subtypes of disorders, and groups of disorders. A disorder in the database can be a disease, a malformation syndrome, a clinical syndrome, a morphological or a biological anomaly, or a particular clinical situation (in the course of a disorder). Disorders may be further divided into clinical, etiological, or histopathological subtypes.

Rare diseases within the Orphanet nomenclature conform to the European definition and affect less than 50 in 100,000 persons in Europe.

Each clinical entry includes a unique numerical identifier referred to as an ORPHAcode, as well as a preferred name, synonyms, and a definition. The ORPHAcode provides a common language across healthcare and research systems for effective monitoring and reporting on rare diseases, thus improving their visibility. ORPHAcodes are used across 40 countries,[24] including much of Europe, parts of Asia, as well as in Australia, Canada, and Argentina. They play an important role in sharing rare disease information across information systems and are used in rare disease registries based in the participating countries.

The Orphanet nomenclature is cross-referenced with other international terminologies and reference databases such as:

- ***ICD-11*** 11th International Classification of Diseases established by the World Health Organization - icd.who.int/en/
- ***OMIM*** (Online Mendelian Inheritance in Man) - www.omim.org
- ***GARD*** (Genetic and Rare Disease) database - rarediseases.info.nih.gov
- ***UMLS*** (Unified Medical Language System®) integrates medical terminologies to support interoperable information systems - www.nlm.nih.gov/research/umls
- ***MeSH*** (Medical Subject Headings) is the NIH's National Library of Medicine controlled vocabulary used for indexing articles in MEDLINE, which is a bibliographic database that contains more than 28 million references to biomedical journal articles - www.ncbi.nlm.nih.gov/mesh
- ***MedDRA*** (Medical Dictionary for Regulatory Activities) is a specialized medical vocabulary used globally to share regulatory information on medical products - www.meddra.org

Academic researchers and the biopharmaceutical industry use Orphanet's datasets to inform research and development decisions. Information on the prevalence and incidence of a condition allow companies to estimate market size. The extent to which a disease is well understood and represented in Orphanet and other major databases also informs the allocation of research funding. Companies also analyze the datasets to develop clinical hypotheses that may lead to new treatment options. [25]

Note the external links and details included for physicians and the public in the Orphanet entry for Kawasaki disease (*Figure 1*):

Figure 1: Orphanet entry for Kawasaki disease (www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=2331)

Kawasaki disease

Suggest an update

Disease definition

A rare inflammatory disease characterized by an acute febrile, systemic, self-limiting, medium-vessel vasculitis primarily affecting children. It often causes acute coronary arteritis which is associated with coronary arterial aneurysms (CAA) that may be life threatening when untreated.

ORPHA:2331

Classification level: Disorder

Synonym(s):
Mucocutaneous lymph node syndrome

Age of onset: Adult, Infancy, Childhood, Adolescent

ICD-10: M30.3

OMIM: 611775

Prevalence: Unknown

Inheritance: Multigenic/multifactorial

UMLS: C0026691

MeSH: -

GARD: 6816

MedDRA: 10023320

Summary

Epidemiology

Although it has been reported worldwide, Kawasaki disease (KD) is over-expressed among Asian populations. In Europe the annual incidence for children under 5 years of age ranges between 1/6,500-20,500. The disease is the most commo cause of acquired heart disease in children in developed countries.

Clinical description

Median age of onset is 2 years (with 75% of patients being under 5 years old). Fever (greater than 39 degrees C) tha persists for greater than 5 days when untreated is a constant feature. Children are usually very irritable. Additional typic manifestations of KD include extremity changes (erythema and edema of palms and soles that desquamate after 2- weeks, usually seen in the subacute phase), polymorphic skin rash (maculopapular, urticarial, or scarlatiniform rash lymphadenopathy (cervical, often unilateral, greater than 1.5 cm diameter), non-exudative bilateral conjunctivitis, an involvement of lips and oral mucosa (erythema, strawberry tongue, lip fissures). CAA is a life threatening complicatio that usually occurs in the subacute phase (6 to 8 weeks after onset) in 20-35% of untreated children. The regression giant CAA (greater than 8 mm) is very unlikely, while minor dilations are usually transient. Atypical manifestations includ myocarditis pericarditis, valvular regurgitation, hepatitis, diarrhea, abdominal pains, hydrops of gallbladder, arthralgi arthritis, myalgia, aseptic meningitis, sensorineural hearing loss, urethritis and sterile pyuria. KD is a risk factor fo ischemic heart disease in adulthood.

Etiology

Etiology is unknown but several pathogenic theories have been proposed (e.g. infection by a toxin-secretin microorganism and a superantigen-driven process). Genetics appear to play a major role, and the disease is much mor common in Asian populations. Genome-wide studies have identified single nucleotide polymorphisms which woul confer increased susceptibility to the disease and to its complications.

Diagnostic methods

Diagnosis is clinical. Complete KD is defined by fever and 4/5 of the standard clinical criteria (extremity change polymorphous rash, conjunctival injection, changes in lips and oral cavity, and cervical lymphadenopathy greater tha 1.5 cm diameter). Incomplete KD can be diagnosed in case of prolonged fever, 2-3/5 standard criteria, and specific sign of coronary disease, particularly CAA when other causes of coronary vasculitis are excluded. Laboratory finding (elevated inflammatory markers and liver enzymes, neutrophilia and thrombocytosis), though non-specific, ar supportive. At diagnosis, patients must be investigated for coronary involvement via transthoracic echocardiography.

Differential diagnosis

Differential diagnosis includes autoimmune and autoinflammatory diseases (e.g. systemic-onset JIA), bacterial infection (i.e. bacterial toxic shock syndrome, leptospirosis, adenophlegmon), viral infections (i.e. measles, enterovirus, Epstein-Ba virus), and toxin or drug reactions.

Management and treatment

Early administration of intravenous immunoglobulin (IVIg) reduces the rate of coronary abnormalities to less than 5% patients. IVIg is administrated at a single dose of 2 g/kg before the 10th day of onset, or even later if persister inflammation. In case of treatment failure, IVIg readministration, corticosteroids, anakinra and infliximab may b considered as second line treatments. Aspirin (30-50 mg/kg/day) are usually given in the febrile phase, followed by lo (antiplatelet) doses (3-5 mg/day) for 6-8 weeks. Following diagnosis, coronary involvement is monitored at 2 weeks an 6-8 weeks by transthoracic echocardiography.

Prognosis

Non-complicated cases resolve without sequelae, while patients with persistent CAA are at risk for major cardiovascula events and their long-term outcome may be complicated by premature ischemic heart disease.

OMIM entries detail Mendelian disorders resulting from a mutation at a single genetic locus. A locus may be present on an autosome or sex chromosome, and it may be manifest in a dominant or a recessive mode. When available, OMIM entries include rich and well annotated details on:

- Disease description
- Clinical features
- Pathogenesis
- Mapping
- Molecular genetics
- Genotype/phenotype correlations
- Population genetics
- Animal models
- History

To the uninitiated, OMIM entries utilize a type of shorthand that seems meaningless. However, the use of symbols as prefixes to the OMIM number and name, or within the Disorder column, communicates characteristics of the entry and facilitate OMIM's computability.

A symbol prior to an OMIM entry number denotes the type of entry.

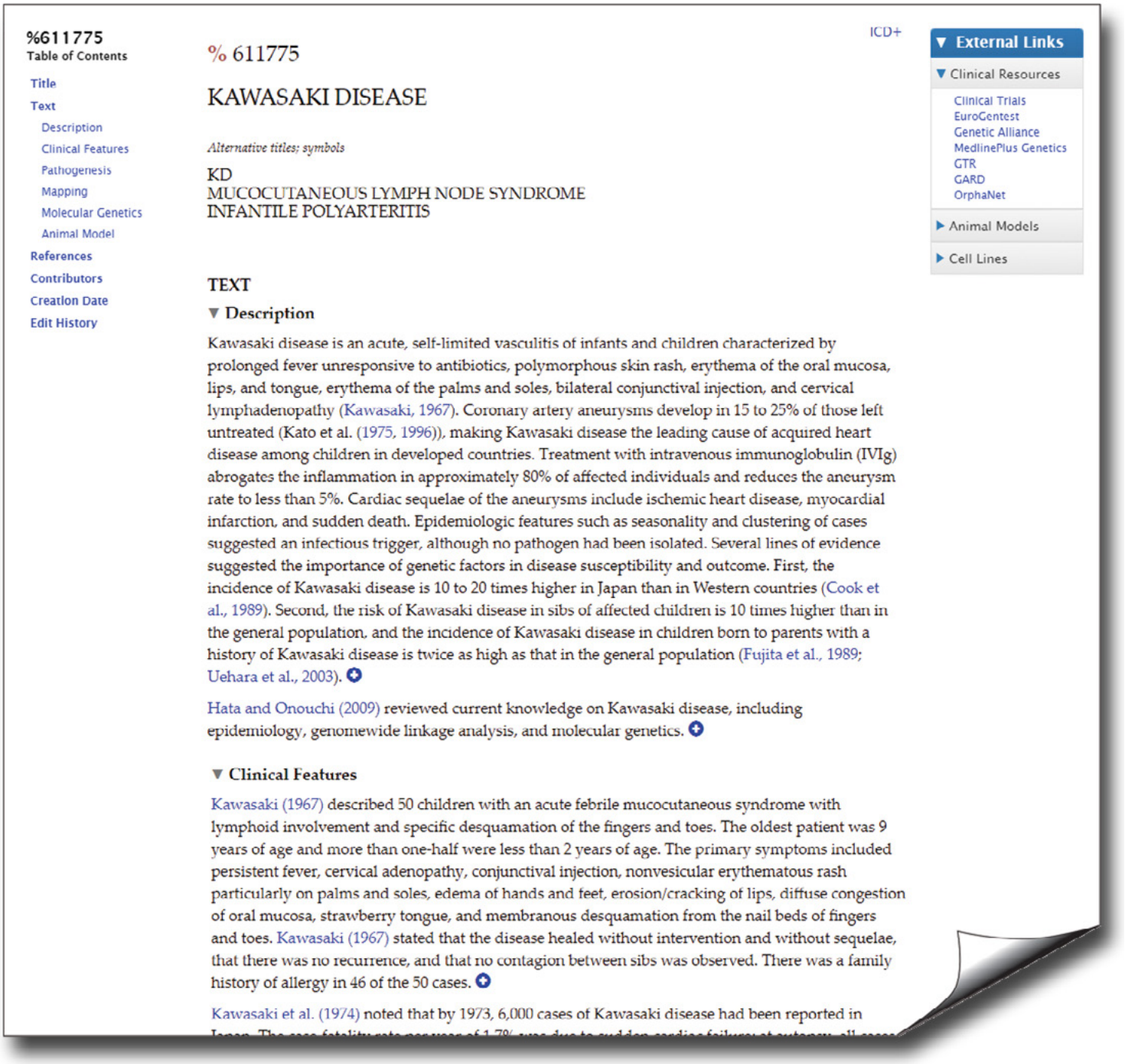
Symbol	Indication
*	Gene entries
#	A descriptive entry, usually of a phenotype that does not represent a unique locus. Discussion of any gene(s) related to the phenotype resides in other entry(ies) that are described in the first paragraph
+	Description of a gene of known sequence and a phenotype
%	Mendelian phenotype without a known molecular etiology
Null	A description of a phenotype for which the Mendelian basis, although suspected, has not yet been clearly established
^	The entry no longer exists because it was removed or moved to another entry as indicated

