

# Guiding Principles of Rare Disease Care and Patient Access

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# Prologue

The process that led to the Guiding Principles contained herein began in 2018 – more than a year before **COVID-19** darkened our shores. At that time, the challenges facing 30 million rare disease patients in the U.S. were already daunting, and they remain so. The Principles we've outlined similarly remain every bit as vital as guideposts for access to care and treatment.

But are there lessons learned from the pandemic that are relevant to the application of the Guidelines in a post-COVID world? Absolutely. And those lessons present new challenges and inspire new hope in our efforts to ensure access to critical care and therapies for rare diseases.

Of the more than 8,000 known rare diseases, less than 5% have approved treatments available. Patients survive by addressing and mitigating symptoms based on best available standards of care -- which might include regular infusions, repurposing of drugs, numerous surgeries, and/or extreme preventive or palliative measures. In the best of circumstances, patients qualify for clinical trials, which can provide effective treatment in the absence of an approved medication.

As the U.S. and other health systems implemented measures to stop the spread of COVID-19, some clinical trials were halted and/or access to clinical research facilities and investigational treatments were restricted. Access to critical testing and ongoing care was also threatened because certain rare conditions and related treatments were characterized as “elective” or non-essential in order to free up facilities, labs or medical staffs to deal with an anticipated increase in COVID-19 patients.

As we look ahead and encourage health system stakeholders to live by the Guiding Principles we've outlined, COVID-19 has taught us the importance of ensuring that measures designed to protect one vulnerable segment of the population don't inadvertently put another large group of vulnerable people at risk.

Fortunately, not all the lessons of COVID-19 point to deficiencies. Importantly, we discovered that, when treating a disease becomes a priority, we can do a number of things better, faster, and more collaboratively. We can dramatically streamline and accelerate the pace of clinical research and regulatory reviews. We can broaden access to critical diagnostic testing and screening. We can find unique and creative ways of accessing care and conducting research, leveraging digital technologies and telemedicine.

So, as you consider the report that follows, we ask you to carefully consider the information and guidance included. And we also challenge you to imagine how much more could be done if we considered rare diseases – which collectively account for 3-10% of all U.S. hospitalizations, and disproportionately impact the youngest and most vulnerable segment of our population (more than half of those living with rare diseases are children, and more than 30% of those children die by the age of 5) – as a public health priority?

# I. Executive Summary

Rare diseases have unprecedented impact on patient and caregiver lives. This report has been developed based on multi-stakeholder workshops and rare disease landscape/literature evaluation flowing from the Rare Access to Critical Therapies (ACT) collaboration, with support of Global Genes and the Child Neurology Foundation. ACT involves leading patient, provider, biotech and pharma organizations, and was formed based on a critical need to identify and articulate key expectations, significant unmet need and care variability in rare diseases, and to ensure the rare disease patient perspective was fully considered as part of broader public discussions and policy formation that could impact patient access to needed therapies, now and in the future.

The report highlights five core Guiding Principles of Rare Disease Care and Patient Access that are universal to all rare disease patients, across markets. These Guiding Principles, established as a set of fundamental expectations for rare disease patient care that all health stakeholders should acknowledge and act upon, are as follows:

1. Timely and sustainable access to diagnostic testing that rapidly informs appropriate patient care and treatments
2. Timely and sustainable access to the highest quality care and most effective treatments that address underlying disease or key symptoms
3. Value assessment processes that provide timely and sustainable access to current and future therapies for which patient-centric benefit is the deciding factor
4. Fulfilling quality of life while lessening the disease burden for both patients and caregivers
5. Standards of care that reflect acceptance of each patient's uniqueness and equality for all patients regardless of disease rarity

The report steps through each of the Guiding Principles, highlighting key areas where we have or are making progress toward achieving the Principles and areas where challenges or additional work remains to accomplish the ideal of each Principle. These Principles also consider factors of diversity, equity and inclusion (DEI) as a common thread key to responsible health decision making.

Areas where additional progress is required (and highlighted in other research) are synthesized here to more comprehensively pinpoint where stakeholders must come together to collectively address desperately needed care and access solutions for rare disease patients. These key areas include, but are not limited to the following:

- Supporting education and access around testing access for rare disease patients, including next generation testing options like whole genome or whole exome testing that can help avoid the rare disease diagnostic odyssey
- Modernization of fast and flexible coding of rare disease so that patients are not precluded from accessing needed therapies, including basic care services such as at-home equipment and ancillary care such as speech or motor therapy
- Ensuring that value assessment processes take into account both the collective magnitude of impact and individual nature of rare diseases to ensure that (a) value assessment approaches applied to broader disease

areas do not inappropriately miss the true value to patients and (b) that price is not the defining factor for access

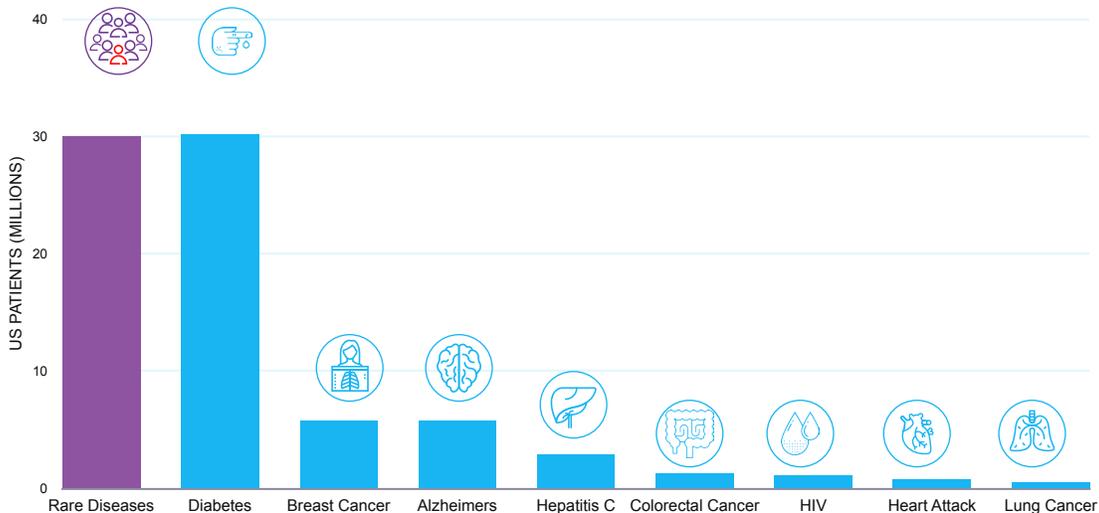
- Ensuring appropriate access to those treatments that provide the best option for optimizing rare disease patient outcomes, including addressing both symptoms and the underlying disease
- Ensuring that value assessment processes appropriately take into account or are driven by patient-centric impacts, including both the patient and caregivers
- Given their profound aggregate patient, clinical and economic impact, emphasis on streamlining and supporting patient solutions for rare disease care are given stronger priority.

The following report describes in detail the core issues around each Guiding Principle and provides additional detail on next steps and a collective way forward.

