

Cover Story

Rare diseases

Challenges for optimal oral health

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ABSTRACT

Background. It is estimated that 30 million people in the United States have a rare disease, and few of these conditions have available cures. The diversity of rare disease etiologies and phenotypes has hindered both diagnostics and treatment approaches. Many rare diseases are caused by pathogenic genetic variations and involve the craniofacial structures and function. Dental care providers are called on to serve the population with rare diseases and support their desire for optimal health. To address these oral health care challenges, JADA is presenting a special issue on rare diseases through a series of articles. These reviews will address some of the more common rare diseases and those that share features such as involvement of the dentition, skeleton, immune system, skin, or facial clefts.

Types of Studies Reviewed. The authors searched the 5 major databases, including PubMed, Google Scholar, Web of Science, Embase, and Ovid MEDLINE, for articles pertaining to rare diseases and disorders affecting oral health and oral health care. The authors conducted an exhaustive search of the literature from 1990 through March 30, 2026, for articles on rare diseases, with a specific focus on oral health care.

Results. There is no existing reliable classification that groups all of these complex syndromes into clinically identifiable clusters. This special issue may be the first of its kind in which the authors attempt to format a meaningful classification to group these entities of similar etiopathogenesis and phenotype.

Conclusions and Practical Implications. The medical and dental management of rare disorders often requires teams of specialists and advocates to address the developmental, structural, functional, psychosocial, and economic aspects that can confront affected patients.

Key Words. Rare disease; genetic disorders; oral health; oral manifestations; craniofacial syndromes; craniofacial anomalies; special needs patients.

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What are rare diseases and why should there be a special issue of JADA dedicated to this topic? In the United States, a rare disorder was defined according to the Orphan Drug Act (1983), whereby these entities were characterized as those occurring in fewer than 200,000 people.^{1,2} There are from approximately 7,000 through 10,000 entities classified as rare disorders affecting approximately 30 million people in the United States.³ The prevalence definition of rare diseases varies in different countries, ranging from 5 per 100,000 people in the Republic of Korea to 80 per 100,000 people in the United States.⁴ Estimates of the global prevalence of rare diseases indicate that from approximately 250 million through 500 million people worldwide have a rare disease.⁴ This lack of consensus and standardization for a definition of rare disease is one of several barriers to the advancement of the diagnosis and management of rare diseases and disorders. We examine the evolving definitions of rare disorders, their underlying etiologies, and clinical presentations. Furthermore, we address the specific obstacles patients and dental care providers encounter when evaluating the potential for a global consensus on rare

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disease classification. For example, osteogenesis imperfecta (OI) and dentinogenesis imperfecta, along with similar entities such as hypophosphatasia and hypophosphatemia, have been grouped as rare diseases involving connective tissue disorders predominantly affecting skeletal tissues. The goal of the special issue series is to provide clinicians with information on diagnostics and best practices in clinical care. As these articles are published, they will become available in the online special issue on the JADA website. Our aim is to help equip clinicians with the latest diagnostic and therapeutic developments to support the provision of evidence-based care for patients with rare conditions.

WHY ARE RARE DISEASES A CHALLENGE?

Apart from the lack of consensus and standardization of definitions and terminology related to rare diseases, several factors make exploring these diverse conditions and their management challenging. These include a relative lack of existing succinct literature as well as research of rare diseases compared with more common health conditions and diseases. The elusive nature of these diseases is evidenced by the fact that rare diseases are referred to as orphan diseases, and the medications used for treating these diseases are called orphan drugs. Patients and caregivers are challenged with a lack of patient and caregiver awareness, a lack of organized interdisciplinary care, and a scarcity of resources for patients and clinicians. Furthermore, these conditions can be diagnostically challenging, having diverse etiologies and pathogenesis, and frequently lacking prognostic and therapeutic guidelines.