Symbols that appear in the Disorder column of the Gene Map indicate the following:

Symbol	Indication
[]	"Nondiseases"
{}	Mutations that contribute to susceptibility to multifactorial disorders or to susceptibility to infection
?	The relationship between the phenotype and gene is provisional

To illustrate the many features of a well described OMIM condition, please refer to the following entry for Kawasaki disease on the next page (*Figure 2*). As you will see, the disease details are exclusively sourced from peer-reviewed articles from medical journals. Physicians and the public can quickly see the provenance of each element included in the OMIM entry and can consult the source material for further information.

Figure 2: OMIM entry for Kawasaki disease (www.omim.org/entry/611775)



%611775
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ICD+

% 611775

KAWASAKI DISEASE

Alternative titles; symbols

KD
MUCOCUTANEOUS LYMPH NODE SYNDROME
INFANTILE POLYARTERITIS

External Links
Clinical Resources
Clinical Trials
EuroGentest
Genetic Alliance
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GTR
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TEXT

Description

Kawasaki disease is an acute, self-limited vasculitis of infants and children characterized by prolonged fever unresponsive to antibiotics, polymorphous skin rash, erythema of the oral mucosa, lips, and tongue, erythema of the palms and soles, bilateral conjunctival injection, and cervical lymphadenopathy (Kawasaki, 1967). Coronary artery aneurysms develop in 15 to 25% of those left untreated (Kato et al. (1975, 1996)), making Kawasaki disease the leading cause of acquired heart disease among children in developed countries. Treatment with intravenous immunoglobulin (IVIg) abrogates the inflammation in approximately 80% of affected individuals and reduces the aneurysm rate to less than 5%. Cardiac sequelae of the aneurysms include ischemic heart disease, myocardial infarction, and sudden death. Epidemiologic features such as seasonality and clustering of cases suggested an infectious trigger, although no pathogen had been isolated. Several lines of evidence suggested the importance of genetic factors in disease susceptibility and outcome. First, the incidence of Kawasaki disease is 10 to 20 times higher in Japan than in Western countries (Cook et al., 1989). Second, the risk of Kawasaki disease in sibs of affected children is 10 times higher than in the general population, and the incidence of Kawasaki disease in children born to parents with a history of Kawasaki disease is twice as high as that in the general population (Fujita et al., 1989; Uehara et al., 2003).

Hata and Onouchi (2009) reviewed current knowledge on Kawasaki disease, including epidemiology, genomewide linkage analysis, and molecular genetics.

Clinical Features

Kawasaki (1967) described 50 children with an acute febrile mucocutaneous syndrome with lymphoid involvement and specific desquamation of the fingers and toes. The oldest patient was 9 years of age and more than one-half were less than 2 years of age. The primary symptoms included persistent fever, cervical adenopathy, conjunctival injection, nonvesicular erythematous rash particularly on palms and soles, edema of hands and feet, erosion/cracking of lips, diffuse congestion of oral mucosa, strawberry tongue, and membranous desquamation from the nail beds of fingers and toes. Kawasaki (1967) stated that the disease healed without intervention and without sequelae, that there was no recurrence, and that no contagion between sibs was observed. There was a family history of allergy in 46 of the 50 cases.

Kawasaki et al. (1974) noted that by 1973, 6,000 cases of Kawasaki disease had been reported in

Other sections of this entry include:

- Clinical Features
- Pathogenesis
- Mapping
- Molecular Genetics
- Animal Models

METHODOLOGY FOR COUNTING THE NUMBER OF RARE DISEASES AND CHARACTERIZING THEM

We leveraged a Rare Disease Map that integrates multiple public and licensed data sources to estimate the number of rare diseases. Orphanet and OMIM were the two primary sources for disease entries. In some instances, disease classifications were verified in GARD. For treatment information we consulted DrugBank, U.S. Food and Drug Administration's Office of Orphan Drug (OOD) website, and work included in Genome to Treatment (GTRx). GTRx (https://gtrx.rbsapp.net/about.html) is a research tool developed by Rady Children's Institute for Genomic Medicine that is a virtual acute management guidance system that includes 1,527 interventions for 421 diseases.[27]

We used published Orphanet-OMIM mappings to assess overlap between Orphanet disorders and OMIM conditions. Our analysis was conducted using OMIM and Orphanet data downloaded on December 11, 2021.

Table 2: Data sources for our analysis.

Sources	Disease inventory	Disease classification	Genetic	Phenotypes	Incidence & prevalence	Interventions
Orphanet	X	X	X	X	X	X
OMIM	X		X	X		
GARD		X				
Hpo.jax.org				X		
DrugBank						X
FDA.org ODD						X
GTRx work						X

Additional Assumptions

We assume any condition in OMIM is a known or suspected genetic condition, and any condition included in Orphanet is by default a rare disease that meets the European definition as one that affects fewer than 50 people per 100,000 in the general population.

Processes

Our process focused on harmonization of both Orphanet and OMIM entries that leverage existing mappings maintained by Orphanet.

Looking at the Orphanet disorder hierarchy, 5,850 disorders do not have any subtype or "child." There are 347 "parent" disorders with a total of 1,010 subtypes or "children." A parent may have more than one child and there are 15 disorder subtypes that have subtypes or children of their own.

Looking at the OMIM conditions, we started by removing data entries that reflected a "susceptibility to", "non-disease", and "moved to", which resulted in 8,229 conditions. Similarly, Orphanet entries that were designated as "inactive", "obsolete", or "moved to" were removed prior to our mapping exercise, which resulted in 6,197 Orphanet disorders.

Based on mappings, 6,164 OMIM conditions overlap with 3,901 Orphanet disorders and 558 subtypes.

We included all OMIM conditions that are a “narrow” match to an Orphanet disorder while removing any “Exact” or “Broader” match. This yielded 2,520 OMIM conditions that can be considered as subtype “extensions” of 563 Orphanet Disorders (i.e., parent disorder).

Not all OMIM conditions are mapped to an Orphanet entry. That’s why we applied a semi-automated curation process to the OMIM-only conditions, removing entries related to traits, non-diseases, and those that signaled a susceptibility to a condition. As shown in the graphic below, this resulted in an “OMIM-only” set of 2,065 conditions.

When possible, we verified the OMIM prevalence information by consulting prevalence information from cancer.org and MedlinePlus genetics.

Figure 3:

