



2012-2021

# A Decade of Innovation in Rare Diseases

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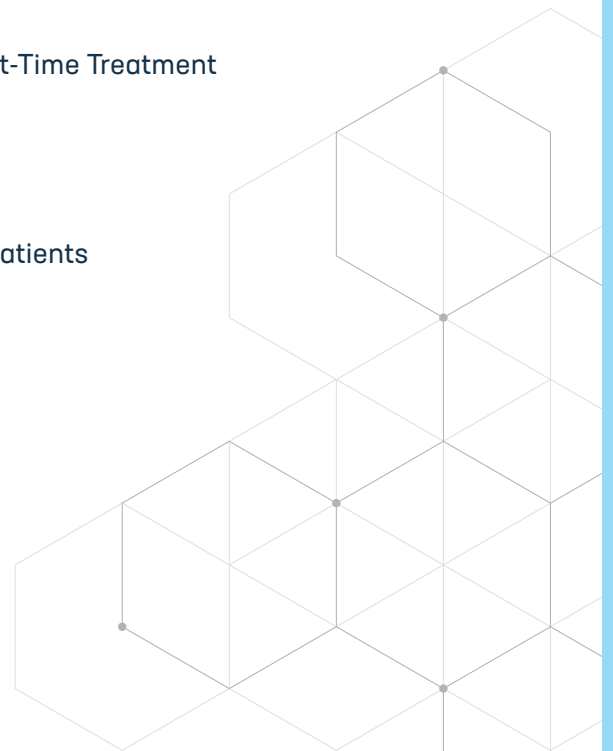
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# Introduction

Over the past decade, a new era of innovation has pushed the frontiers of science, leading to remarkable progress for patients with a wide range of rare diseases.

By definition, a rare or “orphan” disease affects 200,000 people or less in the United States.<sup>1</sup> But collectively, the impact of these diseases is much larger: 30 million Americans and 400 million people worldwide are living with a rare disease.<sup>2</sup>

Approximately 7,000 different rare diseases are known today, with many more still to be identified.<sup>2,3</sup> Eighty-five to ninety percent of these are considered “serious or life threatening,” and for many, there are no known effective treatments.<sup>1,2</sup> About 80% are caused by genetic abnormalities and half of these diseases impact children.<sup>2</sup>

For many with a rare disease, simply getting a diagnosis can be a complicated, lengthy and frustrating journey. Inadequate availability and access to diagnostic tools and limited awareness of rare diseases among physicians makes it difficult to identify and diagnose many of these illnesses. On average, it can take more than seven years and be an often-burdensome process for a rare disease patient to receive an accurate diagnosis.<sup>2</sup>

In addition to diagnostic challenges, developing medicines to treat rare diseases is particularly challenging due to the complexity of the diseases themselves. While some rare diseases have been identified and characterized over time, increasingly linking these diseases to genetic abnormalities or other factors, many more diseases continue to have no known cause or have only more recently been identified as a disease. Still others may have multiple causal pathways, which may also interact with environmental factors or be highly interrelated with different, though very similar diseases.

These knowledge gaps in rare diseases also contribute to specific challenges in conducting clinical trials. Clinical trial design relies on a thorough understanding of the cause and progression of a disease. But in rare diseases this information is often lacking or limited. Additionally, as the affected treatment population is inherently small and there is often a lack of experience and familiarity with these diseases among physicians, recruiting and retaining patients in clinical trials can be extremely difficult.<sup>4,5</sup> Furthermore, patient experiences and disease progression can vary significantly within an individual rare disease, especially considering the many subtypes or variations of these diseases, making not only patient identification for trials difficult, but evaluating treatment outcomes among those participating in trials a particular challenge.<sup>5</sup> Importantly, there are also significant difficulties in recruiting enough clinical trial volunteers to show statistically significant results in such small patient populations.


## Evidence underscores the unique challenges specific to developing new medicines to treat rare diseases:



- A recent report from the Tufts Center for the Study of Drug Development finds that it takes nearly **4 years longer** to develop an orphan drug compared with medicines to treat more common conditions.<sup>6</sup>
- Another study found that just **6%** of orphan drugs in development reach approval, significantly less than the success rate for drugs overall, which has been estimated at **12%**.<sup>7</sup>

Despite the challenges, we continue to see notable innovation in the development of medicines to treat rare diseases. Throughout the last decade, America's biopharmaceutical researcher companies have made significant progress in the development of groundbreaking therapies. The US system has fostered innovation in biomedical research through a range of policies, from intellectual property protections to coverage and payment policies that support patients' access to new medicines. For example, since 1983 the Orphan Drug Act (ODA) has provided important incentives to support research and development of new innovations in treatment for rare diseases.<sup>8</sup> Over the past decade, biopharmaceutical researchers have advanced new technologies to target the genetic causes of diseases or to engage the immune system to fight off illness, offering significant progress and even potential cures for many patients. Many of these treatments are available for diseases for which treatment options had previously been limited or lacking.

However, this incredible progress sits on a backdrop of continued unmet medical need, as still less than 10% of the known rare diseases have an approved treatment available.<sup>9</sup> This underscores the importance of sustaining the critical incentives supporting drug development in rare diseases. Currently, there are more than 700 orphan drugs in development, including crucial treatments in patient populations with significant unmet needs like rare cancers, a wide range of genetic disorders, and neurological disorders like ALS.<sup>10</sup>



## The Importance of the Orphan Drug Act in Supporting the Development of New Medicines for Patients with Rare Diseases

Recognizing the unique challenges of developing drugs for rare diseases, Congress passed the Orphan Drug Act (ODA) in 1982. The ODA provides targeted and predictable incentives to help increase the chances that companies who invest in rare disease research, and manage to get an orphan drug approved, will recoup their costs. Among other incentives, the ODA provides a 7-year market exclusivity period during which the U.S. Food and Drug Administration (FDA) may not approve the same drug for the same orphan indication.<sup>11</sup> These incentives help protect investments and encourage companies to embark on the necessary highly risky research when market-based incentives are insufficient. The ODA has been widely regarded as a success, as over 600 orphan drugs have been approved since the passage of the ODA, in contrast to fewer than 10 medicines for rare diseases in the decade prior to its enactment.<sup>12</sup>

This report highlights progress made during the past decade in several disease areas, representing a wide variety of conditions in terms of prevalence, availability of treatment options, and patient populations. Treatment advances described in depth include those seen for patients with hemophilia A, spinal muscular atrophy, juvenile idiopathic arthritis, inherited retinal diseases, and transthyretin amyloid cardiomyopathy. In addition, the report spotlights rare diseases for which major milestones have driven important treatment advances for patients, as well as rare disease areas that are the focus of cutting-edge clinical research and are on the cusp of significant progress.



# Rare Diseases

Approximately  
**7,000**  
different rare diseases are known to exist today<sup>2</sup>

**50%**  
of people affected by rare diseases are children,  
**30%**  
of whom will not live until their 5th birthday<sup>13</sup>

Less than **10%**  
of the known rare diseases have an approved treatment available<sup>9</sup>

The FDA has approved over  
**600**  
orphan drugs since the passage of the Orphan Drug Act<sup>8</sup>

Rare diseases collectively affect

**30 million** Americans, or **1 in 10<sup>2</sup>**

# Spinal Muscular Atrophy (SMA)

New Treatments Target the Genetic Basis of a Devastating Disease in Children

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## QUICK FACTS

- Spinal Muscular Atrophy (SMA) is a devastating progressive, neurodegenerative disease leading to decreased musculoskeletal control. Diagnosis often happens early in life and most commonly impacts infants and children.<sup>14</sup>
- SMA has been estimated to affect as many as 10,000 to 25,000 children and adults in the United States. It is a leading genetic cause of infant mortality.<sup>15</sup>
- Patients with SMA have a loss of a type of nerve cell called motor neurons, causing a disruption in the signal to the muscles, leading to muscle weakness and wasting. With infant onset, this often affects breathing, crawling, walking, sitting up, and other motor functions.



## A Decade Ago: Early Treatment Options Focused on Relieving Symptoms with Little Improvement

Individuals with SMA do not produce enough functional survival motor neuron (SMN) protein. This protein is needed to maintain motor neurons that support the basic functions of life such as breathing, eating, sitting, crawling, and walking. Once motor neurons are lost, they cannot be replaced. Up until the more recent introduction of novel therapies, available treatments focused on managing the symptoms of the disease—including respiratory, nutritional, gastrointestinal, orthopedic, and psychosocial issues.<sup>16</sup>

There are 5 subtypes of SMA, categorized by age of onset and severity of disease.<sup>17</sup> All individuals with SMA, regardless of subtype, will experience some form of progressive muscle weakness, loss of motor function, and disability.<sup>17,18</sup> SMA type 1 is the most

common and a severe form of the disease, making up 60% of cases.<sup>18</sup> These patients experience symptom onset prior to 6 months of age. Prior to available treatments, these patients would require permanent ventilation and did not live beyond the age of 2. Though the clinical course of SMA in all types is highly variable from patient to patient, those with later-onset disease generally have longer life expectancy.