## II. Introduction

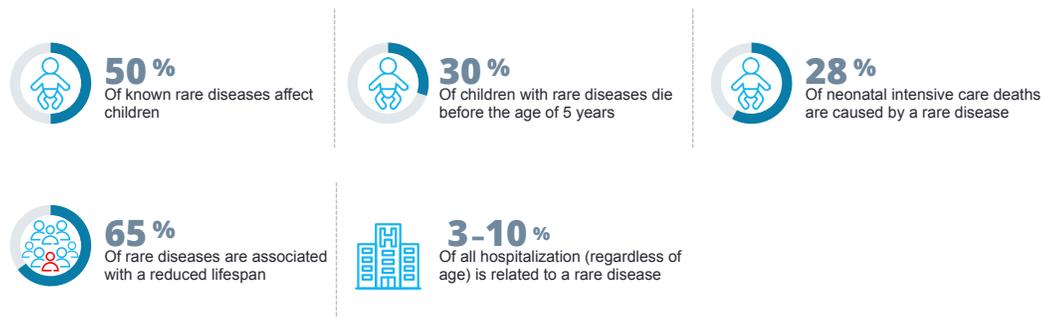
Rare diseases are defined as conditions that affect fewer than 200,000 patients in the US, or one in 2000 patients in Europe.<sup>1</sup> However, while each rare disease is rare in prevalence, they have an aggregate impact similar to or greater than the top national priority disease areas (see Figure 1, below).<sup>2-10</sup> One in ten Americans is living with a rare disease.<sup>10</sup> Current estimates show that there are approximately 5,500-9,000 known rare diseases,<sup>1,11</sup> a number which is expected to increase globally.

**Figure 1: Example High-Prevalence Priority US Diseases**



Over the past quarter century tremendous strides have been made in treatment of rare disease, including advancements such as antibody-based biologicals, enzyme replacement therapies, and more recently cell and gene therapies. Despite this progress, most rare diseases remain devastating for patients and have wide-reaching impact on families and caregivers that support rare disease patients. Rare diseases have substantial clinical impact<sup>12-18</sup> and a wide range of health effects across rare disease categories. For example, while some diseases may strike very early in life and be rapidly fatal without treatment, (e.g., spinal muscular atrophy), others (e.g., mucopolysaccharidosis, Friedreich's ataxia) unfold over decades as progressive cognitive or physical decline (e.g., severe organ damage, physical disabilities). Beyond the health effects, rare diseases often impact every aspect of patient, family and caregiver lives. Such effects may include dramatic impact on activities of daily living, work-life balance, choice of employer, concerns about health insurance, substantial medical costs impacting financial freedom or even viability, ability to pursue social activities, constant stress and severe emotional and psychological implications. Living with a rare disease or caring for a rare disease patient can be like navigating a minefield with a blindfold because of the uncertainty of symptomatic presentation or associated consequences of disease effects.

**Figure 2: Rare diseases have substantial clinical impact**



A key challenge in rare disease care is that current patient access frameworks do not fully or consistently recognize the significant clinical and economic impact of rare diseases. US health decision makers often think of rare diseases, from an access and management standpoint, as having individually limited budget impact that often does not require detailed patient access solutions. Application of risk- and cost-based patient management approaches like those applied to broad diseases can create daunting access challenges for rare disease patients when they do not consider the severity and variability of individual (as well as family and community) burdens specific to rare diseases. There are many aspects of the patient journey in rare diseases where access frameworks were not built with rare diseases specifically in mind, leaving substantial gaps in care. These gaps raise real roadblocks that add to the already substantial burden of living with a rare disease, and in the worst instances, may preclude access to appropriate care altogether.<sup>19</sup> System adjustments to account for these discrepancies would also notionally align with overarching principle of diversity, equity and inclusion (DEI).

Currently, our health system is struggling to adapt to the dual reality of rare diseases: while individually rare, when taken collectively, rare diseases are a substantial and growing segment of the overall healthcare landscape -- yet, the unique and highly variable aspects of each distinct rare disease also make it challenging to apply universal approaches commonly used in broader disease management scenarios. Appropriate patient solutions would properly balance

significant aggregate impact (of a magnitude sufficient to be considered a focal US health priority) in a manner that puts patients first and does not lose the unique impact considerations associated with individual rare diseases. This paper addresses five core Principles of Rare Disease Care and Patient Access that highlight (a) key areas where all stakeholders should be aligned on rare disease patient access objectives and (b) existing gaps in achieving those principles that should be considered by all stakeholders to ensure patient access frameworks appropriate to rare disease care and management.

## III. Methods

The Rare Access to Critical Therapies (ACT) is a multi-stakeholder collaboration involving approximately 45 leading patient, provider, biotech and pharma organizations engaged in ensuring appropriate patient access to emerging rare disease therapies. ACT was established in 2018 with the mission to build awareness and understanding, identify areas of commonality, and ensure that rare disease value assessment and access scenarios appropriately reflect rare disease patient and caregiver perspectives and needs. The need for developing a set of Guiding Principles of Rare Disease Patient Care and Access was identified as a key need during key ACT Summit meetings in 2018 and 2019 to help address gaps and disparities in access for rare disease patients. The key objectives in developing this set of Principles is that they:

- will be viewed as key tenets of care that can be supported by all health stakeholders, including patients, patient advocates, providers, payers, policymakers and other key decision makers involved in rare disease patient care,
- can serve as a lens by which to isolate critical gaps in care, from which solutions to close these gaps can be addressed by a multi-stakeholder community united in purpose, and
- can help patients, families and caregivers in terms of characterizing basic expectations for rare disease care and help support accountability in achieving patient-centric treatment and management solutions and access approaches that consider the special nature of rare diseases.

This study, conducted between September 2019 and January 2020, involves a series of facilitated multi-stakeholder working sessions involving input from more than 150 rare disease patient, provider and manufacturer experts and ACT leadership committee members to discuss and identify the rare disease Guiding Principles, gaps in achieving them, and additional areas necessary for all stakeholders to better address them.

Expert working sessions were also supported by a targeted literature review conducted systematically in PubMed, Embase and grey literature to identify studies from the past seven years. This timeframe was selected to include the broadest net of sources that may consider key issues relevant to identifying key gaps and accomplishment areas relevant to each Principle, as it was viewed that a

five-year window may miss some key literature. Duplicate records were reviewed and articles were screened using the following criteria: 1) English language, 2) publication between 2013–2019, 3) focus on health technology assessment, reimbursement or funding rare disease therapies and/or rare disease patient access needs and considerations, 4) human studies and 5) clinical trials or reviews. Focus was on gaps, barriers and opportunities to accessing rare disease patient care aligned with each of the five areas covered by the Principles.

# Core Tenets of Rare Disease Care and Patient Access

Given the substantial unmet need associated with rare disease, as well as clinical and economic impact on an individual and aggregate basis, the following highlights core Guiding Principles of Rare Disease Patient Care and Access that should be basic expectations for all rare disease patients and other health stakeholders (e.g., providers, payers, and policymakers). These Principles should help guide healthcare decision makers in ensuring appropriate, evidence-based, and balanced patient access practices and policies. Adherence to these principles would both acknowledge the (a) broader aggregate clinical and economic impact associated with rare diseases, while not losing perspective on (b) the severity, special considerations and impact of individual rare diseases on patients, families and other caregivers. These Principles are described herein.