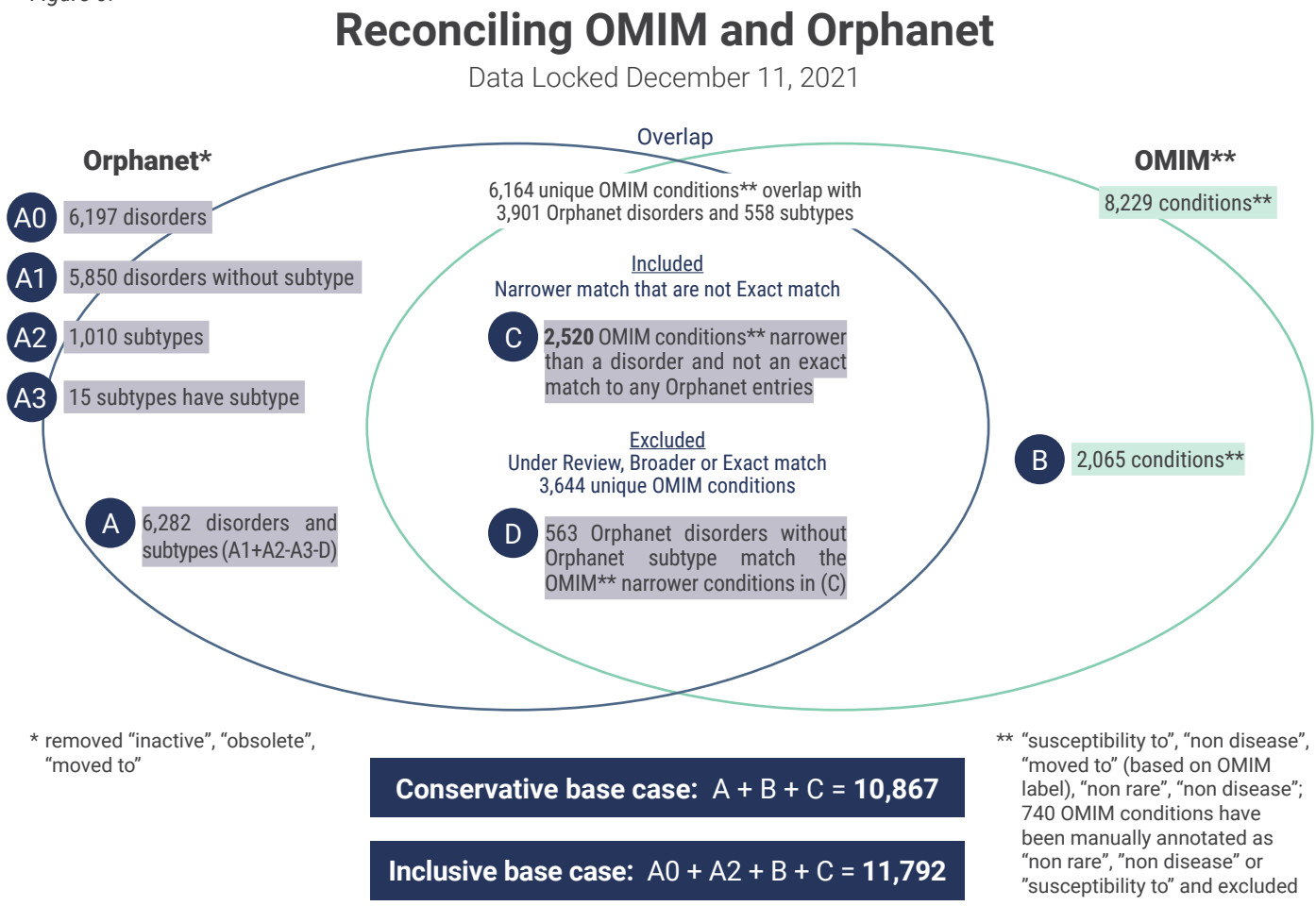
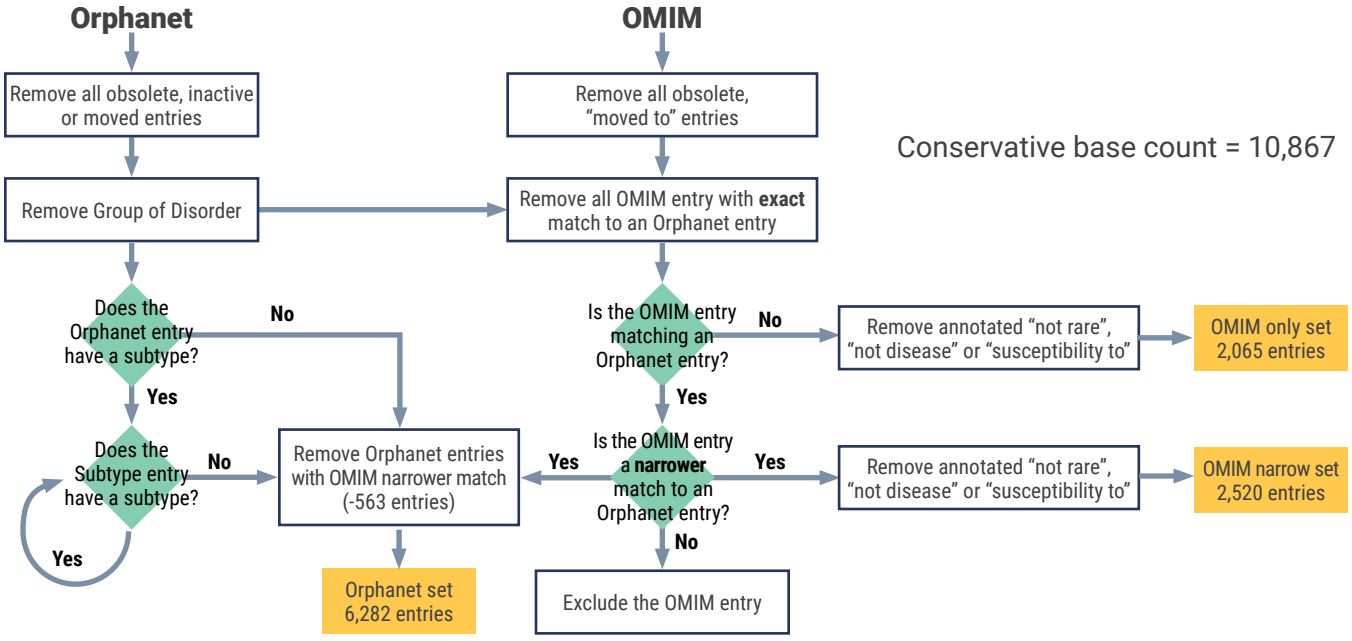


Figure 4:

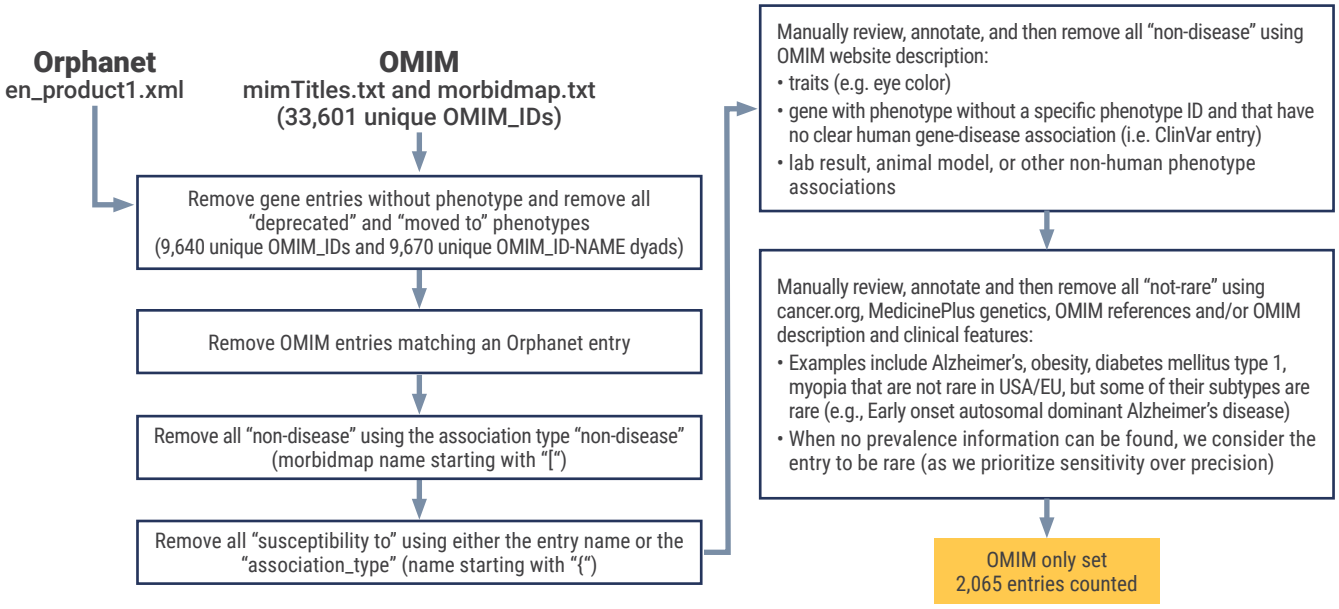
Methodology for Reconciling OMIM and Orphanet



In our conservative base case, we attempted to balance the inclusion of all rare diseases (sensitivity) with how we define a "disease" (precision) to minimize the risk of counting duplicates. We counted all Orphanet disorders with NO subtype, and only the subtypes (or "children") of a disorder. We excluded groups of disorders, all "parent" disorders, as well as all subtypes of subtypes. When combined with the OMIM narrow match set and the OMIM-only set, we arrive at our conservative base estimate of 10,867 conditions. In summary, 6,282 conditions are Orphanet entries, 2,065 conditions come from OMIM and have no match to Orphanet, combined with 2,520 OMIM conditions that are considered a narrower match that might be reflective of a subtype.

Figure 5:

Process for semi-automated curation of the "OMIM-only" data set



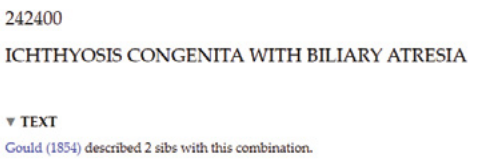
The aim of this paper is to present a patient-focused approach. Therefore, we are mindful that in some instances there are communities of patients that do not identify with any related subtype of their disorder, and thus there are patient communities that exist at the parent level. Our inclusive case count includes all parent disorders and their subtypes.

Characterizing Disease Descriptions By Number of Associated Symptoms

In our analysis, we also characterized how well a condition, disease, or subtype is defined in Orphanet and OMIM based on its listed phenotypes. To do this, we relied on terms from the Human Phenotype Ontology (HPO) (hpo.jax.org/app/), which provides a standardized vocabulary of phenotypic abnormalities encountered in human disease, particularly, but not exclusively, rare diseases. Each term in the HPO describes a phenotypic abnormality, such as atrial septal defect. HPO terms are included in OMIM and Orphanet descriptions.