In the 1990s, scientists discovered that SMA was associated with abnormalities in both copies of the gene responsible for producing the protein necessary for the maintenance and function of motor neurons.<sup>19,20</sup> These discoveries allowed the shift of SMA diagnosis from one of interpreting signs and symptoms to one based on genetic testing.<sup>21</sup> Additional advancements in prenatal testing and newborn screenings have allowed earlier treatment, prior to clinical symptoms and irreversible disease progression.<sup>22</sup> This progress greatly expanded the genetic understanding of SMA and paved the way for recent advancements in disease-modifying therapies that are transforming the lives of patients today.





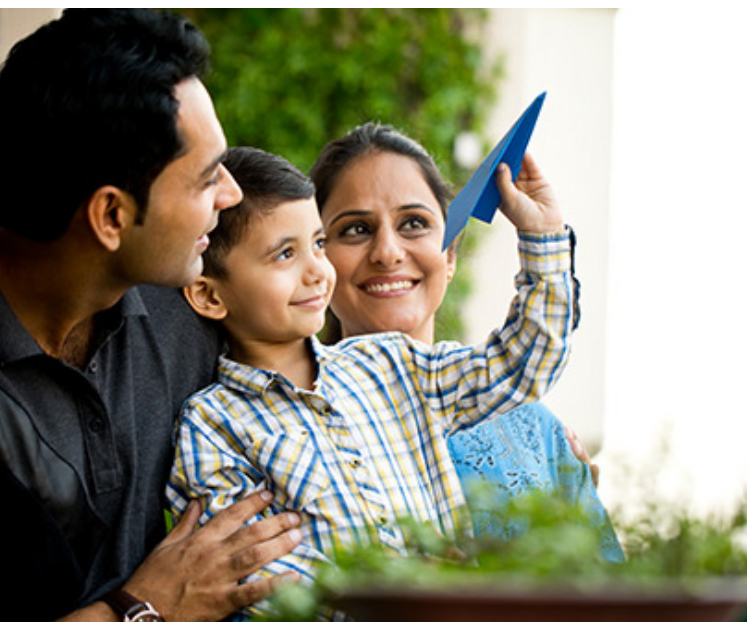
## 2012-2021: Shift from Supportive Care to Treating Underlying Disease

The past decade has seen major advancements in the treatment of SMA. By focusing on the prevention of motor neuron loss and stopping disease progression, the treatment approach has shifted from symptom management to addressing the underlying cause of the disease. The three treatments available today increase the production of the protein that is necessary for the maintenance and function of motor neurons, providing options for patients at all stages of disease progression and severity of SMA.

The first medicine to target the root cause of SMA—nusineren—was approved in 2016 for use in newborns and adults with the disease.<sup>24</sup> Nusineren is an antisense oligonucleotide therapy that affects the process that translates genes into proteins.<sup>25</sup> In some SMA patients, abnormalities in this process result in a gene-splicing error and insufficient production of SMN protein. Nusineren targets this error through an injection delivered directly into the spinal cord, enabling better maintenance and function of motor neurons.<sup>26</sup> Clinical studies have demonstrated nusineren significantly improved survival and eliminated the need for permanent ventilation in patients nearly 4 years following initiation of treatment. Importantly, this remarkable treatment advance, for the first time, has also allowed many patients to hit development milestones in a normal timeframe relative to other toddlers.<sup>27</sup>

**“With the approval of three treatments for spinal muscular atrophy (SMA) and several promising therapies on the horizon, the SMA adolescent and young adult populations are expected to evolve in the coming years.”<sup>23</sup>**

In 2019, the first gene therapy was approved for SMA providing a critical early intervention option for pediatric patients under the age of 2 to address the genetic cause of the disease.<sup>28</sup> Onasemnogene abeparvovec-xioi works by providing a working copy of the missing, or non-working SMN1 gene responsible for SMA to the patient, creating sustained SMN protein expression through a one-time intravenous (IV) infusion.<sup>29</sup> Early treatment, especially before symptoms arise, provides the best opportunity to prevent motor neuron loss in SMA patients and further disease progression.<sup>30</sup> Clinical studies have shown that patients treated pre-symptomatically achieved age-appropriate motor milestones—including sitting, standing, and walking. Patients were also able to eat exclusively by mouth and did not require ventilation support of any kind. This groundbreaking treatment has continued to show sustained benefits following a single administration of the therapy and allowed patients to live years past the historical life expectancy.



In 2020, the FDA approved risdiplam, the first oral treatment option for SMA.<sup>31,32</sup> The medicine was approved for use in newborns 2 months and older as well as adults, providing another treatment option for patients at all stages of the disease. Risdiplam targets the processes that increase the production of functional SMN protein. As it is a daily oral medication, risdiplam enables home treatment, providing a valuable option for patients and caregivers impacted by the disease. When initiated early, risdiplam may also eliminate the need for permanent ventilation in many patients and allow many to hit critical developmental milestones—including sitting without support, walking without assistance, or walking independently.<sup>33</sup>

Relative to a decade ago, the treatment paradigm for SMA patients has completely transformed. Treatments today offer not only the ability to intervene early, offering the best opportunity to slow disease trajectory, but the ability to preserve motor function and survival for patients of all different ages and stages of the disease journey. Advancements in newborn screenings and genetic testing today are also further facilitating early diagnosis and intervention prior to irreversible motor neuron loss. Moving forward, patients will ideally be identified as early as possible, prior to the development of symptoms, to prevent irreversible neuron loss and disease progression, maximizing the potential impact of available treatments. New approaches involving combining available treatments are also offering promise by maximizing therapeutic benefit and preventing disease progression for those who continue to experience motor neuron loss.<sup>30,34</sup>

# Spinal Muscular Atrophy

THEN

2012

- Treatments were focused on management of symptoms for patients with SMA but did not address the underlying cause of the disease.
- Most patients with SMA type 1 needed permanent ventilation, did not experience milestones of sitting without support or walking independently, and did not live beyond the age of 2.

NOW

2021

- The 3 treatments available today target the underlying cause of SMA and increase the production of the protein that is necessary for the maintenance and function of motor neurons, greatly extending survival and offering a range of administration options for patients at all stages of disease progression and severity of SMA.
- Newborn screenings allow for earlier diagnosis and treatment. Early intervention and treatment before irreversible motor neuron degeneration has shown the most improvements in motor function and significant increase in life expectancy.
- Collectively, available treatments and early intervention offer to transform the trajectory of a formerly fatal illness and the best opportunity to preserve motor function and survival in patients born with SMA.

# Juvenile Idiopathic Arthritis (JIA)

Continued Research Results in Treatment Options for All Patients

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## QUICK FACTS

- Juvenile Idiopathic Arthritis (JIA) is a group of six rare autoimmune or autoinflammatory diseases which cause the patient's immune system to mistakenly attack the body's own tissue, commonly known as arthritis.<sup>35</sup>
- JIA in total is estimated to affect approximately 294,000 children in the United States, making it the most common type of arthritis in children and teens.<sup>36</sup> About 1 in every 1,000 children will develop some type of chronic arthritis.<sup>37</sup>
- Though symptoms vary depending on the type of JIA, the disease is defined as causing inflammation, pain, and swelling in 1 or more joints—including those in the hands, knees, elbows, and wrists—for at least 6 weeks with an onset before the patient is 16 years of age.<sup>35</sup>

# Juvenile Idiopathic Arthritis (JIA)

JIA consists of 6 subtypes, categorized by the number of joints affected and additional signs and symptoms of the disease.<sup>35</sup> In some types of JIA, a patient will have few joints involved, whereas in others, the patient may have symptoms in multiple joints. Common symptoms of joint inflammation that patients with all forms of JIA may experience include pain, stiffness, redness, and swelling. In some types of JIA, patients may experience eye inflammation (uveitis or iritis) while others may experience fever or rash. Some types of JIA have symptoms that manifest in other parts of the body, such as skin or internal organs. Early diagnosis and aggressive treatment are important to control inflammation and avoid irreversible joint damage.