## CORE GUIDING PRINCIPLES

1

Timely and sustainable access to diagnostic testing that rapidly informs appropriate patient care and treatments



2

Timely and sustainable access to the highest quality care and most effective treatments that address underlying disease or key symptoms



3

Value assessment processes that provide timely and sustainable access to current and future therapies where patient-centric benefit is the deciding factor



4

Fulfilling quality of life while lessening the disease burden for both patients and caregivers



5

Standards of care that reflect acceptance of each patient's uniqueness and equality for all patients regardless of disease rarity



The following further defines each Guiding Principle, considers key gaps and advancements material to them, and identifies additional activities that would be necessary to close key gaps and achieve the underlying goal of the Principle.

## 1. Timely and sustainable access to diagnostic testing that rapidly informs appropriate patient care and treatments

The patient journey to diagnosis in rare disease is often significantly more complex and impactful to the patient compared to other diseases. The following characterizes key factors associated with rare disease diagnosis and highlights key gaps that remain to be addressed.

### **Patients with rare diseases and their caregivers often endure an extended 'diagnostic odyssey' on the way to effective treatment.**

Approximately 80% of rare diseases have identified genetic origins, many caused by defects in a single gene.<sup>20,21</sup> Nonetheless, the average time from symptom onset to correct diagnosis for a rare disease patient was 4.8 years, based on a Global Genes study, with some patients reporting delays of up to 20 years.<sup>22</sup> During this time, patients can experience worsening clinical symptoms, decreased quality of life, or even death due to lack of access to optimal treatment. The organ and system damage that occurs while waiting for a diagnosis can be irreversible and (in some cases) lethal, leading to a sense of a 'ticking time clock' as the patient's condition worsens. It also generally costs more to manage medically fragile patients with advanced disease than patients with early disease. Early diagnosis has clear clinical and economic benefits for all stakeholders yet remains a challenge in rare diseases.

**'Diagnostic odysseys' take a significant toll on psychological health and social/family functioning.** The typical rare disease patient visits an average of 7.3 physicians before receiving a diagnosis.<sup>22</sup> Rare disease patients receive 2-3 misdiagnoses on average, each of which can involve unnecessary and invasive testing and administration of treatments that do not properly target the right disease.<sup>13,23</sup> Medical pilgrimages to the handful of rare disease specialists who can diagnose include complex referral processes, long waits, and travel that is costly and disruptive to school and work.<sup>24,25</sup> For patients and caregivers, after enduring years of uncertainty, receiving a diagnosis has been described as feeling akin to winning the lottery.<sup>26</sup>

**Recent advances in diagnostics and health informatics have the potential to shorten time to diagnosis significantly but need to be accessible to patients.** Despite the availability of effective diagnostic testing which has the potential to prevent or delay premature death for some patients<sup>14,27,28</sup> it often takes 10 years or more of a costly diagnostic odyssey to identify a genetic etiology due in part to the need for additional physician education around rare diseases and timely access to appropriate testing (see Exhibit 1).<sup>23,29-40</sup> This is increasingly being recognized at a global level by groups such as the UN NGO Committee for Rare Diseases, the European Union Commission, the National Plans for Rare Disease in EU Countries and APEC, with policy recommendations centered around improving diagnostic potential, reducing barriers to test use in rare disease, and removing barriers both within and across geographies to enhance medical information sharing.<sup>41</sup>

**Newborn and family screening programs help avoid diagnostic odysseys.** Newborn Screening (NBS) detects rare, genetic conditions at birth. Abnormal test results generally trigger a confirmatory test and potentially lead to a reduced timeline to appropriate and accurate diagnosis and access to life-saving treatments. The Recommended Uniform Screening Panel (RUSP) includes 35 core conditions and another 26 secondary conditions. However, states ultimately determine what disorders their NBS program will screen for.<sup>42</sup> States can be slow to adopt conditions listed on the RUSP as there is wide interstate variability (numbers of conditions being screened for ranges from 26 to 70).<sup>43</sup> While NBS programs are growing in scope, states can be reluctant to expand programs because of concerns over cost-effectiveness and the states' ability to provide appropriate follow-up care.<sup>44</sup> However, implementation costs are offset by healthcare savings related to earlier detection.<sup>45</sup> Newborn screening has saved tens of thousands of lives, yet more than half of states fail to meet federal recommendations.<sup>46</sup> Federally-recommended newborn screening tests should become widely available in all jurisdictions in a timely manner.

A genetic disease diagnosis also provides information about the risk of other family members also having the disease. Family screening can identify patients before the disease progresses but is sometimes not offered in the absence of symptoms. Family members have a right to know if they are at higher risk, so that they can be monitored and treated in a timely manner. For serious rare genetic diseases, we are increasingly able to provide more definitive information and guidance beyond 'it runs in the family.'

**Whole genome or exome sequencing can test for hundreds of genetic mutations at one time, and has the potential to reduce substantially the duration of the diagnostic odyssey and improve cost-efficiency compared to single-gene tests.**<sup>30</sup> Whole exome testing has also been shown to provide more conclusive diagnoses for some diseases than single-gene testing, because it simultaneously 'rules in' and 'rules out' multiple diseases.<sup>47</sup> The recent introduction of multi-panel gene and whole-exome/-genome testing resulted in challenges in payer coverage of diagnostic testing, stemming from a range of issues including perceptions around cost and concerns about test validation, which in turn has discouraged providers from utilizing such testing.<sup>48</sup>

Some US commercial payers have now begun to cover whole genome/exome testing, recognizing the benefits in specific instances where either (a) no/few alternative testing options are available or (b) broad testing provides advantages to sequential/multiple single marker testing or help reduce likelihood of unnecessary downstream treatments or procedures by helping to render a more informed diagnosis.<sup>49,50</sup> However, many payers, including the Centers for Medicare and Medicaid Services which provide health coverage for low income and disabled patients, do not cover these tests for potentially eligible rare disease patients.<sup>51</sup> While whole genome/exome testing may be viewed a costly vs. single marker tests, there is actually a growing body of evidence indicating that implementing Whole Genome Sequencing may decrease overall cost and improved accuracy of care for diagnostic evaluations of medically complex children.<sup>31,36,40,52,53</sup> Recent proposed US legislation such as, "Ending the Diagnostic Odyssey Act", which allows states to conduct Whole Genome Sequencing testing for children on Medicaid with a suspected genetic condition<sup>54,55</sup> is an example of a positive step toward a broader solution for shortening the diagnostic odyssey for rare disease patients.

## Exhibit 1: Patient Diagnostic Odyssey Experiences

**Example 1:** My child's disease was not diagnosed for several years. This is after experiencing numerous hospitalizations for prolonged seizure activity and profound developmental delay. As a toddler, I watched her body be ravished by an uncontrolled seizure. My daughter was never the same after that event. And still no answers came to 'why' was she seizing? She left that hospitalization with significant brain damage, paralysis, no vocabulary, the inability to feed herself, sit up, crawl or walk.