Some disease entries contain so little information that clinicians may be challenged to diagnose or medically manage them. There is no genetic marker, no phenotypic description other than the title itself.

Figure 6: OMIM entry for ichthyosis congenita with biliary atresia (www.omim.org/entry/242400)


242400

ICHTHYOSIS CONGENITA WITH BILIARY ATRESIA

▾ TEXT

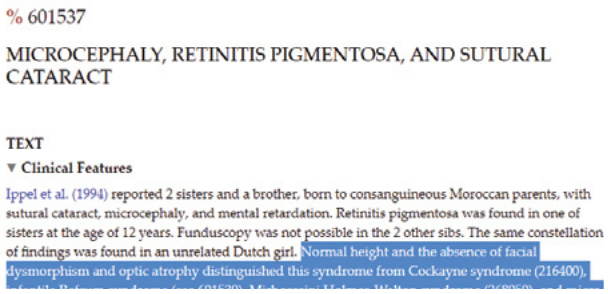
Gould (1854) described 2 sibs with this combination.

Such a condition is nearly impossible to diagnose by even the bests specialists, due to the difficulty of conducting a differential diagnosis. For example, consider ichthyosis congenita with biliary atresia (Figure 6), which is a standalone entry in OMIM. It does not include any phenotypes and is not mapped to any condition in Orphanet. Figure 6 shows the entirety of the OMIM entry.

These spare entries also show why physicians must triangulate multiple knowledge bases to get needed clinical information. While Orphanet does not have an exact match for ichthyosis congenita with biliary atresia, there are currently seven listed subtypes of autosomal recessive congenital ichthyosis—several of which have multiple phenotypes. A patient or clinician who is not accustomed to searching these knowledge bases could potentially miss information.

Another example is the OMIM description for microcephaly, retinitis pigmentosa, and sutural cataract (*Figure 7*). In this condition, some phenotypes are included in the text description. Still, the lack of specified HPO terms means that the condition is not computable, and thus unlikely to be included in digital diagnostic tools.

Figure 7: OMIM description for microcephaly, retinitis pigmentosa, and sutural cataract (www.omim.org/entry/601537)


% 601537

MICROCEPHALY, RETINITIS PIGMENTOSA, AND SUTURAL CATARACT

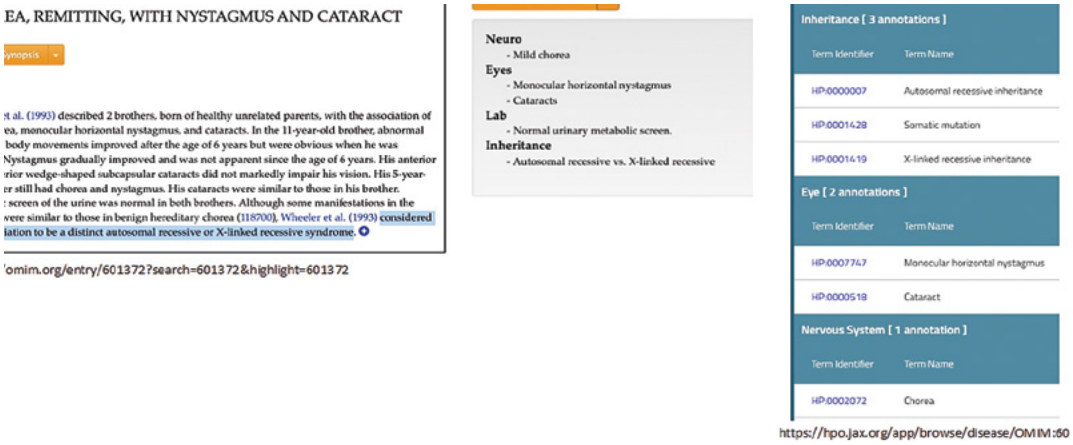
TEXT

▾ Clinical Features

Ippel et al. (1994) reported 2 sisters and a brother, born to consanguineous Moroccan parents, with sutural cataract, microcephaly, and mental retardation. Retinitis pigmentosa was found in one of sisters at the age of 12 years. Funduscopy was not possible in the 2 other sibs. The same constellation of findings was found in an unrelated Dutch girl. Normal height and the absence of facial dysmorphism and optic atrophy distinguished this syndrome from Cockayne syndrome (216400),

In contrast, the entry for remitting chorea with nystagmus and cataract (*Figure 8*), has six associated phenotypes in its clinical synopsis.

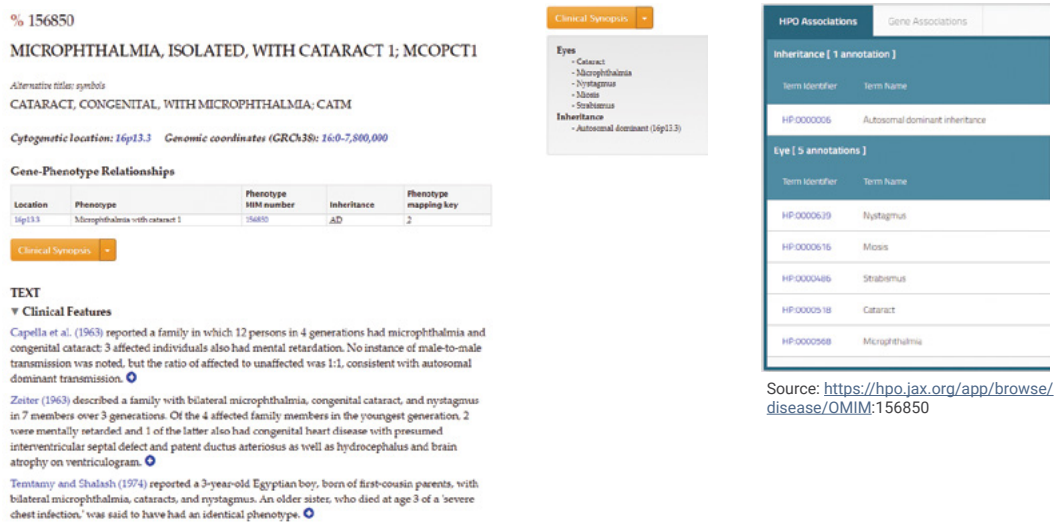
Figure 8: OMIM entry for remitting chorea with nystagmus and cataract (www.omim.org/entry/601372)



Due to the appearance of this condition twice in the same family, the condition is suspected to be genetic. However, a clear disease-gene link has yet to be established. While the gene is unknown, clinicians can use the phenotype within the differential diagnosis to potentially arrive at this condition by ruling out the better-defined conditions.

For isolated microphthalmia with cataract 1 (MCOPCT1), we have a robust disease description that includes both a direct causal gene and six associated HPO terms (*Figure 9*). The more information included in the disease description, the more likely the clinician will make an accurate differential diagnosis.

.Figure 9: OMIM entry for MCOPCT1 (www.omim.org/entry/156850)

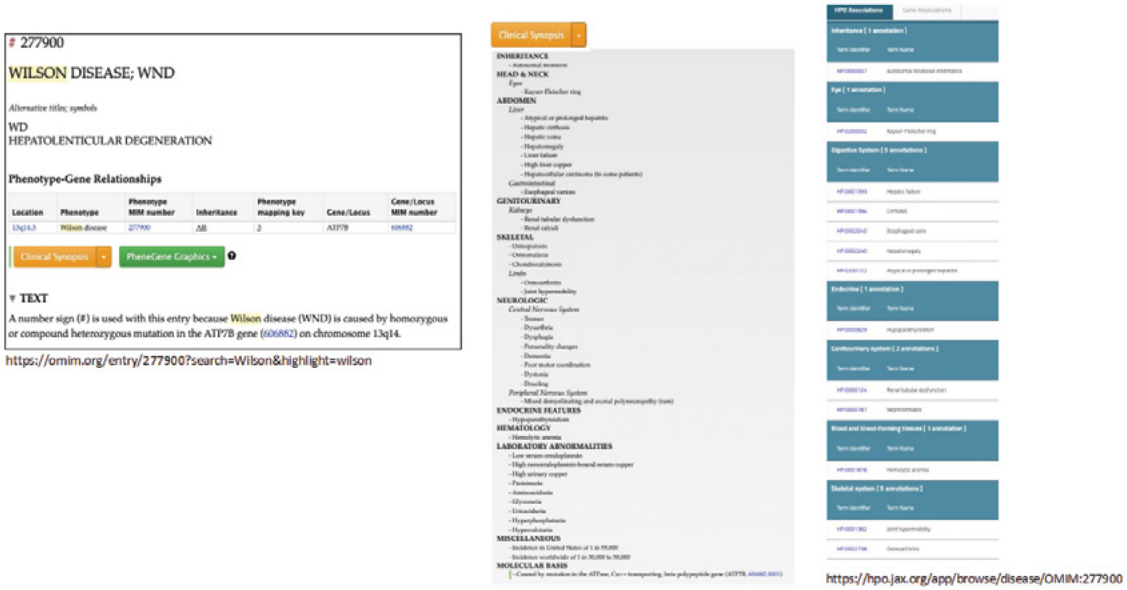


Source: https://omim.org/entry/156850?search=156850&highlight=156850

Source: https://hpo.jax.org/app/browse/disease/OMIM:156850

Lastly, in the case of Wilson Disease (*Figure 10*), we have both an identified causative variant and a robust phenotypic description that includes 34 HPO terms, which will make diagnosing this condition more likely.