## Types of JIA:<sup>35</sup>

- Oligoarthritis
- Polyarticular JIA
- Systemic onset JIA
- Psoriatic arthritis
- Enthesitis-related JIA (also known as spondylarthritis)
- Undifferentiated JIA

“ Twenty or 30 years ago, some of these kids may have been in wheelchairs...We've been able to avoid that recently with these new medications.”<sup>38</sup>

– **NANCY PAN, MD,**  
Pediatric Rheumatologist at the  
Hospital for Special Surgery in New York

## A Decade Ago: Early Discoveries Related to Shared Disease Pathways Across Inflammatory Conditions Lead to the Emergence of Targeted Disease-Modifying Therapies

JIA is termed “idiopathic” because the cause of the disease is still unknown.<sup>35</sup> Thirty years ago, the available treatments for JIA consisted of only non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These treatments only offered short-term relief of symptoms and were associated with side effects that often limited longer-term use.<sup>39</sup> Conventional disease modifying anti-rheumatic drugs (DMARDs) represented the next major advancement. These medicines work by broadly suppressing the immune system and blocking inflammation (e.g. methotrexate).<sup>40</sup> Though conventional DMARDs provided improvements for patients and remain in use today, they do not work for all patients. As the structural joint damage caused by JIA is irreversible, additional treatments were very much needed to prevent long-term functional impairment—particularly given half of children diagnosed with JIA will continue to have active arthritis 10 years after diagnosis unless they receive aggressive treatment.<sup>41</sup>



Though JIA was formerly referred to as “juvenile rheumatoid arthritis;” it is not a pediatric version of an adult disease. But as an autoimmune condition JIA does share some similarities with rheumatoid arthritis (RA)—a disease primarily impacting adults.<sup>35,42</sup> Subsequent research to understand the underlying pathology of both RA and JIA and on the utility of existing RA medicines for pediatric populations with this related disease, paved the way for major improvements in the treatment of JIA. These efforts led to the approval of medicines capable of targeting key inflammatory processes driving disease activity and offering the best opportunity to achieve remission and prevent irreversible damage in children and teens with JIA. Treatment advances in JIA are a profound reminder that innovation does not stop once a medicine is approved. After approval, scientists, and physicians often continue to generate information to develop the medicine for new applications in areas of unmet medical needs—such as diseases impacting pediatric populations.



Biologic DMARDs first emerged in the late 1990s and revolutionized the treatment of RA. These medicines are designed to reduce joint damage by interrupting cellular processes that cause inflammation and structural damage, allowing for better disease control. The success of these medicines expanded on the early discoveries of the molecular drivers of the body's normal immune response and the identification of critical targets involved arthritis. These targets include cytokines, which are molecules known to drive inflammation in the body, such as "tumor necrosis factor" (TNF) alpha, interleukins (e.g. IL-1 and IL-6), and other naturally occurring proteins involved in stimulating the body's immune response.<sup>43,44</sup> Many immunologically-mediated inflammatory conditions share specific pathways with known roles in inflammation and joint and tissue destruction. Because these diseases often share these common molecular underpinnings, biologic agents designed to target a specific component of one pathway have often proven to be effective treatments for multiple other disease types as well.

Following the initial FDA-approval of several biologic DMARDs which target inflammatory

processes for patients with RA, additional research and development led to the approval of these medicines for use in children with 2 forms of JIA: polyarticular JIA and systemic JIA.<sup>42</sup> Polyarticular RA is defined as affecting five or more joints in the body and is estimated to account for about 25% of children with JIA.<sup>35</sup> Systemic JIA is a more severe type of the disease impacting 10% of patients with JIA.<sup>45</sup> Unlike other forms of JIA, it affects the whole body, causing rashes and high fevers, which can occur daily and persist for several days or weeks. As a result of post-approval research on existing medicines approved for RA, two TNF inhibitors, a T-cell modulator, and an IL-6 receptor inhibitor became the first biologic DMARD treatment options available for use in children with these 2 subtypes of JIA.<sup>44</sup>

Though the expansion of several biologic DMARDs approved for use in JIA patients marked a significant milestone for patients in the prevention of irreversible joint damage caused by these diseases, there remained a need for additional treatment options as some patients did not respond to available medicines and many other subtypes of JIA continued to have limited treatments.



## 2012-2021: Critical Advancements Highlight the Importance of Continued Research on Existing Medicines

The understanding of immune cells and inflammatory processes in JIA continued to evolve throughout the next decade, leading to new treatments for patients and underscoring the highly related nature of many inflammatory conditions. The continued innovation to DMARDs through post-approval research and development on existing medicines provided patients with all defined subtypes of JIA the ability to moderate and slow the progression of these diseases and prevent significant disability later in life.<sup>44</sup> Like the previous decade, the expansion of treatment options was based on continued research of drugs originally studied and approved in other inflammatory conditions.

In 2013 a class of biologic DMARDs, known as IL-1 receptor inhibitors, emerged as a critical treatment option for JIA patients. In 2013, canakinumab was approved for use in children with systemic JIA.<sup>46</sup> Canakinumab was originally developed and approved for use in 2 types of an extremely rare autoinflammatory condition known as Cryopyrin-Associated Periodic Syndrome in 2009.<sup>47,48,49</sup> Long-term data for canakinumab showed sustained improvement in symptoms for many systemic JIA patients, including many who achieved disease remission.<sup>50</sup>

**👍👍** **Biologics have absolutely revolutionized the way we treat juvenile arthritis...Kids are doing much better with these newer medications and are able to stay active, play sports, and participate in things they should be taking part in at their age. It's been amazing.**<sup>38</sup>

- **SUSAN SHENOI**, MBBS, MS, Pediatric Rheumatologist at Seattle Children's Hospital and assistant professor of Pediatric Rheumatology at the University of Washington.



In 2020, post-approval research on an existing treatment also led to the approval of an entirely new class of oral DMARDs for JIA patients.<sup>51</sup> Janus kinase (JAK) inhibitors are designed to obstruct the signaling of JAK pathways in cells, which plays an important role in the inflammation involved in RA. The first JAK inhibitor was originally approved to treat RA in 2012.<sup>52</sup> Subsequent research led to the approval of this medicine for patients two years and older with polyarticular JIA.<sup>53,54</sup>

As other biologic DMARDs are generally infused or administered subcutaneously, this medicine, which was approved in two forms—a tablet and oral solution—provided a valuable treatment option for the pediatric patients with this type of JIA.

The last two years of the past decade also brought significant progress for patients with forms of JIA that previously had limited treatment options. In 2020, a TNF inhibitor originally approved for adults with RA received two additional approvals: one for polyarticular JIA and one for children and adolescents with psoriatic arthritis. The latter approval marked the first biologic DMARD approved for use in children with this type of JIA.<sup>55,56,57</sup>

Psoriatic arthritis in children produces both joint symptoms as well as a scaly rash on various parts of the body. The following year, another critical advance came for patients with enthesitis-related JIA. This form of JIA causes pain and swelling where tendons and ligaments attach to bone. Secukinumab was originally approved in 2015 for use in adults with moderate to severe plaque psoriasis.<sup>58,59</sup> This biologic is the first from a new class of medicines directly inhibiting IL-17a, an important cytokine involved in the inflammation of psoriatic arthritis as well as other inflammatory conditions.<sup>60</sup> In 2021, secukinumab received two



approvals: one for children and adolescents with psoriatic arthritis and one for enthesitis-related JIA, making it the first biologic DMARD available to patients with this form of JIA.

The treatment advances seen in JIA underscore the significant value provided to patients by continued research and development on already-approved medicines. Today there are FDA-approved biologics and oral DMARDs for all defined forms of JIA which target underlying inflammatory processes involved in a patient's illnesses. These treatments collectively offer JIA patients the best opportunity to slow disease progression and prevent significant long-term disability. Importantly, none of these treatment advances for children with various forms of JIA would have been possible without continued research on already approved medicines to understand related inflammatory processes across diseases—such as in RA and other rare pediatric inflammatory conditions. This evolution of treatment options not only provides critical insight into the nature of scientific research and the significant overlap in various inflammatory conditions, but the importance of post-approval research to understand potential applications of already-approved medicines for use in pediatric patients where treatment options are often lacking.



# Juvenile Idiopathic Arthritis (JIA)

## THEN

### 2012

- NSAIDs and corticosteroids associated with significant side effects were standard treatments as well as conventional DMARDs, which broadly suppress the immune system and block inflammation. But these options did not work for all patients.
- Through further understanding of JIA inflammatory pathways, multiple targeted biologic DMARDs previously approved for the treatment of RA were studied and approved for patients with JIA.
- Still some patients with JIA continued to have an inadequate response, and some JIA subtypes continued to have limited options.

## NOW

### 2021

- Continued research on existing medicines originally approved for use in other inflammatory conditions led to the critical expansion of treatment options from a range of drug classes for JIA patients.
- Today, there are FDA-approved DMARDs to treat all defined forms of JIA. Some patients can even choose an oral DMARD depending on specific needs and preferences.
- Collectively, these treatments provide JIA patients the best opportunity to slow disease progression and prevent significant disability later in life.