Today, she has a diagnosis, sees 10 different specialists, receives in home therapy 5 days a week and takes 14 doses of 7 different medications to treat the various manifestations of her primary disease. She also has been diagnosed with four additional co-morbidities; which means she will require lifelong assisted care. I live with the uncertainty of 'what if?'

What would my daughter's life look like if her disease had been diagnosed early, and appropriate treatment had been started so she never experienced uncontrolled seizures that took over her developing brain and body.

**Example 2:** Our son's slow progression wasn't a huge concern to us as we attributed it to him being premature. Once the head drops started, life rapidly changed. He seemed to almost immediately forget how to play, say any words and interact with us. We have just passed a year since we received his rare diagnosis, and his symptoms have only worsened, with no answers as to why he has them and he has not responded to medications. His personality has started to come back, and he is just the sweetest little 2-year-old you'll ever know. The unknowns for what his future holds is the most difficult part.

Key actions to secure timely and sustainable access to diagnostic testing that rapidly informs appropriate patient care and treatments

1

Develop appropriate safety net procedures to help patients, caregivers and physicians reduce or avoid the diagnostic odyssey so common in rare disease.



2

Support broader access to whole genome or whole exome testing for rare disease patients where available and/or ensure access to the best available test that can reduce or avoid the diagnostic odyssey in rare disease.



3

Ensure appropriate education of general practitioners and specialists that are most likely to initially see patients with rare disease.



4

Support access to appropriate decision support tools (e.g., machine learning enabled diagnostic platforms) as they become available, given the complexity of characterizing rare diseases.



## 2. Timely and sustainable access to the highest quality care and most effective treatments that address underlying disease or key symptoms

At the end of a challenging diagnostic odyssey, rare disease patients and caregivers can also be faced with another set of hurdles when they try to access treatments and other essential services. A recent publication by the National Alliance for Caregiving, in collaboration with Global Genes, indicated that approximately one third of caregivers indicated that accessing rare disease therapies for patients they care for was difficult to very difficult.<sup>56</sup> The following are the key factors associated with rare disease patient access to quality care and highlight key gaps that remain to be addressed.

**Despite often severe unmet need, rare disease patients do not always have access to the most effective available treatments for their disease. Access decisions for rare disease should be driven by patient-centric requirements and look beyond consideration of price.** Despite recent clinical advancements in rare disease care, patients face real obstacles in accessing these transformative therapies.<sup>57,58</sup> A recent study of caregivers indicated that only 18% of rare disease patients are receiving a medication that treats the underlying cause of their disease.<sup>56</sup> Given the severe unmet need associated with many rare diseases, patients should have the expectation of access to therapies that, at best, treat or cure their underlying disease or, at worst, specifically target the symptoms of the rare disease and/or yield appropriate improvement in symptomatic outcomes and quality of life.

Payer coverage and patient access can be compromised as a result of these challenges. A recent joint study by the National Association of Managed Care Physicians (NAMCP) and Alliance for Regenerative Medicine (ARM) reported that only half of commercial health plans had issued coverage policies for the five marketed cell and gene therapies for rare disease and oncology indications two years after they had become available.<sup>59</sup> **Exhibit 2** characterizes a patient experience and implications when patients do not have access to the highest quality therapy available.

### **Exhibit 2: Patient Impact of Not Supporting Rare Disease Patient Access to the Highest Quality Therapy Available**

**Example 1:** The “waiting game” we are asked to play in order to access effective therapy is debilitating. We have to watch our loved one experience pain, seizures, loss of function or disease regression. And often, while we have no explanation for why an essential therapy is being held from us. This reality causes my wife and I to have greater mistrust of the entire health care system; which is where we should feel the safest when navigating life with a rare disease.

The real risk here, is that in a system not built to address the special considerations of rare disease, many patients can slip through the cracks if our processes do not appropriately recognize what transformative means on an individual disease basis.<sup>60</sup> While curative or near curative therapies are becoming available on an increasing basis, such therapies are currently the extreme exception rather than the rule. We must take caution that access approaches are not distorted by the profound ripple effect that occurs when such therapies emerge and ensure that our system can provide rare disease patients with the best therapies available for that particular disease without compromising or inadvertently denying patient access.

**Lack of adequate coding describing many rare diseases can limit or preclude access to appropriate treatments and other basic services and resources associated with routine care.**

Health care services in many countries are reimbursed on the basis of International Classification of Diseases, 9th Revision (ICD-9) or ICD-10 codes. Of the approximately 5,500 – 9,000 rare diseases, only 500 have a specific ICD diagnosis code.<sup>61,62</sup> In the absence of a specific code, the treating physicians' option is often to use codes that describe symptoms only, but frequently not the underlying disease. This means the burden of making a case for each care step and decision is more complex for rare disease patients that cannot be categorized under a disease-specific code. It also means that, in the absence of such coding, rare disease patients risk not receiving needed treatments targeted to their disease, as well as barriers accessing other routine and needed care (e.g., transportation services, occupational therapy, speech therapy) or equipment (e.g., appropriate wheelchairs, a hospital bed, an in-home lift for transition from the bed to a chair or wheelchair). In the absence of appropriate coding, the family may also have to pay for services that other patients with appropriate coding can access out-of-pocket or take extreme financial measures (e.g., fundraising, seeking charitable foundation grants) to ensure even basic care needs are met (see **Exhibit 3**).

**Exhibit 3: Impact of Lack of Appropriate Coding on Access to Needed Health Services**

**Example 1:** I had a typical healthy pregnancy and birth. I took my baby home and had no concerns for her health. Suddenly, at 9 weeks old she started having symptoms – I knew something was wrong. We took her to her pediatrician and got a referral to neurology. She was admitted for an EEG and was diagnosed with infantile spasms. Overnight, my world became flipped upside down. We struggled to get control. My daughter failed two therapies; and then we found a medication that worked for 2 weeks. In the next 2 years, we gained control and she relapsed 3 different times. Her development stalled. She was diagnosed with a rare genetic disorder, but it did not fit into the definitions in the system. To help her manage her swallow, we had to have a feeding tube placed. I had to leave my job as a teacher to stay home with her. Our insurance has a \$5,000 deductible and even after we meet our deductible they do not pay for her prescription formula (keto cal) or more than 12 combined speech, PT, and OT therapy visits a year.

Of note, there are planned updates to the ICD coding system expected by 2022, with the potential to include over 5,000 rare diseases. In addition to ensuring that rare disease patients can receive appropriate care without unnecessary access hurdles to add to their care burden, these updates will also better enable us to research, understand and improve rare disease patient care for specific diseases by improving the ability to conduct research, define care pathways, and identify clinical and economic efficiencies in rare disease care.<sup>63</sup>

**Variation in insurance coverage for rare diseases can obstruct patients from receiving life-altering therapies.**

It is well documented that cost and utilization mechanisms (e.g., copayments, coinsurance, prior authorization, step therapy and specialty tiers) used to manage rare disease treatment options can vary widely across payers.<sup>64</sup> This inconsistency may lead to access to care challenges in the event a patient transitions from one health plan to another. Transition from one health plan to another can also impact the patient-physician relationship, limiting or precluding the ability of the physician (who may be an expert in a Center of Excellence for rare disease) to provide care and treatment if said provider is not included in the new plan's network. Such transition periods, particularly if there are access changes,

can place patients at risk for potentially irreversible disease progression, loss in function, or even death.<sup>65</sup> Managed care mechanisms that are critical to broader population management, e.g., step-therapy, tiered access, can also be challenging in rare disease scenarios when the limit or preclude access to more effective treatment options. These gaps in access also increase the burden to both patients and caregivers who are often already struggling to navigate an arguably overly complex US healthcare system (see **Exhibit 4**).