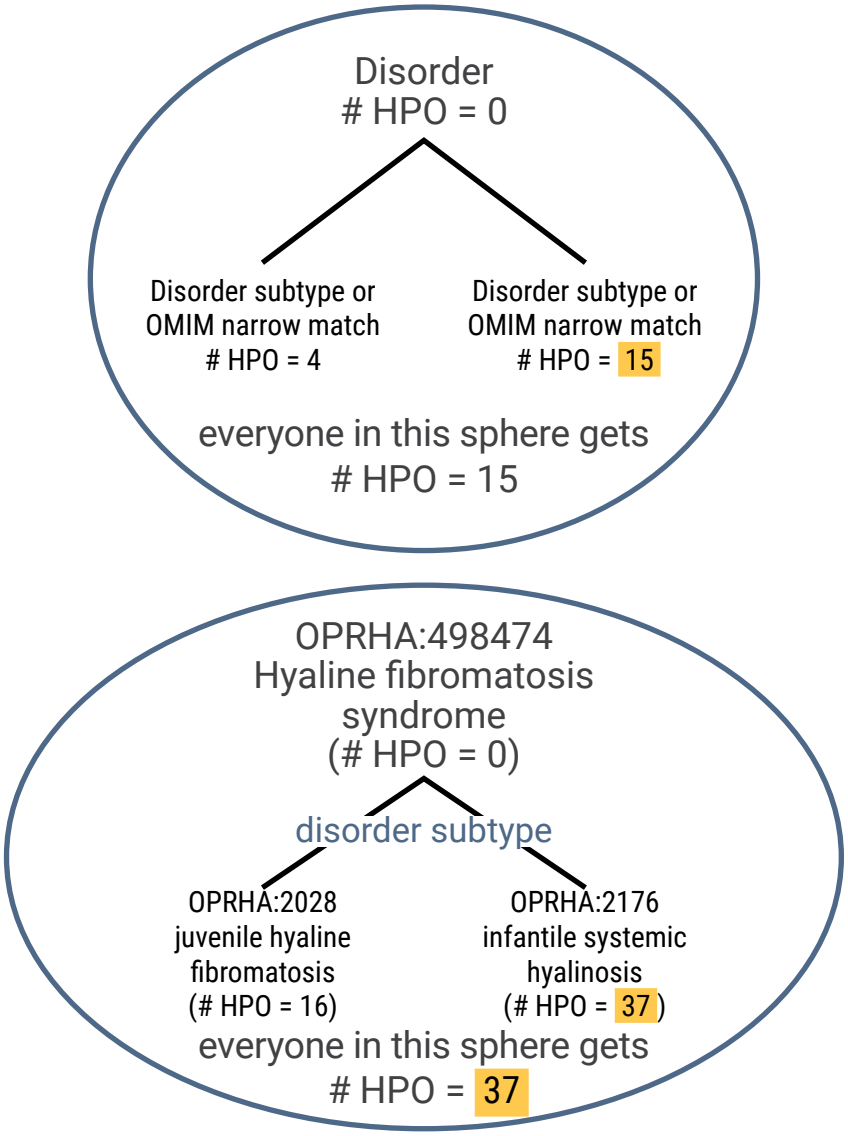
Figure 10: OMIM entry for Wilson Disease (www.omim.org/entry/277900)



During our analysis, we found some instances where the phenotypic description of a disorder or a subtype did not include any HPO entries, yet the condition had an available treatment, which meant it was a diagnosable condition. Upon further review, we found that at the disorder level, or in some instances, a related subtype had a more robust description such that the disorder or subtype are likely diagnosable. To account for this, we adopted a diagnosable sphere concept where we applied the highest HPO count across a related disorder and its corresponding subtypes (*Figure 11*).

The *diagnosable sphere* reasons that if a disorder or one of its subtypes is well defined, then it will help the diagnosis of the disorder and any of its related subtypes. It also normalizes the HPO coverage across disorders and their subtypes given the inconsistency in HPO coverage across disease types and within disease groups, as illustrated by hyaline fibromatosis syndrome.

Figure 11: Diagnosable Sphere



Characterizing rare diseases by their phenotypic signature.

By analyzing the HPO terms included in the description of a disorder or subtype (*diagnosable sphere*), we have categorized all counted disease as either "Poorly Defined" or "Diagnosable." Conditions that include zero to two HPO terms are considered poorly defined in our analysis. Conditions that include three or more HPO terms are considered diagnosable. We acknowledge that while a condition may be theoretically diagnosable, many of these conditions frequently go undiagnosed or are misdiagnosed. The first two phenotypes typically include a pattern of inheritance and a phenotype generally referenced in the name of the condition. The inclusion of a third phenotype begins to provide more clinically relevant details that may help physicians recognize a disorder. Our analysis applies this framework to known genetic disorders, suspected genetic disorders, and non-genetic disorders.

Calculating the number of conditions with available treatments.

We further analyzed all counted rare diseases and estimated the number of conditions with available treatment options that may include both approved or off-label medications, dietary changes, surgery, or medical device. We referenced information contained in the following databases:

1. The **FDA Orphan Drug Database** approved list from www.accessdata.fda.gov

2. The expert-curated dataset used in **Genome to Treatment (GTRx)**, which details treatments for rare disorders frequently seen in the newborns in critical care settings[27]

Cladribine Example

Approved indications:
- [pill] RELAPSING MULTIPLE SCLEROSIS (MS) [Designated/Withdrawn]
- [injectable] HAIRY CELL LEUKEMIA (HCL) [FDA ODD Designated/Approved]

Off-label uses:
- CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) [FDA ODD Designated/Withdrawn]
- NON-HODGKIN'S LYMPHOMA (NHL) [FDA ODD Designated/Withdrawn]
- ACUTE MYELOID LEUKEMIA (AML) [FDA ODD Designated/Withdrawn]
- CUTANEOUS T CELL LYMPHOMAS (CTCL) [not mentioned on FDA ODD]
- SEZARY SYNDROME [not mentioned on FDA ODD]

3. **DrugBank Plus** data by disorders referenced in the "indication" field and then manually validated with WebMD's RxList.com

FINDINGS

There are untold numbers of patients with conditions that have yet to be recognized by OMIM and Orphanet. Unfortunately, there is no means of estimating the number of these conditions that we have deemed "emerging."

Our conservative base count includes only rare disorders without subtypes and the subtypes or child of a disorder while excluding the parent condition. Using this count **we estimate there are 10,867 rare disorders**. Roughly 87% of counted rare diseases have a known- or suspected-genetic basis. When we include all parent disorders our count increases to 11,792.

Figure 12:

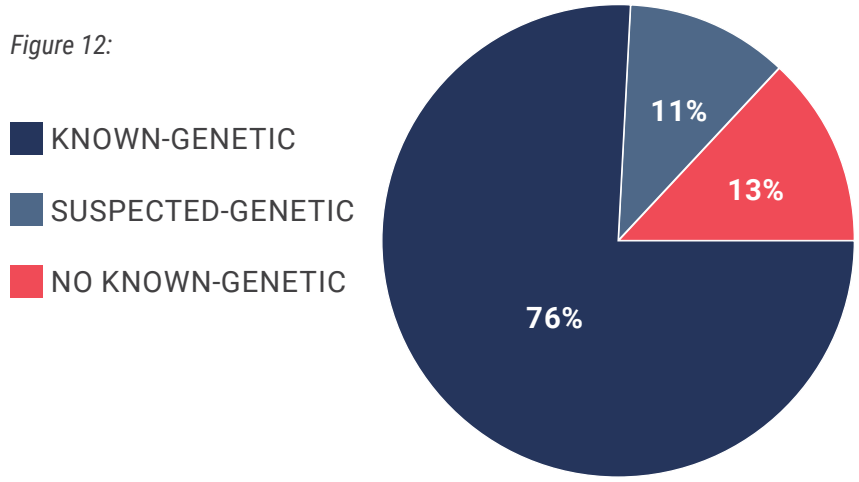
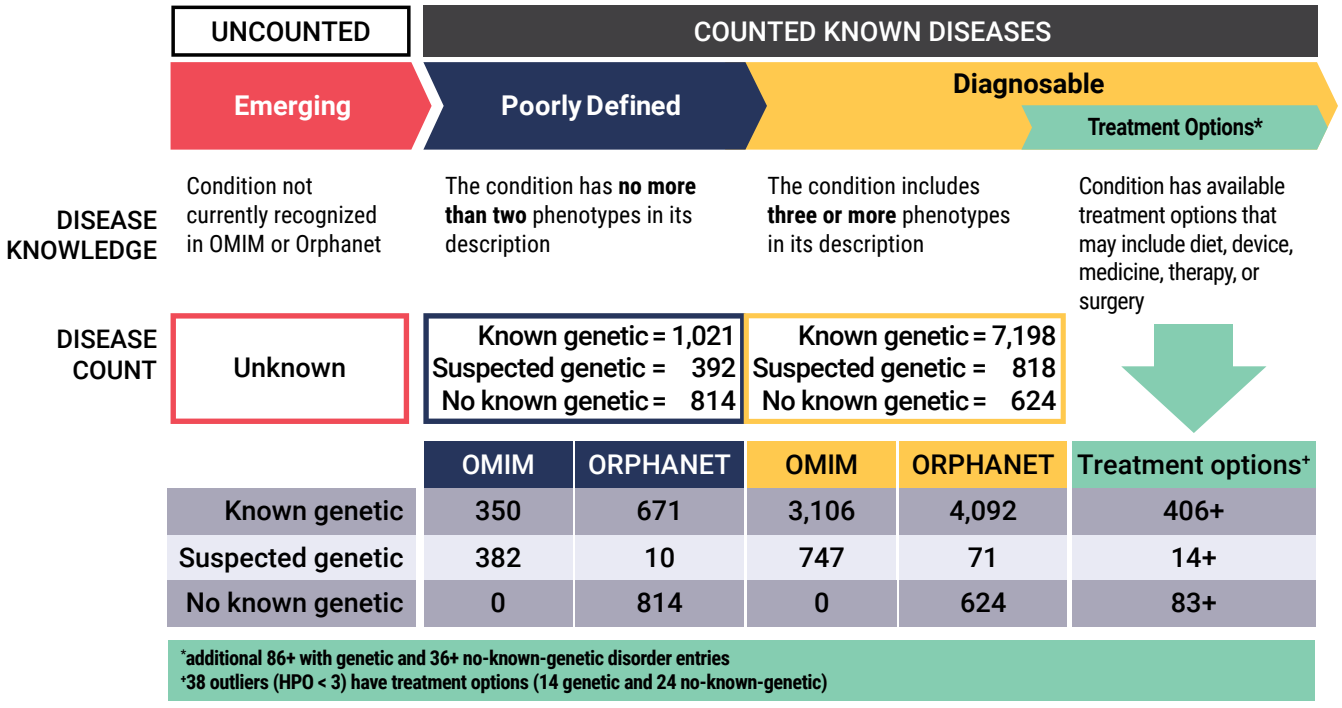