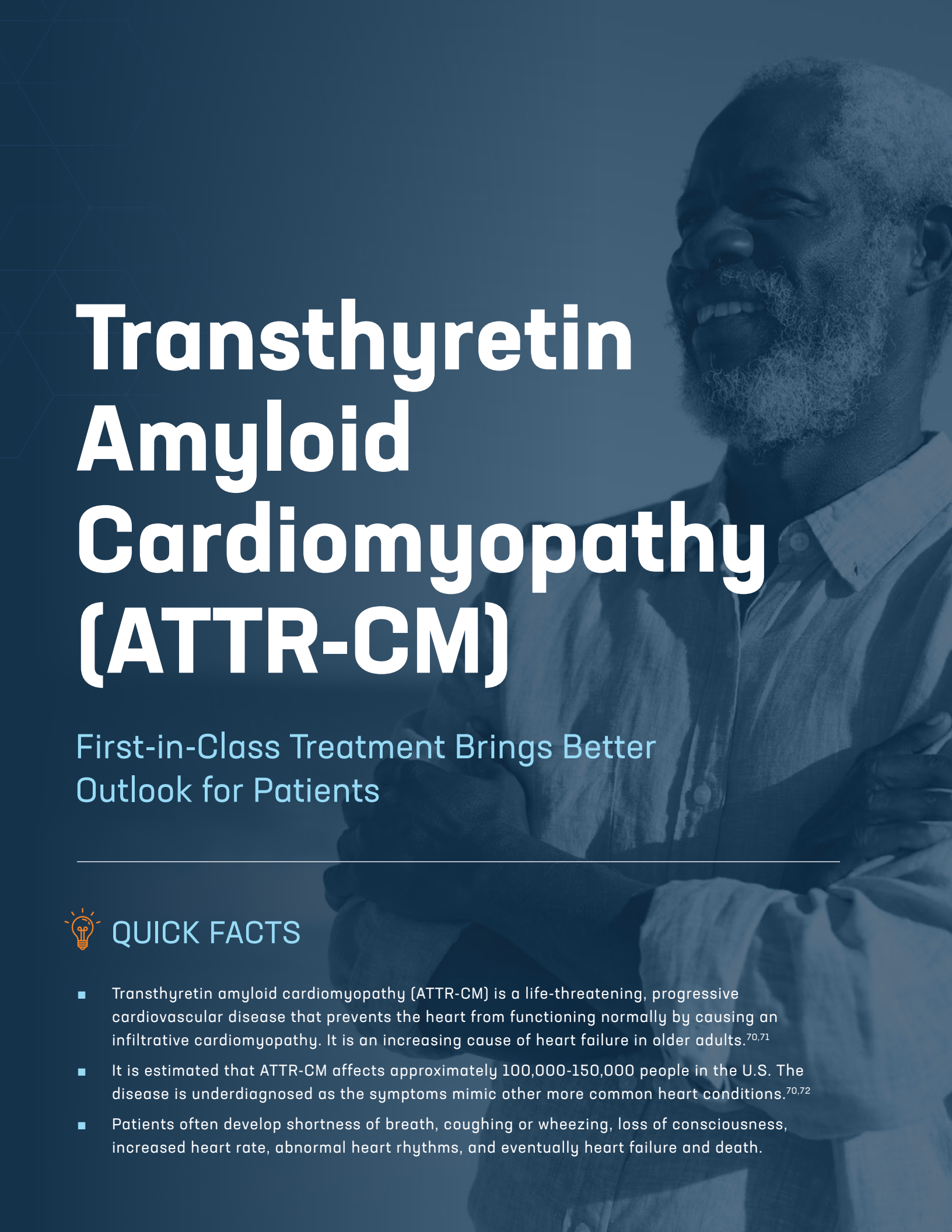
## Spotlight

# Blastic Plasmacytoid Dendritic Cell Neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive, acute leukemia that has historically been difficult to diagnose.<sup>61</sup> Patients often develop skin lesions and over time the disease progresses to multiple parts of the body, including bone marrow, peripheral blood, lymph nodes, spleen, and the central nervous system (CNS).<sup>62,63</sup> The disease is extremely rare, impacting fewer than 1000 patients in the United States each year.<sup>64</sup> Though BPDCN can occur at any age, it often affects older male patients. Historically, chemotherapy regimens offered high initial response rates but patients frequently relapsed, with median survival of approximately 1 year. These treatments were also poorly tolerated and associated with significant side effects.<sup>65</sup>

In recent years, a better understanding of the biology of BPDCN has led to improved diagnosis as well as targeted therapy to treat the disease. In December 2018, tagraxofusp

became the first therapy approved for treatment of BPDCN.<sup>66</sup> Tagraxofusp targets marker CD123 on cancer cells, the hallmark biomarker in BPDCN cancer cell, attaches to the marker, and causes cancer cell death.<sup>67</sup> In clinical trials, more than 90% of patients who never received treatment responded to therapy, with 45% of patients bridging to stem cell transplants, which can lead to long-term remission.<sup>68</sup> A 2019 publication showed that the survival time has at least doubled for patients in the study. Tagraxofusp has since become the standard of care for patients with BPDCN.<sup>69</sup> Additional targeted therapies and immunotherapies are also currently under investigation in clinical trials for BPDCN offering hope in further improving survival and outcomes for patients with this aggressive form of cancer.<sup>65</sup>



# Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

First-in-Class Treatment Brings Better  
Outlook for Patients

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## QUICK FACTS

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening, progressive cardiovascular disease that prevents the heart from functioning normally by causing an infiltrative cardiomyopathy. It is an increasing cause of heart failure in older adults.<sup>70,71</sup>
- It is estimated that ATTR-CM affects approximately 100,000-150,000 people in the U.S. The disease is underdiagnosed as the symptoms mimic other more common heart conditions.<sup>70,72</sup>
- Patients often develop shortness of breath, coughing or wheezing, loss of consciousness, increased heart rate, abnormal heart rhythms, and eventually heart failure and death.



## A Decade Ago: Historically Limited Treatment Options for a Fatal Illness

ATTR-CM is caused by a buildup of abnormal proteins, called amyloid, in the left ventricle, the main pumping chamber of the heart. The buildup is caused by a defective protein called transthyretin. As a result of these amyloid deposits, the heart wall becomes stiff, resulting in the inability of the left ventricle to properly relax and fill with blood and adequately contract to pump blood out of the heart. The buildup of amyloid eventually leads to heart failure. Once diagnosed, the median life expectancy is only about 2.5 to 3.5 years if left untreated. Until recent advances in treatment, there were no medicines approved to treat ATTR-CM; the only available options included symptom management, and in some cases

heart and/or liver transplant.<sup>72,73,74</sup>

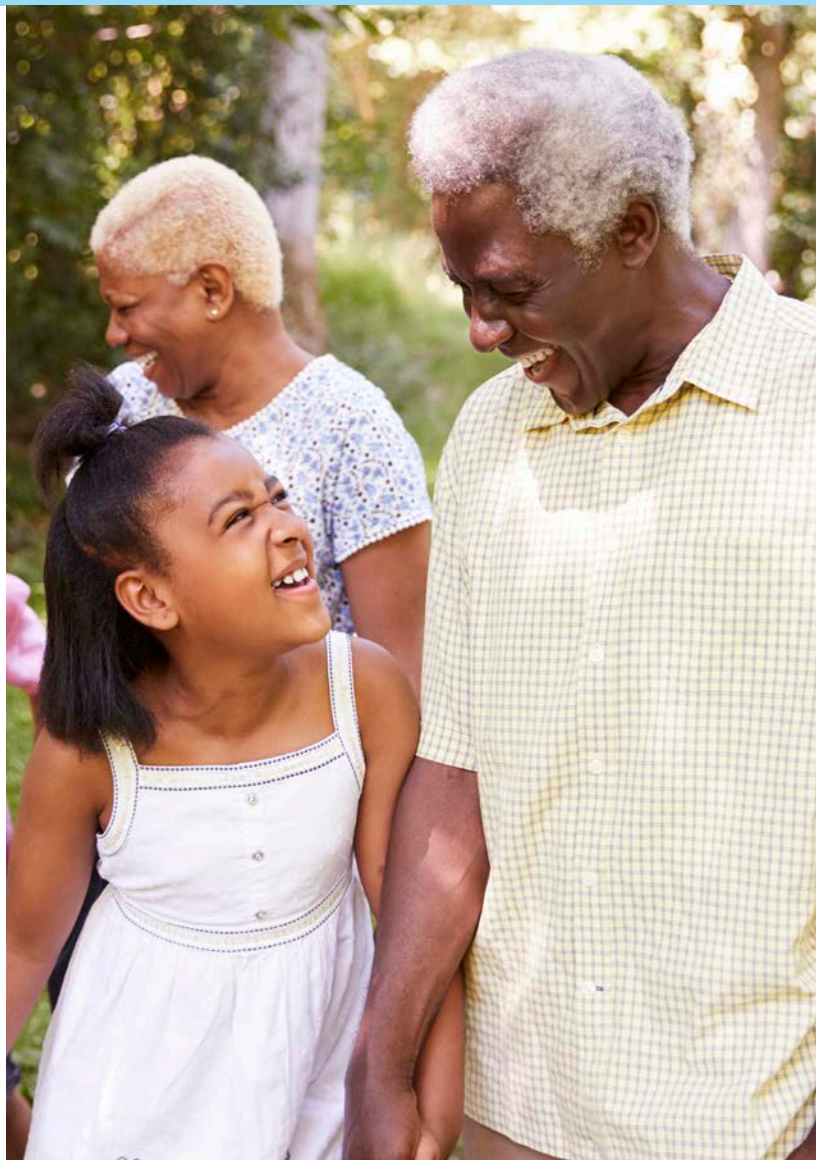
There are 2 types of ATTR-CM. The more common type is termed “wild type,” meaning there is no mutation in the transthyretin gene.<sup>70,72</sup> These patients often experience symptoms beginning at age 65 and older.<sup>72</sup> The second type is hereditary ATTR-CM, which is passed via family members, and patients can start showing symptoms anywhere from age 20 to age 80.<sup>70</sup> Hereditary ATTR-CM is caused by a mutation in the transthyretin gene. Different mutations in this gene are more common in people descending from certain parts of the world—including people of African descent. In the United States, the most common mutation almost exclusively affects African Americans. Approximately 3 to 4% of African American patients have a genetic mutation associated with hereditary ATTR-CM.<sup>70,75</sup> Hereditary ATTR-CM is an underdiagnosed cause of heart failure in individuals with African ancestry.<sup>76</sup>