In recent years, patient-centric and other initiatives have been launched by patients and patient advocates to address the impact of this variability and ensure an appropriate safety net for rare disease patients.<sup>66</sup> However, given the growing number of rare disease treatments and concerns about expanding budgetary impact and cost of individual therapies, public and private payers may instead increase access restrictions and hurdles for rare disease patients.

#### **Exhibit 4: Impact of Health Plan Coverage Variability on the Patient Experience**

**Example 1:** We experienced access issues as a result of shipping and delivery shipment. If there is a logistical delay or payment/ coverage change, and the delivery of the medication is changed – we are often not notified until it is too late. For my loved one, the absence of one dose of medication can mean life or death. Pharmacies, insurers, and delivery services need to understand the catastrophic effects of their schedule lapses or customer service ‘issues.’

**Example 2:** One access issue can arise when your medication is switched from a brand form of the medication to the generic. I was not notified on my call of the change; it just arrived at my house that way. If it had been brought to my attention, we would not have proceeded with the order. At that time, my son was having aggressive behaviors from a side effect of another medication, and we were in the process of a medication wean. It was imperative that we kept his other medications stable. To get all the medication we needed, it took over 3 hours, multiple phone calls and escalation to pharmacy management.

#### **Non-conventional channels for healthcare delivery, like telehealth and specialty care pharmacies, are appropriate for rare disease patients and can help ensure equitable delivery of care and reduce care burden.**

Local care models often applied to broad diseases can be unsuitable or even infeasible for rare disease patients that may have to travel long distances, sometimes with specialized equipment such as respirators, to see specialists at rare disease Centers of Excellence.<sup>67</sup>

Telehealth is an under-leveraged tool to address the challenges of wide geographic dispersion, travel burden and access to specialty care experts for rare disease patients.<sup>20,68</sup> Telehealth may also provide economic efficiencies compared to traditional in-person care when leveraged alongside conventional approaches appropriately.<sup>69</sup> While many states mandate that Medicaid and private insurers provide coverage for telehealth to the same extent as coverage for in-person / local care, the reality is that payer and access trends in telehealth vary widely with no two states defining, reimbursing, or regulating telehealth in the same way.<sup>70-73</sup> Such variability can also be addressed by managed care policies that seek to reduce variability and better align care approaches to the specific needs of rare disease patients. Lessons from COVID-19 suggest that telehealth can be relatively easy and vital solution for supporting patients with special system

access considerations or risk factors. Further ensuring this access for rare disease patients to address avoidable access barriers is an extension of best practices flowing from the rapid healthcare streamlining practiced during COVID-19.

Similarly, specialty pharmacies have evolved in recent years to help address the requirements associated with logistics and handling of complex biological products (e.g., that must be stored at specific temperatures), as well as complex supply chain scenarios that are difficult to run profitably under conventional pharmacy models. In general, 87% of orphan drug spending falls within specialty drugs, which makes specialty pharmacy a key player in provision of rare disease therapies (depending on whether access is managed via medical or pharmacy benefit – in some cases a PBM or direct hospital pharmacy purchase is involved).<sup>13,74</sup> As specialty pharmacy models have expanded, payer cost management of this distribution channel has also increased. Rare disease patients may find themselves lost in the constantly evolving and complicated process for specialty pharmacy prior-authorizations (e.g., constantly documenting that they still have a genetically-inherited disease), detailed and heterogeneous access pathways that span providers, private and public insurance entities involved in the chain of care, and often confusing and uncertain paper trail and authorization process involved in routine specialty pharmacy access. Given the burden of managing many rare diseases, solutions to streamline and de-complicate specialty pharmacy access should also be an expectation of rare disease care.

The variability highlighted herein, while understandably imbedded in operating principles that services the collective healthcare needs, enable many rare disease patients, their families and caregivers to get lost in a system that was not built with rare disease populations specifically in mind. Efforts to close these gaps can help ensure equity and inclusion of care access for such vulnerable patient populations.

## Key actions to ensure timely and sustainable access to the highest quality care and most effective treatments that address underlying disease or key symptoms include

1

Put the patient first. Ensure that evidence and access approaches are appropriately defined for the disease and that rare disease patients have access to the best available care that addresses the underlying disease and/or key symptoms.



2

Modernize our coding processes to ensure that rare disease patients have a safe harbor, do not fall through the cracks in the system and are not inequitably denied basic care and services.



3

Identify common avoidable care barriers or inefficiencies associated with rare disease care and rethink/align care approaches appropriate to this patient population with significant and special care needs (e.g., reduction of access barriers to solutions like telehealth or specialty pharmacies).



4

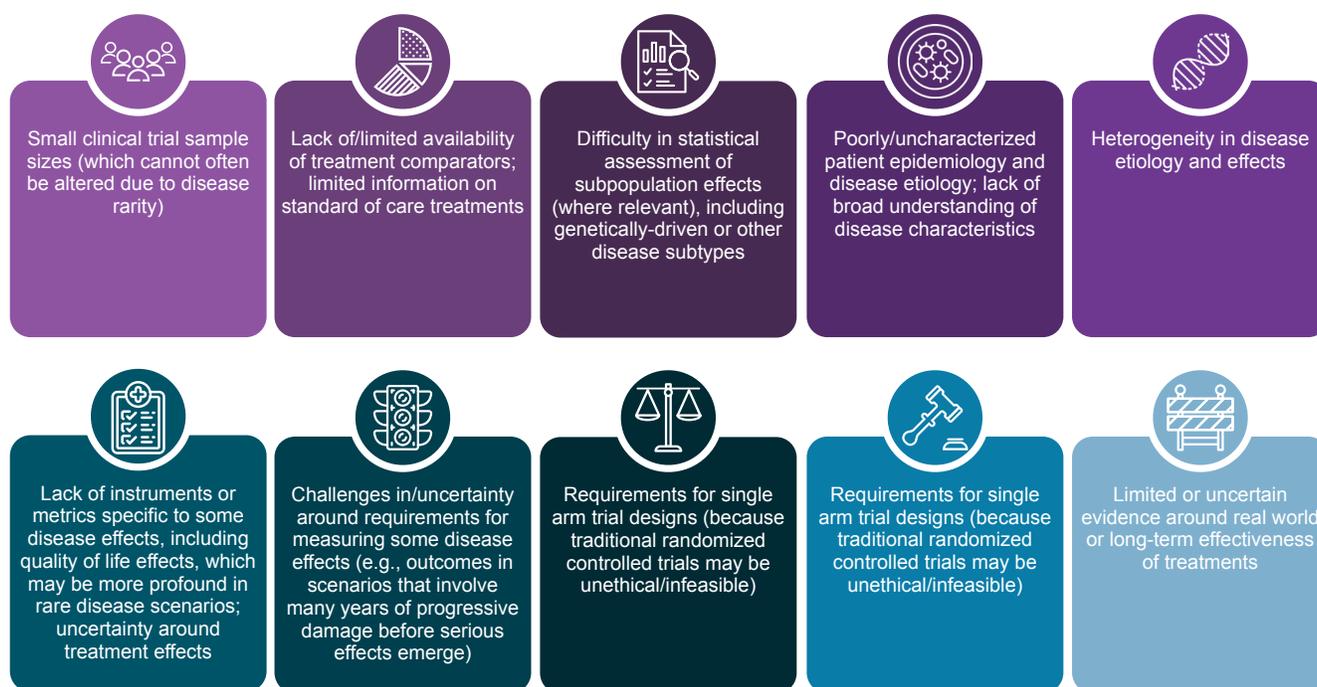
While a functional healthcare system must consider financial impact and overall affordability, it is imperative to reconsider patient-centric value in the context of rare disease and ensure that therapy pricing is inappropriately the core criterion in determining access.