Health care for people with rare diseases has historically been directed at managing symptoms and complications of the disease due to an inherent lack of a cure for the disease. Molecular- and genetic-based therapies continue to advance our ability to diagnose and manage the symptoms of rare diseases and, in some instances, actually provide a cure.⁵ Heterogeneity of the causes and phenotypes of rare diseases makes the development of consensus and standardization of management protocols problematic.⁶ Consequently, people with rare diseases sometimes wait years to receive an accurate diagnosis, many receive incorrect diagnoses, and as a result many patients may undergo inappropriate pharmacotherapy and interventional procedures.

A stumbling block for the pharmaceutical industry as they attempt to develop drugs for rare diseases is the risk to cost-benefit ratio.^{7,8} The exorbitant cost involved in various phases of drug development can be prohibitive due to the small number of people potentially using medications, and therapies that are costly to develop and bring to market.⁷ The added burden of access and unmet needs of orphan drugs is a global issue that is being addressed through a variety of mechanisms.⁹ Although there is a global increase in the number of countries with an active orphan drug program, the considerable disparities in national incomes, gross domestic products, and the lack of financial incentives make advancing drug development challenging.¹⁰

RARE DISEASE DEFINITION

A rare disease is a chronically debilitating condition that affects a small proportion of the population. As alluded to above, there is a wide range of definitions based primarily on the geographic location of the population. In Europe, the prevalence required to be considered a rare disease is 50 per 100,000 people, and in the United States, a rare disease is defined as a condition with fewer than 200,000 affected people.¹¹ The World Health Organization defines a rare disease as having from approximately 0.65 through 1 affected person per 1,000 globally.¹² The National Organization for Rare Disorders has loosely defined a rare disease as “a disease, disorder, illness or condition that affects fewer than 200,000 Americans.”¹³ Considering such an entity that may affect fewer than 200,000 people in the United States, but may be affecting many more people in another geographical population, leads to confusion and discrepancies in defining a rare disease. These discrepancies contribute to the lack of consensus globally on the management of a rare disease. Beyond prevalence, rare diseases are often of genetic origin, clinically heterogeneous, pose a diagnostic challenge, and may be associated with limited management options, leading to a considerable physical, psychological, and socioeconomic impact on patients and their families.¹⁴

The definitions of rare disorders and diseases as they appear in the literature are heterogeneous. The [table](#) contains a summary of these definitions.

ABBREVIATION KEY

CF: Cystic fibrosis.

OI: Osteogenesis imperfecta.

OMIM: Online Mendelian Inheritance in Man.

Table. Definition of rare disease.

REGULATORY ORGANIZATION	DEFINITION
World Health Organization	A condition that affects fewer than 65 of every 100,000 people ¹²
European Union	"[T]he life-threatening or chronically debilitating conditions that affect maximum 5 persons over 10,000" ¹⁵
Orphanet	"Rare diseases are diseases which affect a small number of people compared to the general population. Their rarity creates unique challenges for research, care, and treatment." ¹⁶
Online Mendelian Inheritance in Man	No definition reported
Genetic and Rare Diseases Information Center	Per the Rare Diseases Act of 2002, ¹⁷ the Genetic and Rare Diseases Information Center defines a rare disease as one that affects fewer than 200,000 people in the United States ¹⁸
National Organization for Rare Disorders	The National Organization for Rare Disorders ¹³ adopted the same US regulatory threshold as the Orphan Drug Act ¹ and the Rare Diseases Act of 2002 ¹⁷
Shafer's Textbook of Oral Pathology ¹⁹	No definition reported
Oral and Maxillofacial Pathology ²⁰	Does not offer a numerical or regulatory definition of rare disease.

EPIDEMIOLOGY AND ETIOLOGY

The prevalence of rare diseases is difficult to establish with a high degree of accuracy for several reasons, including their rarity, unclear diagnostic criteria, and the lack of comprehensive health registries in most countries to document the prevalence of rare diseases. Results of an evaluation of the Orphanet rare disease database showed that approximately 70% of rare diseases have a genetic etiology and a pediatric onset.⁴ Using the Orphanet data to estimate rare disease prevalence, we found that from approximately 3.5% through 6.0% of populations across the globe have rare diseases.⁴ This would translate to approximately 250 million through 450 million people using the European definition of 50 per 100,000 people and excluding rare cancers.⁴ Assuming a US population of 430 million and a prevalence of 3.5% through 6.0%, there would be from an estimated 15 million through 30 million people with a rare disease in the United States.²¹ The prevalence estimation is slightly higher if the US definition for rare disease of 80 per 100,000 people is used. Although exact prevalence data are unavailable, patients with rare diseases constitute a substantial portion of the total population. The widespread use of electronic health care records provides a new approach to estimating the prevalence of rare diseases and should allow more accurate estimates of overall prevalence and specific rare disease prevalence in the future.²²