## 2012-2021: First Approved Treatment Helps Patients Live Longer

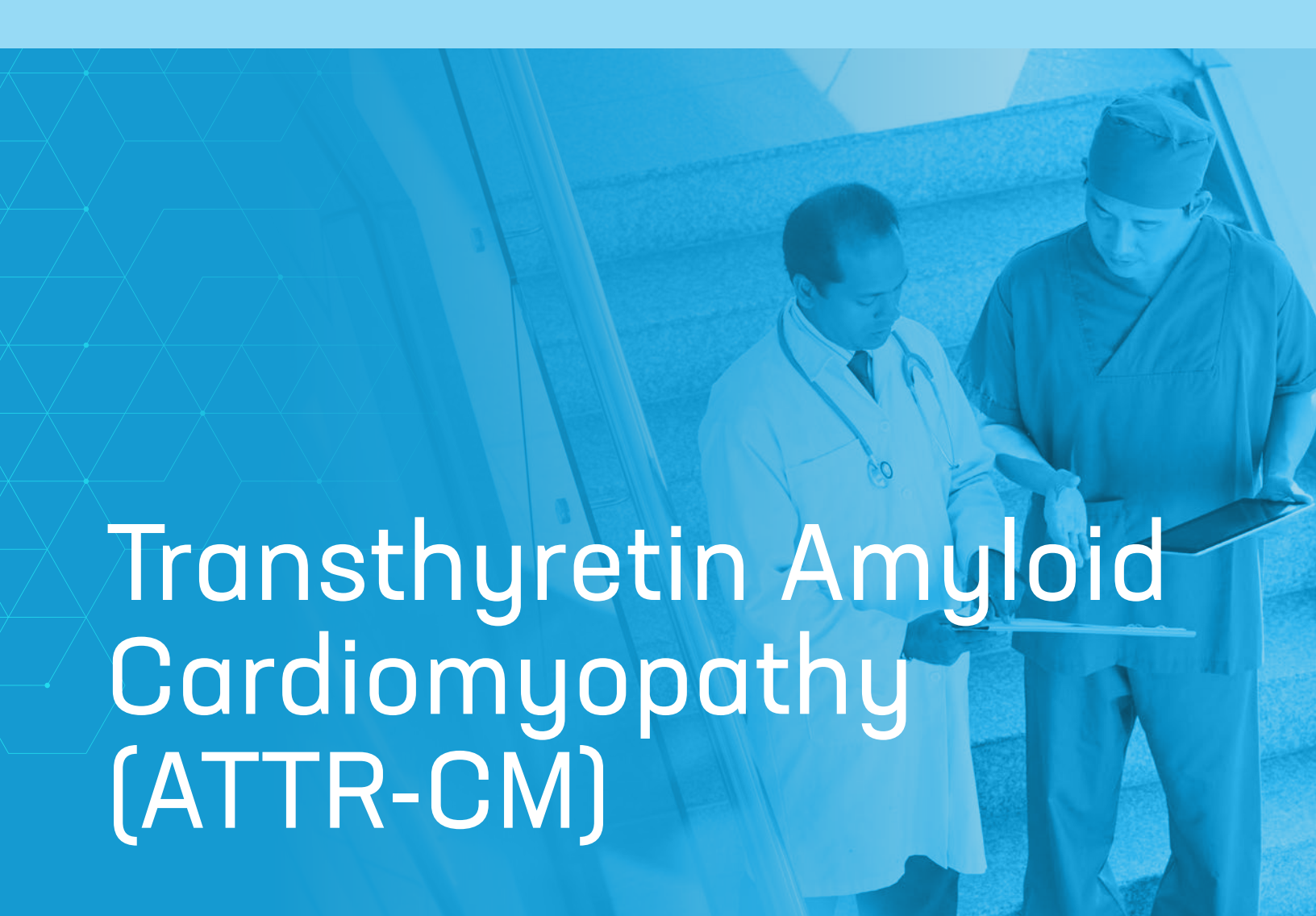
Extraordinary progress has been made in diagnosis and treatment for patients with this debilitating disease.<sup>74</sup> The emergence of treatment that can slow disease progression and extend survival for the first time is dramatically improving the outlook for patients diagnosed with ATTR-CM.

In 2019, the FDA approved tafamidis to reduce cardiovascular mortality and cardiovascular-related hospitalization in adults with either the hereditary or wild type form of ATTR-CM.<sup>77</sup> Tafamidis is a first-in-class transthyretin stabilizer that works by reducing the amount of amyloid proteins that deposit in the heart of ATTR-CM patients.<sup>78</sup> It is available in two oral formulations to provide greater convenience for patients. Tafamidis is available as 4 capsules taken once daily; whereas the other formulation, tafamidis meglumine, provides a single tablet option for the once daily dose.<sup>73,79</sup>

This remarkable treatment advancement not only decreases hospitalizations but provides a significant survival benefit. In clinical trials, patients taking tafamidis experienced fewer cardiovascular-related hospitalizations and lived longer.<sup>80</sup> An additional long-term study in 2021 also showed that patients continuously taking tafamidis had a median survival of approximately 5.5 years, almost double previous trends in life expectancy for untreated patients following diagnosis.<sup>81</sup> The survival benefit reported in this study underscores the critical importance of early diagnosis and treatment.



Looking forward, improvements in non-invasive diagnostics are also providing hope by enabling easier identification of patients with ATTR-CM and helping to bring a greater awareness of the disease as distinct from other cardiovascular conditions that closely mimic ATTR-CM. These improvements are also particularly impactful for the African American communities that are disproportionately affected by the mutation causing ATTR-CM, who already face significant barriers to diagnosis and treatment.<sup>70</sup> Just 1-2% of patients with the disease are estimated to be diagnosed today. Improved diagnostics and the emergence of effective therapies collectively offer to significantly advance the treatment of ATTR-CM.<sup>74</sup>



# Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

THEN

**2012**

- There were no medicines approved to treat ATTR-CM; the only available options included symptom management, and in some cases heart or liver transplant.
- Once diagnosed, the median life expectancy of the disease was just 2.5 to 3.5 years.

NOW

**2021**

- The first approved ATTR-CM treatments decrease hospitalizations and extend survival.
- Improvements in non-invasive diagnostics are providing hope by enabling easier identification of patients with ATTR-CM and helping to bring a greater awareness of the disease as distinct from other cardiovascular conditions that ATTR-CM closely mimics.
- Together, these advances are paving the way for early intervention and treatment.