### 3. Value assessment processes that provide timely and sustainable access to current and future therapies where patient-centric benefit is the deciding factor

Clinical and economic value assessment processes that are standard in virtually all payer environments were initially developed around evaluation of treatments targeted often to common disease scenarios, well before truly transformative rare disease treatments began to emerge. There has been significant debate over the past several years that our value assessment processes, often referred to as health technology assessment (HTA), do not appropriately address the special and in some cases unique aspects of rare diseases.

#### Exhibit 5: Common Clinical Value Demonstration Challenges for Rare Disease



A range of clinical value assessment issues have been noted as key challenges. These challenges in clinical evidence development, coupled with the higher cost of therapies required to cover developer return on investment (ROI) and increasing number of rare disease therapies coming to market, have resulted in challenges in HTA and pricing acceptance for some rare disease therapies. The following highlights key HTA challenges for rare disease that should be addressed to achieve this patient guiding principle.

#### Evaluating rare disease value via ‘single yardstick’ approaches more suitable for common diseases may limit or preclude access for patients with substantial unmet need/limited or no treatment solutions. It

has been well documented that payer and health technology assessment bodies groups do not always consider the special evidentiary considerations that accompany the rare disease patient experience.<sup>75-77</sup> These include development of more clear, consistent and realistic expectations around the study design challenges noted above, but also include other considerations described as follows.

While it may be arguably impossible from a practical perspective to have a unique HTA process for each of the thousands of rare diseases, the specific criteria and/or weighting of them can be considered and calibrated to the specific disease.<sup>78,79</sup> This avoids unintended consequences such as precluding access because the full range patient-centric impacts do not fit neatly into common evaluation approaches. It is also possible to consider different value drivers associated with common rare disease archetypes, (e.g., early/fast fatal, stage-based, flare-based, continuously progressing) and calibrate decision criteria accordingly. Achieving the appropriate of specificity and recognition of value drivers in rare disease is critical to ensure appropriate patient focus and access.<sup>80-82</sup>

In the coming years, US health care decision makers will be challenged (and have the opportunity to) create a more focused framework for evaluating rare disease therapies as the number of therapies and their cost impact expands. Lessons from ex-US experiences may provide key insights into models that best fit our complex and disperse US public and private health system. Lack of clarity and limits on early engagement are of poor consolation to rare disease patients that see promising products hamstrung by the system at launch.

**Health economic approaches and acceptance thresholds may under-recognize the value of new treatments.** The heterogeneity and uncertainty around HTA requirements for clinical evidence also translates into challenges in assessment of economic impact. This is particularly true in scenarios where patient-centric and caregiver impacts in rare disease may not fit into economic impact assessments across or within markets (either cost-effectiveness or budget impact). Some stakeholders have proposed that multi-criteria decision approaches with flexibility to dial or weight the components of value according to the individual disease.<sup>75,80,83</sup>

Others have also suggested that economic acceptance thresholds (e.g., cost per quality adjusted life year (QALY)) may inadvertently adversely impact rare disease because they were not built with rare disease in mind. In the US, patient organizations and other stakeholders have questioned whether the processes of Institute for Clinical and Economic Review (ICER) adequately consider rare disease assessment appropriately, citing that 'single yardstick' methods set rare diseases up for unfavorable reviews.<sup>84,85</sup> The National Institute of Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) are examples of global HTA bodies that have begun to adjust value assessment processes to better account for the unique considerations associated with rare disease. However, other organizations and collaborations highlight that there are still significant strides needed to achieve truly patient-centric rare disease evaluation.<sup>79-81,86</sup>

As the rare disease area continues to grow, with expanding patient and economic impact, it will be important to ensure value assessment processes in the US adequately consider and adopt economic modeling considerations appropriate for rare disease.

**HTA processes are not designed with patient-centricity as a driving factor.** How value is specifically defined in a rare disease can be profoundly informed by patients and their families living with disease. This can be accomplished via a variety of channels and tailored to the complexity and evidence questions driving decisions in a specific rare disease, including traditional PRO research, patient preference assessment, social media research and including patients/caregivers/patient advocates directly in decision processes.

**Most payers have not invested in a specialized sub-body with sufficient focus primarily or exclusively in rare disease/niche populations, even though rare disease development accounts for over a third of R&D spend today.<sup>87</sup>**

In the US, in both the commercial and public payer segment, specialized HTA units focused on rare disease remain the exception rather than the rule for a number of reasons. Without a specialized focus on rare disease / niche populations, driven by experts that truly understand the dynamics of rare disease care, it can be challenging to ensure that decisions are consistent and appropriate for this highly vulnerable patient population. Among leading US private payers, 67% have voiced concerns over the growing rare disease pipeline, but less than 20% have developed specific strategies in place for rare disease. Among Health Technology Assessment bodies that do have a strategy in place, a majority indicate that they remain unsure about appropriate clinical and economic assessment tools for evaluating rare disease therapies.<sup>79,88</sup>

While HTA bodies and payers do not have infinite resources to address every disease or new technology type, outside of the US, several HTA agencies are taking steps to establish more tailored approaches for evaluating rare disease therapies.<sup>89</sup> Approaches include adjusting traditional cost-effectiveness methods or developing novel approaches that do not explicitly consider cost-effectiveness.<sup>90</sup> Acknowledging that evaluating rare disease treatments requires a different approach, NICE launched the Highly Specialized Technologies Unit specifically to address the vulnerability of small patient populations with limited treatment options. HST evaluations aim to balance value, access, and affordability against uncertainties around clinical efficacy.<sup>91</sup> Reimbursement decisions are based on a broader set of value and decision criteria including, nature of the condition, therapeutic impact, quality-of-life impact on patients and caregivers against a modified acceptance threshold, lower discount rates, and of the data collection challenges associated with rare disease.<sup>92</sup>

**Rare disease therapies face multiple development challenges and require incentivization for appropriate medical innovation.** Recent research found that the average rare disease therapy takes nearly four years longer to develop compared to non-rare therapies (11.8 years vs 8 years) at substantial cost and requiring higher pricing to ensure appropriate ROI.<sup>93</sup> These factors suggest that we need to carefully consider the incentive structure surrounding development of novel rare disease treatments.