The etiologies of rare diseases are diverse, with genetics being the most common cause. Most rare diseases with a genetic etiology have an autosomal recessive or autosomal dominant mode of inheritance.²¹ There are now more 7,000 conditions listed in the Online Mendelian Inheritance in Man (OMIM) database that have a phenotype description and known molecular basis.²³ Advances in knowledge resulting from studies of the human genome have markedly changed our ability to diagnose many rare diseases that previously had unknown etiologies. The use of gene panels, microarrays, and exome sequencing is helping identify the molecular basis of many rare and unknown diseases, not only providing a diagnosis but often actionable findings as well.²⁴ Despite these advances, one of the barriers to optimal care is the large number of patients with a rare disease who still have not received a diagnosis. Integrated approaches that include deep phenotyping, family-based exome sequencing, RNA sequencing, international collaboration, and machine learning will aid in reducing the number of undiagnosed diseases.²⁵

MOST COMMON RARE DISEASES

As noted above, there are millions of people who have a rare disease. The likelihood that people with a rare disease will seek care at any given dental practice is high. A major challenge for patients is finding health care providers with the knowledge and expertise to manage their rare disease. Similarly, health care providers are challenged with providing health care to a population that, in some instances, may require a variety of modifications to those treatment approaches used more typically. Patients with a rare disease that is severely debilitating or that requires interdisciplinary care may seek care at major medical centers, and others will be treated in the community.

One of the most common rare diseases is sickle cell disease; approximately 100,000 people in the United States have this condition.²⁶ This is an autosomal recessive condition caused by sequence variations in the β -hemoglobin gene²⁷ leading to periods of acute illness and progressive, multi-system organ damage. The congenital muscular dystrophies are a clinically and genetically heterogeneous group of disorders with a broad range of severity and central nervous system involvement. Duchenne and Becker muscular dystrophies (OMIM 310200 and 300376), the most common types, are estimated to have a pooled prevalence for definite and probable cases of approximately 1.4 per 10,000 people in the United States.²⁸ This indicates that there are more than 60,000 people affected with these forms of muscular dystrophy.²⁹

Ehlers-Danlos syndrome, another common rare disease, is a group of hereditary connective tissue disorders characterized by joint hypermobility and skin that can be hyperextensible and fragile. Prevalence is estimated at 1 through 5,000 people ($\approx \geq 60,000$ people in the United States), but could be much higher, as there are likely many mild cases that are undiagnosed.³⁰ OI is the most prevalent of the hereditary connective tissue disorders affecting the skeleton primarily, with a prevalence cited as 1 per 15,000 through 20,000 people.³¹ Researchers in Sweden reported the prevalence of the major OI types as 7.4 per 100,000 people. This would translate to approximately 30,000 affected people in the United States.³¹ OI often manifests with dentinogenesis imperfecta. A distinct, similar entity that primarily affects enamel is amelogenesis imperfecta.

Cystic fibrosis (CF) (OMIM 219700) is the most common lethal disease in White populations and is much less prevalent in non-White populations.³² This autosomal recessive disease occurs in 1 per 3,000 White people in the United States, causing pulmonary disease and pancreatic dysfunction.³³ New therapeutic approaches have increased the lifespan of people with CF by several decades, changing the demographic characteristics of this population and their long-term needs for oral health care.

There are rare diseases that have a low prevalence with only a few case reports published in the global literature, and other conditions, such as CF and sickle cell disease, are much more likely to be seen in a health care provider's patient pool.