## Spotlight

# Neuroblastoma

Neuroblastoma is a cancerous tumor that occurs when neuroblasts, or immature nerve cells, do not mature into nerve cells and fibers, but rather go on to cause a tumor.<sup>82</sup> Neuroblastoma is often diagnosed before 5 years of age and can even be diagnosed prior to birth during an ultrasound.<sup>83,84</sup> Neuroblastoma is the most common cancer among infants younger than 1 year of age.<sup>85</sup> Patients may experience fevers, fatigue, weight loss, and a loss of appetite.<sup>86</sup> If the cancer spreads to the bones, the bone pain can be severe, sometimes causing the child to limp or refuse to walk. Approximately 700 to 800 children are diagnosed annually in the U.S. Though low- and intermediate-risk patients are often cured by surgery alone, for high-risk children, 5-year survival has been approximately 50%.<sup>87</sup> Historically, treatment for high-risk neuroblastoma has included surgery, followed by chemotherapy, radiation, or in more severe cases, stem cell transplant.<sup>88</sup>

In 2015 and 2020, 2 anti-GD2 monoclonal antibodies, dinutuximab and naxitamab, were approved, respectively, by the FDA for certain eligible high-risk patients.<sup>89,90,91</sup> The 2015 approval marked the first medicine approved specifically for this form of the disease. Both medicines are from a class of immunotherapy that targets GD2, a substance seen in excess on the surface of neuroblastoma cells, allowing the body's immune system to recognize and exclusively destroy the cancer cells.<sup>92</sup> Anti-GD2 therapies in combination therapy with other therapies are becoming a standard of care for eligible patients.<sup>93</sup> This treatment approach has demonstrated improved outcomes with increased survival, providing significant hope for patients and their families.<sup>94</sup> Looking forward, there continues to be studies on new combinations to bring the potential for extended life to more high-risk children with this devastating disease.<sup>95</sup>



# Inherited Retinal Diseases (IRD)


Advances in Genetic Understanding Bring a First-Time Treatment Targeting the Cause



## QUICK FACTS

- IRDs are a group of genetic disorders caused by genetic abnormalities across any one of more than 270 different genes important in the development and function of the retina within the eye. Most of these disorders cause progressive degeneration of the retina and therefore affect vision.<sup>96,97</sup>
- Collectively, it is estimated over 200,000 patients in the U.S. have one of the many types of IRDs.<sup>98</sup>
- IRDs cause progressive severe vision loss or blindness.<sup>96</sup> Vision loss in patients with IRDs may begin at any time from birth to late adulthood, resulting in blurred vision, light sensitivity, reduced central and/or side vision and accidental bumping into or tripping over objects.<sup>99,100,101</sup>

Though there are many types of IRDs, the most common include retinitis pigmentosa, choroideremia, Stargardt disease, cone-rod dystrophy (CRD), and Leber congenital amaurosis.<sup>102</sup> Each type affects different parts of the eye related to the retina and can present many different symptoms, such as night blindness, reduced peripheral vision, tunnel vision, central vision loss, light sensitivity, loss of ability to see color, uncontrollable movement of the eyes, crossed eye, and an inability to see objects close. A patient's vision loss symptoms can begin at almost any age, progress at different rates, and cause a range of vision loss, from partial loss to complete blindness.



“ A world without blindness is no longer a dream. Gene therapies are restoring vision in blind children... Thanks to science, soon everyone will see.”<sup>103</sup>

– **GORDON GUND**  
Chairman, Foundation  
Fighting Blindness

## A Decade Ago: Limited Treatment Options Provide No Options to Slow Down or Reverse Disease

Historically, there were limited treatment options, and none that would prevent or slow disease progression or reverse the retinal cell damage caused by the disease.<sup>96</sup> Management of these

diseases at the time focused on supportive measures to help patients maintain daily function with vision loss as well as corrective interventions to maximize vision potential (e.g. glasses, magnification devices) and minimize disease-related impacts.<sup>104</sup> An increased understanding of the genetics of IRDs began in the 1980s when centers were reporting genetic abnormalities of their patients with IRDs.<sup>105</sup> With growth in knowledge of the genetic basis of these diseases, new therapies addressing specific gene abnormalities became a focus of research, allowing for the development of first-time treatments.<sup>102,106</sup>

## 2012-2021: Breakthrough Leads to the First Opportunity to Restore Vision Loss

While the study of gene therapies has been underway for decades in IRDs, the first gene therapy was not approved to treat an IRD until 2017. The approval of voretigene neparvovec-rzyl for use in children and adults with vision loss due to a specific type of IRD called biallelic *RPE65*-mutation associated retinal dystrophy provided a first-of-its-kind, groundbreaking therapy for patients with this form of IRD.<sup>106,107</sup> Babies born with this gene mutation suffer from severe vision problems, including night blindness and as the disease progresses, they lose all functional vision—often during childhood or adolescence—and can eventually become totally blind.<sup>104</sup> The disease affects approximately 1,000 to 3,000 patients in the U.S.<sup>108</sup>

Voretigene neparvovec-rzyl is delivered via a single administration to each eye and works by delivering a normal copy of the mutated gene directly to retinal cells, which in turn instruct the cells to produce the normal protein that converts a retinal pigment to a form that allows it to detect light in the retina to restore vision loss.<sup>107</sup> Following administration patients continue to experience long-term benefits. In fact, continued clinical studies show at year one, 65% of participants had improved functional vision. These improvements in functional vision were sustained for 5 years and observation is ongoing.<sup>109</sup>



As the first gene therapy approved in the United States for a genetic disease, voretigene neparvovec-rzyl represents a significant milestone in the broader field of potentially curative gene therapies, which could be applied to a wide range of devastating diseases, including other challenging forms of inherited blindness.<sup>102</sup> And as the first treatment for any form of IRD, voretigene neparvovec-rzyl demonstrates incredible progress to the children born with this life-altering condition by providing, for the first time, the opportunity to prevent progressive vision loss and a life with reduced visual impairment.

Importantly, the availability of gene therapy has also led to increased diagnosis of IRDs associated with this mutation and likewise more regular diagnostic genetic screening to identify patients eligible for treatment. This increase in testing also allows for greater screening and diagnosis of patients with a broad range of IRDs caused by different genetic abnormalities which in turn, helps to identify patients eligible for numerous other gene therapy clinical trials. As a result, new treatments on the horizon offer incredible promise to improve vision and transform the lives of patients with a wide range of IRDs.

A blue-tinted background image showing a microscope and laboratory glassware, including a test tube and a pipette, with a hexagonal grid pattern overlaid on the left side.

# Inherited Retinal Diseases

## THEN

### 2012

- Previous treatments for patients with IRDs predominantly focused on palliative strategies to maximize vision potential and minimize disease-related impacts.
- Given the limited treatment options, comprehensive genetic testing also remained limited.

## NOW

### 2021

- The approval of the novel gene therapy voretigene neparvovec-rzyl provides the first treatment for patients with a form of childhood blindness associated with a specific genetic mutation, and the first opportunity to restore vision loss in these patients with a single administration.
- The availability of gene therapy has also led to increased genetic screening and diagnosis of IRDs more broadly and likewise the identification of patients eligible for clinical trials exploring additional gene therapies with the potential to offer first-time treatments for patients with other types of IRDs.



# Hemophilia A

New Treatments Transform Day to Day  
Life for Patients

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## QUICK FACTS

- Hemophilia A is a genetic bleeding disorder, generally presenting in infancy, characterized by insufficient levels of a blood protein called factor VIII, which the body needs to clot blood.<sup>110,111</sup>
- Hemophilia A affects approximately 1 in 5,000 newborn males. Approximately 20,000 people in the United States live with hemophilia A.<sup>112,113</sup>
- Without treatment, many individuals are at risk for painful, severe, and life-threatening internal or external bleeding events, which can arise from minor injuries or even spontaneously without an obvious cause.<sup>110</sup>

# Hemophilia A

Hemophilia comprises a group of hereditary bleeding disorders that occur due to the absence or deficiency in specific blood clotting proteins—the most common of which include hemophilia A, hemophilia B, and von Willebrand disease.<sup>114</sup> Among these, hemophilia A is the most common and caused by a mutation in the F8 gene located on the X chromosome. The disorder affects mostly males and impacts all races and ethnicities equally. It is categorized from mild to severe based on the level of deficiency in factor VIII made by the patient.<sup>115</sup>

Patients with moderate and severe hemophilia A experience bleeding episodes following an injury and may also have spontaneous and painful bleeding episodes into joints and muscles, without an obvious cause.<sup>110,115</sup> Individuals with the severe form of the disease account for half of the hemophilia A population. If left untreated, frequent spontaneous bleeding events can be life-threatening. Prior to the development of treatment, life expectancy was just 13 years of age.<sup>116</sup>





## A Decade Ago: Advances Help Shape Approach to Treatment

The cornerstone of hemophilia A treatment, particularly for those with severe disease, has been factor VIII replacement therapy.<sup>110</sup> Originally factor VIII replacement was limited to episodic treatment of bleeding episodes, but by 1995, there was a shift to the use of factor replacement therapy prophylactically to prevent bleeding episodes.<sup>116</sup> Lifelong management of the disease with regular factor infusions represented a remarkable advance in the management of the disease, reducing pain, decreasing the damage caused by chronic bleeding and enabling patients to live long, healthy and active lives. However, prophylactic treatment requires regular infusions multiple times a week which can be burdensome to hemophilia A patients and their caregivers—particularly over the course of a lifetime. The introduction of recombinant factor replacement therapies, beginning in the 2000s, reduced the frequency of infusions to 2-3 times a week for severe patients.