Figure 13:

Breaking down of 10,867 counted rare diseases by associated phenotypes and genetic basis



Our analysis found that 8,640 (80%) of counted rare diseases have disease descriptions at the parent or subtype level with three or more phenotypes, theoretically placing the condition in the diagnosable zone. Within this cohort, nearly 83 percent have a known genetic basis, 9 percent a genetic cause is suspected, and only 7 percent are non-genetic diseases. Of the 2,227 rare diseases considered poorly defined, meaning they include no more than two phenotypes, 46 percent have a known genetic basis, 18 percent have a suspected genetic cause, and 37 percent are non-genetic diseases.

We also found that treatment options were available for just over 500 of the rare diseases we counted, which is approximately five percent of the total. For our analysis, we counted only the subtype, so the drugs not approved for a specific subtype are excluded from our summary data. However, there may be treatments available at the disorder level that may be used at a clinician's discretion. We calculate there are approximately 86 genetic disorders and 36 suspected genetic entries that fall into this situation.

Some patients do not identify with any of the current subtypes and have formed a community at the parent level. If we take a more inclusive approach and count all disease subtypes and parent conditions, the estimated number of rare diseases grows to 11,792.

While most analyses focus exclusively on the overall number of diseases, there is value in understanding where a disease resides on the disease continuum to help provide critical guidance to patients, families, and rare disease advocates to ensure that their respective condition is counted and well-defined. Because clinicians rely on the information found in rare disease knowledge bases, the lack of associated symptoms compromises the clinical utility of these entries. These diseases or disorders have insufficient information to attract significant research efforts based on discussions with biomedical research and development experts. While outside the scope of this analysis, we observed that disease entries with fewer than three HPO terms were also less likely to include other important dimensions of disease descriptions like pathophysiology, incidence or prevalence, age of onset, etc.

We identified more than 500 conditions (5 percent) for which available therapies may consist of medication, diet, surgery, or medical device. Our examination of available treatments was mapped to conditions based on the number of HPO terms annotated in its "diagnosable sphere" and confirmed that diseases with more phenotypes have more treatments, although the relationship is non-linear. We did identify several outliers. There are 38 treatments associated with poorly defined disease descriptions with zero phenotypes. Upon manual review, these treatments were almost exclusively used in rare cancers, infectious diseases, or diseases resulting from environmental toxins – conditions for which HPO terms are not generally applied. While included in OMIM and Orphanet, more comprehensive disease descriptions are included in specialty-focused knowledge bases that were not part of our study.

Figure 14:

Characterization of Rare Diseases by HPO Terms & Genetics

Conditions by maximum HPO count using the "diagnosable sphere" concept

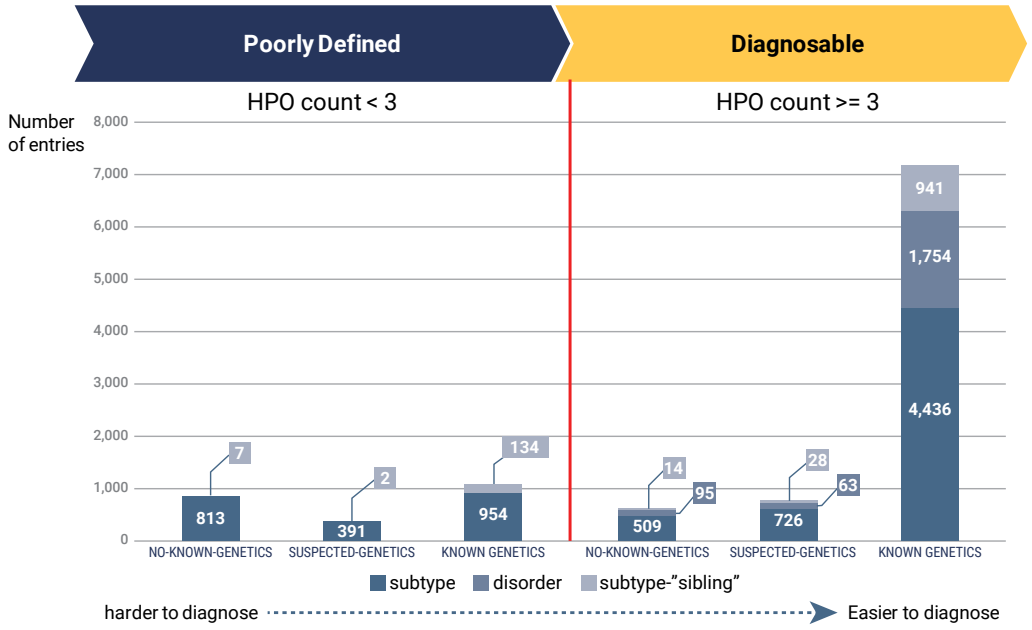
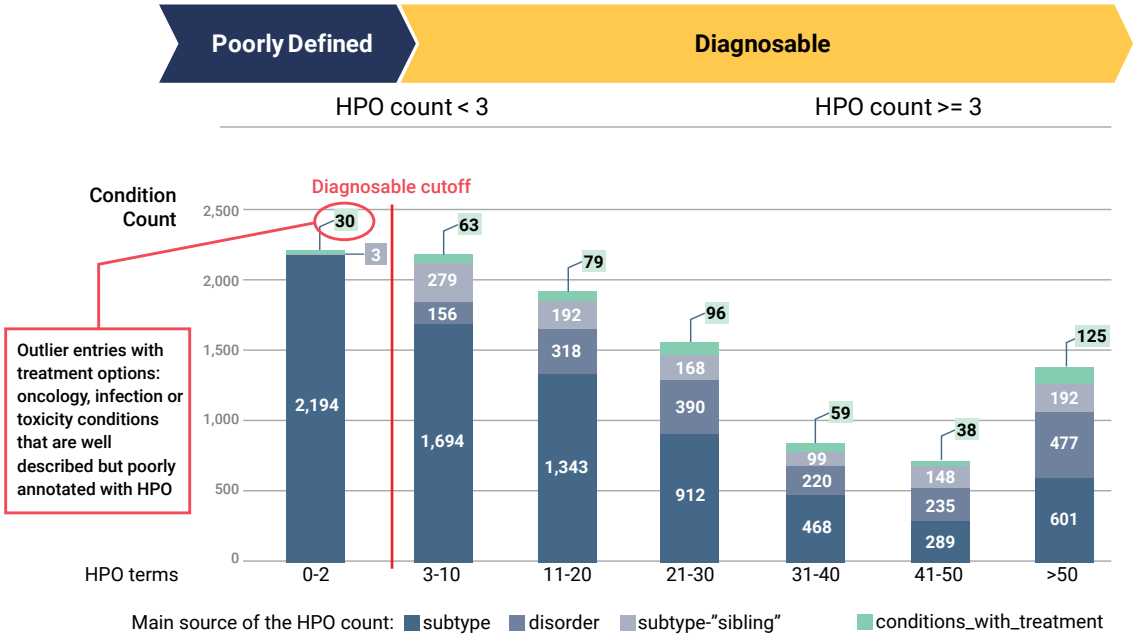


Figure 15:

Condition and Treatment Options by HPO Count



While our scientific understanding of all diseases is constantly evolving, the challenge for patients and clinicians alike is that this information is codified in multiple, discrete knowledge bases and is incomplete 24 percent of the time. The lack of consensus around critical definitions delays efforts to harmonize data and improve the accessibility of disease information. Until then, disease information essential to clinicians is fragmented, difficult to search, and in some cases available only behind a paywall. The onus falls on doctors and often patients themselves, to locate, synthesize, and reconcile critical information required to diagnose, counsel, and provide care to patients suffering from a rare condition. For thousands of rare diseases included in these knowledge bases, the disease information is incomplete and has limited clinical utility.

THE POWER OF BEING COUNTED

Patients afflicted with a rare disease, along with their families and caregivers, report high levels of depression, anxiety, and isolation.[17] They must also contend with significant social, emotional, and financial challenges while navigating medical and health system obstacles. On average, it takes between five to eight years before such a patient receives an accurate diagnosis. During this diagnostic odyssey, patients may see as many as eight doctors. They must undergo batteries of tests, while being subjected to unnecessary procedures and treatments. They also receive two to three incorrect diagnoses.[28,29] The challenge of finding a diagnosis turns patients and their families into sleuths, searching for clues to unlock insights into a condition. In some cases, parents of children with progressive ultra-rare conditions find themselves in a race against time. These patients and their families often experience severe psychological distress as they search for a diagnosis.[30] They may be trying to put a name to a disease for which none exists, and for which the compendiums of rare diseases contain no description. This is why accurately counting and cataloguing rare disease is important on a human level.