DIVERSITY OF CONDITIONS

Rare diseases have myriad clinical manifestations that are diverse, given the complexity of molecular and developmental biology. There are approximately 20,000 protein-coding genes in the human genome, with additional DNA that is transcribed and involved in gene expression and cell function.³⁴ Given the developmental and homeostatic complexities of humans, there are thousands of diseases with diverse etiologies and variable clinical manifestations. Clinically, patients with rare diseases have thousands of phenotypic features. Some of the more frequent clinical manifestations include neurologic involvement, intellectual disability, developmental delay, seizures, and epilepsy. Hypotonia, growth abnormalities, and dysmorphic features are common as well.

The craniofacial, oral, and dental manifestations associated with rare diseases are diverse. The dentition may have variations in tooth number, shape, size, composition, eruption, and exfoliation as well as differences in the risk of and resistance to developing caries and periodontal disease. The [figure](#) provides an example of the intraoral clinical features of a patient seeking oral health care with a high probability of a rare or genetic disorder. Some rare diseases, such as those associated with sequence variations in the *p63* gene, can manifest as facial clefts. Soft-tissue manifestations, such as the soft-tissue fragility, oral blistering, and healing with scarring seen in epidermolysis bullosa, can have devastating effects on a person's oral health and make the delivery of routine oral health care difficult.

OPTIMAL ORAL HEALTH: A RARE DISEASE PERSPECTIVE

Although there have been various attempts to define oral health, good oral health may take on a different meaning for those with rare diseases. The widely recognized integral components of oral health include, but are not limited to, function without pain and discomfort, smile and social interaction, speaking and self-presenting without embarrassment, and disease and disorder or condition status.^{35,36} The World Health Organization³⁷ defines oral health as



Figure. Undiagnosed rare disease associated with multiple congenitally missing and malformed teeth. The child had maxillary insufficiency with a class III malocclusion, crossbite, and hair and skin anomalies.

Oral health is the state of the mouth, teeth and orofacial structures that enables individuals to perform essential functions such as eating, breathing and speaking, and encompasses psychosocial dimensions such as self-confidence, well-being and the ability to socialize and work without pain, discomfort and embarrassment.

Some of the challenges in achieving a patient's desirable level of good oral health for those with rare diseases include

- Definition of oral health and what is optimal oral health
- Lack of standardization and consensus
- Diversity and heterogeneity of the phenotype
- Variation in the degree of affliction
- Differences from patient to patient within the same spectrum
- Permutation and combination
- Associated alteration in the oral flora

Rare diseases often involve the craniofacial complex with diverse clinical manifestations affecting the soft tissues, salivary function, dentition, and skeletal and facial structures. Even people with the same genetic etiology can have markedly distinct levels of involvement and severity (eg, number of missing teeth and facial clefting). Researchers have found that many rare diseases, especially those with craniofacial manifestations, are associated with a decreased quality of life resulting from the person's diminished oral health.^{38,39} The clinician or health care team members should assess each patient's concerns, and, when possible, have them articulate and discuss their specific oral health care goals related to eating, speaking, function, pain, esthetics, and their psychosocial concerns. Developing health care management plans often involves establishing short-term and long-term goals that need to be clearly defined, realistic, and achievable.

CHALLENGES AND OPPORTUNITIES

Rare diseases pose complex scientific and clinical challenges due to a limited understanding of their pathophysiology and their highly variable clinical manifestations as well as limited availability of curative therapeutics. This makes the diagnosis and management of rare diseases difficult, resulting in variable success for clinical programs providing care for this population. Therapies for rare diseases have historically been limited, and medicines, referred to as orphan drugs, are less successful than other medications.⁴⁰ This makes it commercially challenging for pharmaceutical firms to invest in rare disease treatments. Policies related to the development of new therapies for rare diseases continue to evolve and vary in different countries. Regulatory agencies such as the US Food and Drug Administration have modified approval mechanisms to assist in bringing new medications to patients with rare diseases.