Unfortunately, in some instances patients develop resistance to factor replacement therapy. Approximately one-third of patients with severe hemophilia A develop antibodies, or inhibitors, to treatment.<sup>115</sup> These inhibitors can attack and destroy the factor VIII within factor replacement therapy products, dampening the effectiveness of treatment and making it more difficult to stop a bleeding episode. For many patients, intensive and more frequent administration of factor replacement can resolve the inhibitor, but for some, alternative treatments are needed.<sup>117</sup> The first bypassing agents were developed in 1997, offering patients an alternative product to help stop bleeding events and joint damage.<sup>116</sup> These agents work by “bypassing,” or circumventing the need for factor replacement therapy. As patients with inhibitors are twice as likely to be hospitalized for a bleeding episode and face greater risk of death, advancing treatment options to help these patients remain of critical importance.<sup>118</sup>



**👏👏 The treatment of hemophilia has made great progress in the past 3 decades. Hemophilia has transitioned from a neglected and often fatal disease to a group of disorders with a defined molecular basis for which safe and effective treatments are available.”<sup>119</sup>**

**– DR. SUCHITRA S. ACHARYA**  
MD, Pediatric Hematologist

## 2012-2021: New Medicines Reduce Treatment Burden and Expand Treatment Approaches

The decade that followed continued to bring new factor replacement therapy products to patients, both with and without inhibitors, offering patients not only reduced frequency of infusions but entirely novel approaches to managing this incredibly burdensome disease.

The continued development of prophylactic factor replacement therapy options offered the potential for patients to reduce the frequency of infusions and improve quality of life for patients who manage infusions over the course of their lifetime. Since 2014, the FDA has approved a number of “extended half-life” factor replacement therapies.<sup>120,121,122,123,124</sup> A half-life is a measure of how long a medicine remains active in the body.<sup>125</sup> Extended half-life therapies are formulated to extend the activity of a therapy, thereby offering the potential to reduce the frequency of prophylactic infusions, a remarkable advance for patients managing weekly factor infusions.<sup>126</sup> The first extended half-life prophylactic factor therapy, efmoctocog alfa, approved in 2014, extended the half-life to 19 hours, which is 1.5 times that of “standard” half-life factor FVIII replacement therapies. This increase in half-life allowed patients to move from infusing every 2-3 days with standard half-life therapies, to twice-weekly and up to once every 5 days.<sup>120</sup> Subsequent FDA approved treatment options also became available to patients, collectively offering a 1.3-to-1.7-fold increase in half-life and a 30% reduction in factor infusions.<sup>127</sup>



A novel approach to hemophilia treatment emerged in 2017, providing the first infusion free option for prophylactic treatment for patients with hemophilia A. In 2017, emicizumab was approved for the prevention and reduction of the frequency of bleeding episodes in patients with inhibitors.<sup>128,129</sup> Emicizumab works differently than factor replacement therapy, as it works in the presence of inhibitors. The therapy activates other important factors in the coagulation pathway important for clotting without the need for factor VIII.<sup>130</sup> Emicizumab is a self-administered injection delivered either once weekly, once every 2 weeks, or once every 4 weeks.<sup>128</sup> In 2018, the FDA also approved emicizumab for treatment of patients with hemophilia A with or without inhibitors, providing

the first non-infusion prophylactic treatment option for both hemophilia A patients with inhibitors as well those without inhibitors.<sup>128</sup> For patients with hemophilia A who rely on prophylactic treatment to manage their disease, the introduction of this treatment option marked a significant milestone in reducing the tremendous treatment burden of regular factor infusions and/or bypassing agent infusions, often multiple times a week.

Today, patients with varying severities of hemophilia A, including those with inhibitors, have a range of treatment options available to manage their condition and lead long, healthy, and active lives. Importantly, the expansion of treatment options provides patients and their caregivers the opportunity to consider what matters most to them—including options that reduce the frequency of infusions or those which may eliminate infusions all together. Looking forward, additional novel therapies in the late stages of clinical development offer a range of different dosing options to fit the wide range of needs for patients managing hemophilia A, including a novel approach to prophylactic treatment using small interference RNA (RNAi) technology which enables once-monthly dosing.<sup>131</sup> Additionally, gene therapies in the late stages of development are offering to further shift the treatment paradigm by offering potentially curative treatments delivered via a one-time infusion. These therapies in clinical trials have shown promise to dramatically reduce bleeding events and almost eliminate the need for factor replacement therapy. Additional studies looking at these therapies in patients with inhibitors are also showing promise in transforming treatment for these patients and in reducing significant burden associated with the management of this very challenging disease.<sup>132,133,134,135</sup>





# Hemophilia A

## THEN

### 2012

- Prophylactic factor VIII replacement therapy infusions requiring administration 2-3 times a week to prevent dangerous bleeding events are the cornerstone of treatment—particularly in severe patients—reducing pain and damage caused by chronic bleeding and enabling patients to live long, healthy, and active lives.
- Patients developing inhibitors have limited treatment options and face greater risk of hospitalization and death.

## NOW

### 2021

- The development of extended half-life blood factor replacement therapy products offers the potential to reduce the frequency of infusions and improve quality of life for patients who manage infusions over the course of a lifetime.
- A novel approach to treatment provides the first infusion free option for prophylactic treatment for hemophilia A patients with and without inhibitors. The treatment is an injection self-administered as infrequently as every 4 weeks.
- Additional novel therapies in the late stages of development offer a range of dosing options—including gene therapies that offer one-time administration—providing the opportunity to dramatically reduce treatment frequency and burden for patients with this incredibly burdensome illness.



# New Frontier in Innovation

## Emerging Therapies in Rare Diseases

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Scientists and researchers continue to make progress in the fight against rare diseases as innovative science has opened new opportunities. These new frontiers in innovation highlight the importance of leveraging recent technologies and the growing understanding of the genetic basis for many rare diseases to develop groundbreaking therapies to continue to serve patients.



# Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that weakens muscles, impacts physical function, and leads to irreversible damage in the cells in the brain and spinal cord. Although the disease can strike at any age, symptoms most commonly develop between the ages of 55 and 75. It is usually fatal within 2 to 5 years of diagnosis.<sup>136,137</sup> ALS is also referred to as motor neuron disease (MND) or Lou Gehrig's disease.<sup>138</sup> Approximately 30,000 people in the United States are living with ALS.<sup>139</sup> The majority of ALS cases are termed "sporadic," meaning a person has no family history of ALS. But about 5-10% of cases are familial ALS, meaning a person does have a family history. About two-thirds of individuals with familial ALS and 10% of people with sporadic ALS have a known ALS-associated genetic mutation.<sup>140</sup> Current treatments are focused on managing symptoms and providing palliative care. Only 2 products have been approved to date for ALS, offering certain eligible patients the potential of slowing functional decline.

A greater understanding of the genetic underpinnings of ALS as well as the mechanisms of the disease have led to the exploration of promising potential treatments—many targeting genetic abnormalities associated with the disease. **Antisense oligonucleotides (ASOs)**, which are short fragments of nucleic acids that can alter the way abnormal RNA or DNA works, are currently showing promise in clinical trials for patients with ALS. For example, tofersen targets the superoxide dismutase type 1 (SOD1) gene mutation which is seen in 2% of ALS cases.<sup>141</sup> Another investigational candidate targets abnormalities in the C9orf72 gene, which is present in 40% of familial ALS cases and 8-10% of sporadic ALS cases.<sup>142</sup> Perhaps most exciting are the range of different **gene therapy approaches**—including many currently in clinical trials—targeting multiple mutations in patients with both sporadic ALS and familial ALS which may offer a potential cure for some patients.<sup>143</sup> ALS remains an area of critical unmet need, but continued research is leading to a future where there are dramatically improved options for patients with ALS.