To address incentives, the US and EU markets have introduced tax initiatives to encourage the development of orphan/rare products. For example, since its passage by the FDA in 1983, the Orphan Drug Act (ODA) provides incentives to drug manufacturers that include clinical research grants, waived PDUFA fees, research and development tax credits for and a greater period of market exclusivity.<sup>94-96</sup>

This is a step in the right direction for empowering rare disease research. As the healthcare system continues to evolve, it is critical that incentives for orphan drug development be maintained given that 95% of rare diseases currently have no treatment options and rare diseases impact approximately 10% of the US population.<sup>12</sup>

The following overviews key actions that should be considered to ensure that HTA and access processes adequately consider and are updated for rare diseases.

## Key actions to ensure appropriate HTA and value assessment processes specific to rare disease

- 1** Integrate patient and caregiver perspectives into key stages of clinical development, health technology assessment and pricing decision flow 
- 2** Develop a balanced set of evidentiary and decision criteria for health technology assessment that truly take into account disease uniqueness and patient-centric impacts including quality of life, where cost is not the deciding factor 
- 3** Ensure that assessment processes appropriately take into consideration rare disease archetype and scope and nature of effects versus adopting a “single yardstick’ approach for value estimation 
- 4** Given that the challenges with clinical development are well characterized, develop core metrics and/or expectations for clinical and economic value demonstration that do not lose individual and variable effects of a particular disease 
- 5** Ensure that health technology assessment processes either involve a specialized evaluation group and/or appropriate training in rare disease evidence evaluation issues 
- 6** Develop economic requirements for rare disease that appropriately take into account special decision criteria/factors appropriate to rare disease 
- 7** Ensure funding and incentives continue to support development of successful rare disease treatment and patient management solutions. 

### 1. Fulfilling quality of life while lessening the disease burden for both patients and caregivers

Quality of life and patient-centric impacts of disease is increasingly becoming a key priority globally. Over the past 10-15 years, the FDA has increasingly encouraged inclusion of the patient perspective in drug development. This has grown from trying to better understand the patient experience to required focus on patient-centered outcomes, including under the more recent patient-focused drug development section of the 21st Century Cures Act.<sup>97</sup> While payers acknowledge the importance of patient-centric data in decision making around access to new treatments, there is also significant variability both across and within markets regarding how and to what extent this information is weighed versus other outcomes.<sup>98-100</sup> The following describes key considerations and challenges in ensuring the highest quality of life for rare disease patients.

**For patients suffering from a rare disease, quality of life is often significantly lower compared to patients who are otherwise healthy or have more common diseases.**<sup>101,102</sup> Recent studies indicate that rare disease patient quality of life, as measured by the Health Utilities Index (HUI) (which allows for comparison to individual in perfect health), is significantly lower when compared to patients with more common diseases like arthritis (24%

lower), HIV (41% lower), coronary heart disease (44% lower) and stroke (46% lower).<sup>23</sup> For the many rare disease patients for whom there is no available treatment, quality of life is substantially worse (58% lower in the US and 60% lower in the UK) than rare disease patients with available treatment.<sup>22</sup> In addition to functional considerations, other factors such as psychological well-being, coping, and perception of illness factors are also more profound in rare disease.<sup>100</sup> **Exhibit 5** below provides some key examples of the profundity and impact of rare diseases on patient quality of life.

### **Exhibit 5: Example of Patient-centric Effects Associated with Rare Disease**

**Example 1:** Our son was diagnosed with a rare disease at 3 months old. We deal with uncontrolled symptoms on an almost daily basis. He has been hospitalized more times than we can count. The longest being 38 days. He ended up needing a tracheotomy a year ago. We have no nursing available near us. This means we take turns sleeping by him in the event he needs help in the night. His health limits a lot of things we do as a family and being able to go out together.

Patients should expect support to achieve significantly improved quality of life (QoL), where possible. At the HTA- and payer-level, this means ensuring that QoL is given sufficient weight in decision processes in comparison to harder morbidity and mortality outcomes and variability in acceptance of QoL is diminished by establishment of clearer expectations.<sup>103,104</sup> It also means consideration of whether QoL metrics are sufficiently patient-centered and aligned with rare disease patient realities.<sup>105</sup> From a daily care perspective, we need to also reconsider the scope and nature of support services that can improve patient QOL, including but not limited to access to education/information (including access to biomedical publications), special logistic and support services (including in-home), psychosocial support, and ability to plug into a broader network of community and regional support services aligned to the needs of rare disease patients.<sup>60,106-110</sup>

**Caring for a rare disease patient can inflict substantial health and financial burdens on families and caregivers.** Caring for someone with a rare disease is often a full-time job, with some patients requiring 'around the clock' care at their home. Approximately 75% of rare disease caregivers characterizing their care burden as 'high' and sacrifice much, including often their employment and financial stability, social life and relationships, and their own health. Around one third of rare disease caregivers do not receive outside assistance and 70% report that at least one caregiver family member must stop their professional lives to care for their family member's rare disease.<sup>110</sup> Given that nearly 10% of the population has a rare disease, direct and indirect health and economic impacts are likely significantly underappreciated. **Exhibit 6** provides some key examples of the impact that care for a family member with rare disease can have on caregivers.

## Exhibit 6: Example of Caregiver Impacts Associated with Rare Disease Care

**Example 1:** While she proves she is stronger than the diagnosis, she's still randomly affected by symptoms of the rare disease with no medical plan in place to help her as nothing has yet. Her multiple hospital stays and visits including no one near us accepting her for daycare, we have lost our home and my husband has lost his job. We are currently homeless and staying with friends/family as welcomed between hospital visits. It's been a difficult road. She is growing daily and in multiple therapies, thankfully impressing everyone! It's a constant struggle, especially with holidays upon us. But we are blessed with one another.

**Example 2:** Her rare disease has impacted our family so much between her dad quitting his job because she couldn't attend daycare because of her medical care. As her mother, I am working double to try to keep us financially afloat, plus trying to juggle our other child, and helping our family understand why she has this disease. She is behind in development a lot. We make too much money to get state assistance for her therapies that she desperately needs.

**Example 3:** My daughter actually has been given a preliminary diagnosis of one rare disease and has since been diagnosed with another rare disease. It has been hard; we live in a remote area and have to fly once a month to see specialists because there are none in our hometown. She requires medication four times a day and feeds via g-tube, her needs are so complex that I feel uncomfortable sending her to daycare which is unfortunate because I was planning on starting work again soon. I spent over a month total now in the hospital with her, away from her older brother and father.