It is a victory for patients with a rare disease when their condition is finally added to one of the major knowledge bases. For these patients and their families, inclusion of their disease in the medical knowledge bases brings the hope that others who similarly suffer, now or in the future, may at last be diagnosed, and connected to a community. It brings hope that these patients might receive the appropriate care, and that further research will one day find a cure. Just as a patient may progress from the diagnostic odyssey to the therapeutic odyssey, there is a path that most rare diseases follow that takes it from obscurity to a condition that is well understood, readily diagnosed, and treated. Inclusion in the knowledge bases of rare diseases is the first milestone on this path. If it can't be named and adequately described, it is unlikely to be studied by researchers, attract necessary funding, or enable the formation of a patient community.

There is power in having a fully described rare disease. As the medical community develops more complete disease descriptions that include such things as the biological pathways involved and the causative genes, similarities across diseases will become more apparent and may unlock treatment opportunities, including the ability to repurpose existing drugs.

On a societal level, there is power in presenting an accurate representation of the number of rare diseases and the patients, families, and caregivers affected. Armed with current, citable statistics, as well as the lived experiences of those from the rare disease community, advocates can have a productive dialogue with policy makers and legislators to make the case for all necessary resources. Only recently has research into the economic burden of rare disease in the United States been published.

As a result of our analysis and that of the Monarch Initiative, it is time for the rare disease community to recognize the significant undercounting in oft-quoted numbers and adopt a more accurate description of the actual number of rare diseases that exist.

Calls to Action

Based on our research, which included interviews with a cross-section of stakeholders, we offer the following recommendations for patients and advocacy groups to help ensure all rare diseases are included and properly reflected in the rare disease databases. Patients, families, and caregivers are the true experts in their rare disease and in many instances, are the force driving research forward. Our

recommendations are intended to help ensure that the limited time and resources these communities have are spent in activities that will have the most benefit to all involved.

Emerging Conditions

For patients with ultra-rare conditions yet to be recognized in the major knowledgebases, there are steps you can take that may ultimately lead to a community and attract for research attention.

Find your community. The process of seeking out patients with similar genetic variants and common symptoms is an essential part of the diagnostic odyssey, especially for those with ultrarare conditions. Platforms like Matchmaker Exchange are a helpful resource for clinicians and researchers looking to find patients with matching genetic variants to establish a clear disease-gene link. Unfortunately, a limited number of clinicians use these matchmaking platforms. For patients and their families, platforms like MyGene2 (https://mygene2.org/MyGene2/) and GenomeConnect (www.genomeconnect.org) allow patients to search for and contact other patients and families with a similar condition or genetic variant.[32] These tools, along with Internet searches, blogs, and social media, can help connect patients and form the nexus for a patient community.

If there isn't a community already formed, creating one is the greatest catalyst for advancing awareness and understanding of your rare disease. The task may seem daunting, and you may feel you are on your own, but many patients and families have gone before you and are willing to share their experiences organizing and advocating to raise awareness among physicians and the general public.

Engage researchers who have published on your condition. Once you have a community, the next natural step is to look for all available research on your condition and the researchers publishing on it. The process of scouring the medical literature for clues that may lead to a diagnosis is not new to many patients and their families. Two valuable tools that can assist you in uncovering any published research are Google Scholar (https://scholar.google.com) and PubMed (https://pubmed.ncbi.nlm.nih.gov). Both search tools are free and allow you to identify academic publications. PubMed is specifically focused on the search and retrieval of biomedical and life sciences literature. Its database contains more than 33 million citations and abstracts that include authors' names and their affiliated institutions. For more detailed guidance, please refer to Global Gene's Becoming an Empowered Patient: A Toolkit for the Undiagnosed (https://globalgenes.happyfox.com/kb/article/18-becoming-an-empowered-patient-a-toolkit-for-the-undiagnosed/) which includes a detailed section on how to become your own research advocate, including details on how to use these and other tools.

With ultra-rare conditions in particular, researchers are constrained by the limited number of patients available for study. It takes on average five to six years after the publication of the first case report for researchers to identify others who may have the same condition. Make yourself known to those who have previously published. This can be done by simply emailing study authors, journal editors, and anyone associated with the publication. Peer-reviewed publications are essential to ensuring a rare disease is both counted and well-defined. Early publications, particularly for rare genetic diseases, may be limited to case reports of individuals or families that share a particular genetic variant and certain phenotypes. These case reports merely introduce the possibility of a disease-gene link. Once researchers become aware of a larger pool of people affected by this disorder, they can conduct small cohort studies. It is the findings of these small studies that begin to validate these early hypotheses. They help physicians understand disease variations, including the phenotypic spectrum, onset of disease, and disease progression and prognosis. The experts who curate the major knowledge bases place more value on cohort studies than case reports, as do clinicians

seeking medical guidance on how to diagnose and treat a patient with a suspected condition. By engaging researchers, you may make such studies possible and subsequently elevate your condition to those who curate knowledge bases.

Poorly Defined

If your condition is one of the many included in OMIM or Orphanet with minimal information, or if it fails to reflect your lived experience accurately, researchers desperately need your information.

Get sequenced. If your condition is suspected of having a genetic basis, but the specific disease-causing gene has yet to be identified, you need to get sequenced. More than half of the genes underlying rare disease have yet to be discovered.[32] Even if your diagnostic journey has already involved some type of genetic testing, you may benefit from whole genome sequencing (WGS), the cost of which has dropped dramatically over the last several years and now may be covered by insurance in some instances. If a genetic disease is suspected, parents and even siblings may be asked to undergo genetic testing to examine familial patterns of genetic variants. You may also qualify for one of several research programs that provide genetic testing at no cost.

The Rare Genomes Project at the Broad Institute of MIT and Harvard is a research program that combines genomic analysis with the experiences of patients and families to unlock rare disease insights that can be translated into improved clinical care. Patients may apply to the program via their website. If accepted, and patients consent, they will have their genomic data analyzed, and their de-identified data, along with symptoms, will be shared with scientists. If the cause of your condition is identified, you will be notified of your results.

www.raregenomes.org

Researchers are working to address limitations in their understanding of genetically driven rare disease in diverse groups with shared ancestry. In 2003 the Human Genome Project completed a 13-year effort to discover the complete set of human genes and make them available for research. A significant limitation of the reference genome against which DNA results are assessed is its over-representation of individuals of European descent. There is a higher likelihood that a genetic test of someone from African, Asian, Native American, or Pacific Island ancestry will return a non-diagnostic result.[33,34] There is a lack of literature on phenotypic differences in the presentation of rare pediatric disease in people of different ancestries, which imperils the promise of precision medicine.[34] For this reason, there is a need for rare disease patients of non-European descent to contribute their genetic data so that genetic databases reflect the full spectrum of DNA.

In many cases, regardless of race, genetic testing results are inconclusive. Incidental findings or variants of uncertain significance (VUS) may be identified due to the lack of a proven disease-gene association. If you've already been sequenced and received a non-diagnostic result, periodic reanalysis of your DNA may be warranted. Previously categorized variants of unknown significance may now be categorized as pathogenic or disease-causing. There are few processes for the systematic reanalysis of these VUS so consult with your physician to explore whether you may benefit.

Contribute your data. The scarcity of information on rare disease creates an urgent need to share demographic, phenotypic, genetic, and patient experience data. In some instances, a registry may be associated with a biobank that also collects and stores biological samples such as blood or tissue for research studies. Many organizations establish and maintain disease-specific registries, including patients and their families, advocacy groups, clinicians, and life sciences companies. The intent behind disease registries typically clusters around five objectives:[35]

1. Connect communities of patients, families, and clinicians
2. Study the epidemiology, natural history, risks, and prognosis
3. Research the genetic, molecular, and physiological basis of rare disease
4. Create a pool of patients who may potentially participate in trials of new therapies or monitor the safety and efficacy of available treatments
5. Understand the experiences and preferences of patients and their families using patient-reported outcome measures

The size of a registry may be used to estimate the number of patients with a condition, and the degree to which a community is active and willing to participate in research. Participants in a disease registry must consent for their information to be included. During the enrollment process, you will be told how your data will be used, your rights for preserving your privacy, and how you may control your data. You may also be asked whether you would like to be recontacted so researchers can gather additional information or inform you of new clinical trials and therapies that might be right for you.

You may also be asked to respond to surveys that help elucidate the psychosocial implications of a rare disease. This gives researchers a better understanding of the unmet needs of your community. The experiences of patients and their families are the most important means of evaluating the quality of healthcare.[34,36]

This contribution of your time, expertise, and experiential data have a meaningful, sustainable impact on the scientific understanding of rare conditions.

"Unless we can count the people with rare diseases, rare disease patients don't count."

Chris Austin
CEO-Partner at Flagship Pioneering and formerly Director of National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health

Sharing phenotypic features and genetic information with disease registries accelerates essential research by creating a dataset that may unlock novel insights into disease presentation, progression, and prognosis. Individuals and communities can contribute their data to platforms like RARE-X (https://rare-x.org), MyGene2 (a node in MatchMaker Exchange), GeneMatcher, and other commercial endeavors.

Platforms like RARE-X enable patient communities to easily collect, manage, and share their de- identified health data with researchers worldwide. Patient communities leveraging the RARE-X platform benefit from existing robust data governance and flexible consents, a universal Institutional Review Board (IRB), and standardized survey modules, using existing validated measures and organized by domains. RARE-X makes it easy for patients to update their data. Patient communities interested in working with RARE-X can make a request at https://rare-x.org/connect/.