# Cystic Fibrosis

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Cystic Fibrosis (CF) is a life-threatening progressive disease caused by mutations in the CFTR gene that results in the formation of thick mucus that builds up in the lungs, digestive tract, and other organs. It leads to severe respiratory and digestive problems as well as life-threatening infections. The disease affects more than 30,000 children and adults in the United States.<sup>144</sup>

Remarkable progress has been made in the past decade in both improving and extending the lives of CF patients. The FDA has approved 4 CFTR modulator therapies that are designed to correct the malfunctioning protein that results from mutations in the CFTR gene. These treatments are available for patients with a range of mutations associated with the disease, including the most common which is estimated to represent 90% of the CF population.<sup>145,146,147</sup> Advances in the treatment of CF have led to significant improvements in life expectancy, with patients today living, on average, to nearly 50 years of age. Relative to a decade ago, life expectancy has increased by nearly 10 years.<sup>148</sup>

Innovative approaches are currently under exploration to advance game changing new treatments for patients with all forms of CF, including those with mutations that are not addressed with existing CFTR modulators:

- **Gene editing** and **gene therapy** approaches are generating significant excitement due to the potential curative effects of these treatments. As these approaches involve repairing or replacing DNA, they offer significant potential for patients with all forms of CF regardless of genetic mutation.<sup>149,150</sup>
- Rather than deliver the DNA code for the faulty CFTR gene, some researchers are exploring a different approach with **RNA therapies**. For example, one approach in clinical development uses messenger RNA (mRNA) to enable production of functional CFTR protein. RNA therapies also offer to help patients with CF regardless of their genetic mutation.<sup>150</sup>
- For patients with rare mutations that do not respond to CFTR modulators, **antisense oligonucleotide (ASO) therapies** are being explored. These rare mutations disrupt the normal function of mRNA and block the synthesis of normal CFTR proteins. ASOs correct the faulty instructions caused by the mutation to produce a functional CFTR protein.<sup>150</sup>

While significant progress has been made for CF patients in recent years, these approaches offer the potential to completely transform the treatment paradigm for this devastating illness.



# Pediatric Gliomas

Pediatric Glioma is a type of tumor in children that is found in the brain or spinal cord. Central nervous system tumors are the most common type of solid tumor in children, appearing in approximately 5 per 100,000 children, with gliomas making up approximately 75% of these tumors.<sup>151</sup> The standard treatment consists of surgery, chemotherapy, and often includes radiation.<sup>152</sup> Though most pediatric low-grade gliomas (pLGG) are highly treatable, certain standard treatments can have side effects with long-term health implications.<sup>153</sup> For more serious pediatric high-grade glioma (pHGG), called glioblastomas, prognosis remains poor. The median survival for these patients ranges from 13 to 73 months (about 6 years) and the likelihood a patient will live 5 years is less than 20%.<sup>154</sup>

A range of innovative treatment approaches, including many that are already approved for use in adults and other treatment populations, are under investigation for pediatric glioma patients.<sup>152</sup> Research on already-approved medicines to understand the potential utility of existing cancer treatments in other forms of cancer is particularly important to bringing new treatments to pediatric cancers. As researchers seek to understand the underlying mechanisms in pediatric gliomas, many previously approved and new treatments currently under investigation are emerging as promising approaches in pediatric gliomas--including **therapies targeting BRAF, MEK, CDK 4/6, ALK/ROS1/NTRK, PI3K, and mTOR mutations**. Early clinical trials are also exploring **immunotherapies** that work to boost the patient's immune response against cancer cells.<sup>155</sup> Immunotherapies have been game-changing for the treatment of many other forms of cancer. Additionally, **CAR-T cell therapy** is being explored to target specific gene overexpression with a potential for complete remission. CAR-T is a form of gene modified cell therapy which involves permanently altering a patient's T-cells to recognize, target and kill cancer cells. Several CAR-T cell therapies have already been approved for use in pediatric cancers, with some having shown to cure some children and adolescents with advanced leukemia.<sup>156</sup> The potential use of CAR-T cell therapies, immunotherapies, and therapies targeting specific genetic mutations in pediatric gliomas offers tremendous promise. The research underway also underscores not only the value of research and development in pediatric cancers but the critical importance of continued research of existing medicines in driving advances for these patients.

# Sickle Cell Disease

Sickle cell disease (SCD) is caused by a mutation in the  $\beta$ -globin gene and characterized by the formation of malformed red blood cells, resembling a crescent or “sickle” shape.<sup>157</sup> These sickle or crescent-shaped blood cells can get caught on the walls of tiny blood vessels forming clumps and leading to severe pain and other serious problems. The disease typically manifests in children before 1 years of age and life expectancy averages 54 years.<sup>158</sup> Pain is the most common manifestation of the disorder, with 50% reporting pain half of their days and 30% reporting pain most of the time.<sup>159</sup> Though SCD is a rare disease affecting 100,000 Americans, it is far more common among African Americans who are disproportionately affected by the disease. SCD affects 1 out of every 365 black or African American births.<sup>160</sup>

When sickle red blood cells become stuck in blood vessels, they can lead to pain crisis, known as vaso-occlusive crisis, and if they prevent the flow of oxygen to the chest, they can cause a serious complication known as acute chest syndrome. Blocked flow of oxygen to the brain can also lead to stroke. Treatments today include red blood cell transfusions and medications which are generally focused on preventing disease complications and managing symptoms. Bone marrow transplant is another potentially curative option for a small portion of severe pediatric patients, but this option has limited utility as it is often difficult to find a matching donor.<sup>161</sup> Though these options may help to prevent these serious and life-threatening complications, patients with SCD experience frequent hospitalizations. SCD patients visit the emergency room 2 to 3 times a year on average, most commonly due to pain crisis.<sup>162</sup> They are also hospitalized more than once a year on average for significant pain.<sup>163</sup>

The future of SCD has never been more promising with new treatment approaches that could bring potentially curative options for patients.<sup>164</sup> Recent progress has been seen in **gene therapies in clinical development**, specifically through viral vectors or CRISPR technology – both of which modify the mutations causing the disease. For example, a potential gene therapy in the late stages of development which works by delivering functional copies of a the  $\beta$ -globin gene into a patient’s own blood stem cells, has demonstrated an almost complete reduction in pain crisis and acute chest syndrome in the years following a one-time administration of therapy.<sup>165</sup> Another approach works by unlocking the potential for a patient’s own stem cells to be genetically modified and used for their own transplant.<sup>164</sup> In the years ahead, it is possible the treatment of this debilitating and painful disease may experience a significant transformation.

A blue-tinted photograph of a male doctor with glasses and a stethoscope, smiling and shaking hands with a patient. The background shows a window with blinds. A hexagonal grid pattern is overlaid on the left side of the image.

# Continued Progress for Patients with Rare Diseases

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The last decade is a testament to the current policy and regulatory environment working to incentivize innovation and bring patients with rare diseases new treatments. The advancements highlighted in this report speak to how scientific progress can transform patients' lives for the better. For some rare diseases that previously had limited or no treatments, new medicines have targeted the underlying cause of the disease, completely changing the outlook for patients and their families.



Despite this progress, there continues to be a significant unmet medical need, as over 90% of the known rare diseases having no approved treatment option available.<sup>9</sup> Unfortunately, the development of new therapeutic options remains a challenge as the underlying cause of many rare diseases is often not well understood. Additionally, clinical trials are uniquely difficult as inherently small patient populations can hinder recruitment of enough patients and robust evaluation of data from clinical trials to assess potential new treatments.<sup>5</sup>

Despite these challenges, American biopharmaceutical researchers continue to pursue high-risk, resource-intensive research and development to produce groundbreaking innovations for these patient communities. As a result, over the last decade, over 350 orphan drugs were approved by the U.S. Food and Drug Administration (FDA)—many are improving patients' quality of life, and in many cases, allowing patients to live longer.<sup>166</sup>

Beyond the progress that has been made, researchers continue to pursue new approaches in disease areas with continued unmet need. This report highlights several of these disease areas where ongoing research is providing tremendous promise in driving significant progress for patients. But these diseases only scratch the surface in terms of portraying the promise in the pipeline. There are currently over 700 orphan drug products in development, many exploring innovative approaches with the potential to transform treatment for many patients with rare diseases.<sup>9</sup> Advances in cell and gene therapies as well as personalized medicines, which are often targeted to the genetic characteristics of the patient, are

among the many approaches that are creating new opportunities to advance new treatments.

Researchers in biopharmaceutical companies, government, and academia are building on recent breakthroughs and exploring new targeted mechanisms for treatment. In fact, as drug development has become increasingly focused on genetic factors, 31% of medicines in the overall biopharmaceutical pipeline target rare diseases, up from 18% in 2010.<sup>6</sup> This unprecedented progress in the fight against rare diseases is precisely *because* researchers are following science and defining diseases more accurately and narrowly than was possible in the past. It is also exactly the kind of innovation we should be incentivizing to advance progress for patients with rare diseases.

America leads the world in biopharmaceutical innovation because our unique biomedical research ecosystem is supported by a policy and regulatory framework that incentivizes and rewards innovation. To continue to advance new treatments for patients with rare diseases and overcome the many scientific hurdles surrounding the development of these medicines, we need to continue to sustain our robust biomedical research ecosystem. That means maintaining the incentives that have made the Orphan Drug Act such a success as well as public policies that support strong intellectual property protections and a science-based regulatory system that evolves with the pace of science. With these policies in place, we have the potential to change the outlook for the 30 million Americans with a rare disease.<sup>2</sup>

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