Access to care and reimbursement for treatment remain a challenge. Care for rare diseases affecting the dentition is often considered esthetic and is not covered by medical insurance, and most dental insurance programs are not sufficient to cover extensive dental reconstruction that may involve multiple phases of extensive care (eg, implants, crowns, and orthodontics). Having health care providers who are appropriately educated and trained to manage the diverse needs of this population continues to be a challenge. Dental school curricula, in general, may be relatively inadequate to optimally prepare dental care providers to effectively address the specific oral health care needs of this

Box. Rare disease resources.

ORGANIZATION OR DATABASE	WEBSITE ADDRESS
Online Mendelian Inheritance in Man	https://www.omim.org
Orphanet	https://www.orpha.net
National Organization for Rare Disorders	https://rarediseases.org
Genetic and Rare Diseases Information Center	https://rarediseases.info.nih.gov
Rare Disease Research (Rare Disease Clinical Trials)	https://www.rarediseaseresearch.com

cohort of patients, due to multiple factors. Specialty programs and residencies can add additional training for dental care providers but will vary substantially in the types of patients and experiences provided. New tools, such as artificial intelligence, are helping in the diagnosis, acquisition, and analysis of data related to a patient's condition and could help improve care for this population.

Health care providers are positioned to support people with rare diseases, helping them establish access to care, receive a diagnosis, receive appropriate treatments and therapeutics, and be their advocates. Dental care providers may be the first to suspect that a patient has a rare disease. Referring them for appropriate management (eg, genetics and medical testing) is critical. Advocating for the patient can include communication with their insurers to help garner financial support for treatment. It may also include supporting policy initiatives by means of lobbying appropriate political leaders who can support rare disease legislation.

Resources and data

Clinicians and patients have access to a variety of resources, including websites and databases, support groups, and disease-focused organizations. Health care professionals and research team members can offer essential support for those with rare conditions. In addition, family support groups and organizations serve as vital tools for accessing medical information, treatment guidance, and peer connection. Family support groups can serve as a valuable resource for health care information, guidance for best practices and treatments, research programs, and opportunities for discourse with people with the same rare disease. The common data sources for rare diseases are summarized in the [Box](#).

PRACTICAL IMPLICATIONS

Screening for, identifying, aiding in differential diagnosis, raising a red flag, making prompt referrals, and facilitating succinct interdisciplinary care are some of the ways dental care providers are equipped to help manage the treatment of patients with rare diseases and genetic disorders. The unmet dental needs of this special population is substantial compared with other populations.⁴¹ Dental care providers can pick up subtle signs and symptoms along with the more overt ones, representing groups of conditions. Many of the pathognomonic symptoms and signs are oral manifestations. Dentists, therefore, are the guardians for these patients to aid in early recognition, identifying phenotypes that are outside the norm, making appropriate prompt referrals, and facilitating a patient's entry into the medical and oral health care systems. For example, premature eruption and exfoliation of teeth, taurodontism, multiple hyperplastic frenulae, hypodontia, and microdontia combined with appropriate medical features such as short stature, rhizomelia, and genu valgum is suggestive of Ellis-van Creveld syndrome.⁴² Another example is a patient with micrognathia, cleft palate, and glossoptosis, along with other craniofacial features, which may be suggestive of Pierre Robin sequence.⁴³

Conversely, manifestations may be mild, such as a few missing or conical-shaped teeth, which may portend the presence of a rare disease that could have substantial comorbidities that remain undiagnosed. Recognizing these conditions is a critical first step for dental care providers.

CONCLUSIONS

Although it is unrealistic to expect dental care providers to be knowledgeable about all of the rare diseases in their patient population, it is possible to have a general understanding of some of the different classes and more common rare diseases. Knowing what resources are available to help educate dentists and their patients regarding the clinical manifestations and best practices and

treatment approaches is also reasonable. Being part of the health care team and caring for those with rare diseases can be challenging but equally rewarding. ■

DISCLAIMER

Davis C. Thomas serves as a guest editor on this special issue of JADA. J. Tim Wright serves as Editor-in-Chief for JADA and as a guest editor on this special issue of JADA. Drs. Thomas and Wright were not involved in decisions about the article they wrote, and peer review was handled independently.

DISCLOSURE

Drs. Thomas and Wright did not report any disclosures.

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