Patient-led research or citizen science. Patients and patient communities do not need to wait for academic researchers to take an interest in their condition. Instead, patients and their caregivers can organize communities and begin to assemble disease insights, share information on medical management, and provide guidance on what's important to them. While registries can help gather data, patient-initiated gatherings or conferences also provide researchers with opportunities to engage communities of patients and make observations that can then be published in peer-reviewed journals. RARE-X is committed to helping support patients and communities in developing disease characterization and disease progression models that are important early steps in filling in gaps of our understanding of the disease and increase the chances of the literature being reviewed by medical curators who serve as gatekeepers to OMIM and Orphanet inclusion.

Develop a research publication strategy. The publication of rare disease research in peer-reviewed journals is vital to enhancing awareness and disease understanding. However, publication in and of itself does not guarantee impact. Here are some suggestions [37,38] to help ensure a publication has the desired effect:

1. Develop a systematic approach based on assessing knowledge gaps around your condition. Your gap analysis can be done by reviewing published literature and current disease descriptions in major knowledge bases. What information do clinicians need now in order to help future patients?

2. Recognize the power of expert-based evidence when it comes to medical management of a rare condition. Researchers frequently use The Delphi method where questions are posed to experts and the aggregated responses are then circulated for the respondents to review. Experts are then permitted to adjust their response based on how they interpret the group readout. The process may require multiple iterations to arrive at a consensus. The use of well-designed Delphi studies to present consensus findings regarding clinical management of physician experiences can help overcome the limitations of small sample sizes. Communities that can unite clinicians interested in their rare condition and encourage co-authorship of publications are more likely to be successful.

3. Ensure publications are open access and not hidden behind paywalls where patients and some clinicians cannot easily read.

4. Qualitative research methods that collect non-numerical data like patient, family and caregiver experiences, for example, are a valid way of developing evidence on patient values and preferences that can inform policy, research approaches, and regulatory frameworks.

Diagnosable

Understand how life sciences companies make R&D investment decisions. It is essential to recognize the level of disease understanding required to attract research attention and investment. Without a comprehensive understanding, the risks of investing are too high. For this reason, patient communities should be focused on ensuring their diseases are fully described in OMIM, Orphanet, and other sources.

To provide some insights into the level of detail required, here are some of the foundational questions research and development executives must answer before approving research projects:

- Is this a disease with a genetic cause?
- Do we have a precise understanding of the genetic cause?
- Do we understand the epidemiology, which includes disease prevalence and incidence?
- Do we have the means of developing the necessary diagnostic tools?
- What is the age of onset?
- What are the phenotypic features we can target?
- What is the prevalence or incidence of the disease?
- Can we design clinical trials with the right clinical endpoints and recruit enough patients to complete the trial?
- What is the commercial viability of this drug based on the addressable market size and reimbursement model?
- For non-genetic diseases, do we understand the pathophysiology, biologic pathway, mechanism, or receptor responsible?
- For non-genetic diseases with adult-onset, can we understand the range of causes in play, including environmental factors?

Patient communities should engage industry partners where possible. Pharmaceutical companies with patient advocacy leaders are willing to engage communities in the disease areas aligned with their research and development pipeline. Rare disease patient advocacy groups, including Global Genes, can help bridge connections to pharmaceutical companies as well. Contacting leadership at companies that may be interested in your disease, inclusive of research and development leaders, is another path.

Be clinical trial-ready. Because most rare diseases do not have an approved treatment, research is vital. Rare disease drug development is an expensive and risky endeavor. Clinical trials are essential to establishing the effectiveness and safety of a therapy. Clinical trials for rare disease drugs have added challenges. Limited disease understanding creates unique challenges in designing clinical trials, including selecting appropriate endpoints. It may also be difficult to recruit enough people to complete the trial due to small patient populations, or patients may be geographically dispersed and unable to easily access a clinical trial site. For rare diseases that affect newborns and small children, additional precautions are taken when conducting pediatric trials. For pharmaceutical companies, organized communities with active biomarker development programs and patient registries help reduce the risks of clinical trial programs by providing needed information on the etiology and progression of disease, which is useful in trial design. These communities can also validate population size and create a channel for patient recruitment into clinical trials.

The FDA recognizes the value of patient participation in clinical trials and has provided guidance and tools to aid communities in helping develop drugs. In 2012, the FDA established the Patient-Focused Drug Development (PFDD) initiative (https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development) to ensure that patient perspectives on rare disease and current therapies was incorporated into the drug development process. As part of this program, communities can attend meetings that are FDA-led to share information on their condition, impact on daily living, and perspectives on treatment approaches (https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings).

Support the development of standards that ensure data is computable and interoperable. The statutory requirements for marketing approval for drugs to treat rare and common diseases are the same. Yet, it's harder to bring a drug to market in the context of a rare disease for which there is often limited medical and scientific knowledge, natural history data, and drug development experience. For example, contributing to FDA disease guidance documents that describe how the FDA currently interprets policies and regulations regarding clinical development programs and trial designs. If the patient community is helping build the knowledge base, the true patient experience will be better reflected in these documents. Ultimately, there is also a need for HPO terms and ICD codes to develop prevalence and cost estimates—diseases need to be trackable, as well as diagnosable and treatable.

Treatable

Provide physicians with better tools to diagnose, treat, and manage patients with a rare disease. Patients and advocacy groups are a powerful force for change. One of the areas where they can advocate is for the development and dissemination of better decision-support tools. Despite the availability of approved and effective therapies, clinicians are still challenged to recognize the symptoms, diagnose, and treat rare disease patients.[39] Physicians report wanting more tools that aid them in identifying these conditions and provide easy access to information on diagnostics and available therapeutics.[40] Given the nature of small populations, developing evidence-based treatment guidelines is difficult. Similarly, limited information is available to provide insights into response to treatment. This information needs to be developed as part of a comprehensive approach to better define these conditions.

In a 2020 paper, researchers from Europe and the United States called for developing a publicly available Treatabolome, a knowledge base that would help clinicians identify treatable gene variants and also help researchers identify cohorts of similar patients and bio-samples available for study.[41] Such an approach overcomes the primary challenge of rare disease research – identifying an appropriately sized cohort for research. Making meaningful progress toward understanding these diseases and available therapeutic options requires sample sizes that cannot be obtained in a single hospital, health system, or country. An international data-sharing effort must be mounted to shorten the diagnostic and therapeutic odysseys.[42] "Solve-RD" is a European effort to accomplish this and help ensure patients are put on the precise path to the appropriate therapy and additional research.[41,43,44]

More research should be done to understand the issues and challenges physicians face in recognizing and diagnosing rare diseases, the information they need, and how best to deliver it. From a Belgium study[40] of general practitioners and specialists:

> ***Experts claim that physicians need a tool to input patient symptoms and test results and retrieve a rare disease differential diagnosis as output. On top of a rare disease differential diagnosis, possible treatment options, contact details of acknowledged experts, and reference centers of patients' associations could be valuable output as well, according to interviewed experts. The ideal information source should be an up-to-date digital platform, freely available in physicians' language of choice and validated by numerous rare disease specialists and experts.***

Build the evidence base of treatment effectiveness. Many rare disease drugs lack long-term evidence of their clinical significance. Given the high cost of rare disease drugs, this data is valuable in establishing clinical guidelines for disease management. In addition, new payment models are needed as newer cell and gene therapies are brought to market. In some cases, these therapies are curative, transforming patients' lives with conditions like spinal muscular atrophy (SMA). Companies are working with payers to test value-based payment models that tie drug payments to clinical milestones. However, one of the most challenging parts is objectively quantifying the disease impact for these patients and their caregivers who often have to leave the workforce.

CONCLUSION

We believe there is inherent power in being counted. We owe this to all patient communities that work so hard to support one another and advocate for the resources they or their family members require. This paper is intended to provide a transparent and reproducible approach to counting rare diseases so that all stakeholders may confidently embrace the reality that there are nearly 11,000 rare diseases. This number is dynamic and will continue to grow, which is a testament to the success of researchers, patients, and the communities that advocate on their behalf. Our hope is that we will update this report periodically and will be able to report that more of those unknown conditions are now part of the medical knowledge bases, and diseases that are poorly defined become more fully understood. Our approach is grounded in our desire to encourage disruptive thinking to advance research, further needed policies, and catalyze new care models. At the heart of everything lies the patient, who has more power to transform our understanding of rare disease than they may even know.

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RARE-X

Authors:

- Kirk Lamoreaux
- Sebastien Lefebvre, M.S.
- Daniel S. Levine
- Wendy Erler
- Tom Hume

Special thanks to the following people and organizations for their input and collaboration:

- Alexion Pharmaceuticals
- Chris Austin, M.D.
- Katherine L Beaverson, M.S.
- Nicole Boice
- Jennifer Briggs Braswell, Ph.D.
- Amy Brin, MSN, APRN, ACCN
- Amy Clugston
- Stan Crooke, M.D., Ph.D.
- David Dimmock, M.D.
- Peter Goodhand
- Melissa A. Haendel, Ph.D.
- Ada Hamosh, M.D., M.P.H.
- Walter Kotoniuk, Ph.D.
- Craig Martin
- Tomi Pastinen, MD, Ph.D.
- David Pearce, Ph.D.
- Gianluca Pirozzi, Ph.D.
- Ana Rath, M.D.
- Heidi Rehm, Ph.D.
- Holly Snyder
- Jackie Johnson Steinberg, MPH, BSN
- Jamie Sullivan
- James Valentine, MHC, J.D.

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