In rare disease, caregiver burden is often not considered. For example, caregivers for cystic fibrosis, lysosomal storage disorders (e.g., Fabry and Pompe disease), and Sanfilippo syndrome have been documented as having significant, long-term economic burden and decline in well-being, including increased rates of clinical depression, job turnover and forgone career opportunities.<sup>111-113</sup> By documenting the impact of rare disease on caregivers, the need for appropriate support services can be better characterized and solutions identified. Caregiver support services may include assistance navigating extremely complex reimbursement scenarios, access to medical experts, patient and caregiver education, and other services. Understanding caregiver impact may also shed light on the broader clinical and financial halo effect of supporting a family member with a rare disease.

### Key actions to fulfilling quality of life while lessening the disease burden for both patients and caregivers

1

- Recalibrate evidence expectations in rare disease to ensure that quality of life and other patient-centric considerations are appropriately taken into account/weighted as being equally important to harder clinical outcomes (e.g., morbidity, mortality).
- This would include emphasis in clinical trials, outcomes and patient-centric research, as well as appropriate emphasis and weighting at the regulatory and health technology assessment/payer levels.



2

- Quality of life impacts should be truly patient-centric for a specific rare disease and involve patient and caregiver input to ensure they adequately capture the patient condition



3

- Given the substantial family and caregiver burden in rare disease, including both health and economic impacts, stakeholders should seek to better understand impacts on caregivers as part of a comprehensive evidence package.



## 5. Standards of care that reflect acceptance of each patient's uniqueness and equality for all patients regardless of disease rarity

Rare diseases are arguably under-represented as a public health priority. While from an individual disease perspective, rare disease patients can be considered a minority, overall, they comprise a substantial component of the total population. Despite growing awareness of rare diseases over the past decade, there remain inequities in availability of treatment and care, with some patients having to fight seemingly every step of the way to obtain care for severe or even tragic disease scenarios. This can be particularly true when an individual disease is not recognized by the system.

There is a growing need to prioritize rare disease as a category. As noted, this prioritization should ideally balance consideration of the group against the need to appropriately address the uniqueness of a specific rare disease and offer solutions accordingly. While rare disease patients do have unique needs, they should equitably expect the same rights to care prioritization as non-rare disease scenarios, particularly given the substantial aggregate patient and system impact.

The following highlights key considerations in striking this balance.

**Rare disease matters. It is imperative to consider rare disease a key health priority, while at the same time ensuring that the individuality of rare disease is understood and supported in terms of achieving optimal patient-centric outcomes.** Rare disease patients are entering a healthcare system that is not built to accommodate the nuances of living with a rare disease. Considering rare disease, in the aggregate, as a priority disease in a manner that does not inadvertently diminish access can help ensure solutions aligned to the special considerations and profound unmet need of this significant segment of the US population.

**Rare diseases often have heterogenous symptoms and variation in genetic cause, making it challenging to apply a single treatment paradigm from one patient to the next.** There is a common misconception that patients with the same rare disease can be treated in the same way, whereas in reality treatment strategies can vary markedly from individual to individual.<sup>114-116</sup> This means that rare disease clinical practice approaches and guidance must preserve sufficient physician latitude to treat the patient according to their needs, versus applying a "one size fits all" approach that may be reasonable for other diseases.

**It can be difficult for rare disease patients to find healthcare professionals with adequate rare disease experience to provide the best quality care.** Rare diseases, by nature, can be complex for a number of reasons, including limited understanding of the biological underpinnings of some diseases, lack of ideal treatment options and limited experience.<sup>117</sup> Given the gaps in healthcare for rare disease patients, caregivers are also forced to wear many different hats including roles such as lay expert, advocate, case manager, medical navigator, and parent.<sup>118</sup> Education on rare diseases is also key for optimizing patient outcomes. Solutions may include, but would not be limited to broadening funding for rare disease research, supporting development of evidence and information repositories, ensuring open access to the latest medical research, ensuring easy access to patient communities and rare disease networks where learnings are shared, and supporting provider training in rare disease spanning from diagnosis throughout disease progression (to include front-line general practitioners

and others that may misdiagnose in the absence of clearer guidance on potential for a rare disease to be at the root of confounding signs and symptoms).

The following identifies key actions that will help ensure that standards of care for rare disease both prioritize this disease category and do not miss the level of inter-disease individuality that is required to enable the most patient-centric treatment possible. This balance is also important in addressing basic DEI tenants of patient care.

Key actions to ensuring standards of care that reflect acceptance of each patient's uniqueness and equality for all patients regardless of disease rarity

1

- Ensure that rare disease is a healthcare priority commensurate with its impact on a significant portion of the US and global population, while also ensuring that practical and policy solutions do not diminish or preclude the latitude to address the needs of rare disease patients on an individual basis.



2

- Ensure that practice and policies do not let rare disease patients or their families slip through the cracks in accessing essential services because the healthcare system was not built with rarity in mind.



3

- Support and broaden learning, education and information sharing on rare diseases for all stakeholders. When we know better, we can do better. In this digital age where a world of information is at our fingertips, access to information should no longer be a barrier to achieving the highest quality, patient-centric outcomes possible.



## IV. Conclusions and Next Steps

These Guiding Principles of Rare Disease Care and Patient Access, developed by a multi-stakeholder collaborative, including input from patients and caregivers dealing with rare disease scenarios, highlight five key areas that all stakeholders should agree are basic principles and expectations for rare disease care. Through the lens of these five Principles, areas where progress is being made have been acknowledged and gap areas with significant unmet need have been highlighted, including specific key actions intended to help achieve each Guiding Principle. These actions call out the need, but are not intended to be exhaustive, merely a focus for development of more detailed plans and next steps.

Simply based on the aggregate numbers, rare disease matters. It is clear that rare diseases impact a significant, potentially under-recognized and arguably underserved segment of our US population, with aggregate prevalence that is similar to or exceeds many diseases now considered national health priorities (e.g.,

diabetes, some forms of heart conditions and leading cancers). Not only are rare diseases prevalent enough in the aggregate to warrant a refocus of thinking about this category of disease as a priority, they also arguably have substantial clinical and economic impact on both patients and health systems. This is particularly true in many scenarios where no therapy targeting the underlying disease currently exists.

As rare disease treatment development continues to grow, currently representing around 40% of the development spend, it will be critical to shift our thinking around rare diseases. We must move from today's focus on rare disease as literally thousands of different, potentially unrelated diseases to a grouping of diseases that have (most often) strong genetic origins and very special health considerations. This must be balanced by simultaneously ensuring that diversity, equity and inclusion (DEI) are addressed and accounted for appropriately to address unique disease, patient, and care needs. We must also accept that treatment needs for rare disease are often well beyond most broad or common diseases and adapt our thinking about treatment models to align to the needs of this unique patient group. To ensure that patients are not lost in this shift, however, we must develop, implement and adopt policies that take into consideration the unique aspects and care needs that can be associated with each disease – a set of population solutions with individual touch and care focus. This shift also must come with (a) incentive and delivery models appropriate for rare disease that span all stages of care and (b) recognition that many of the breakthroughs in transformative and potentially curative therapies now occurring in rare disease, have potential to illuminate and open the door for solutions and care efficiencies in more common diseases.

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