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A Transformative Therapy Value Model for Rare Blood Diseases



WHITE PAPER

January 2020

Alliance *for* Regenerative Medicine

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EXECUTIVE SUMMARY

- Cell and gene therapies (CGTs) have the potential to offer durable and perhaps curative therapies to patients, as well as tremendous economic, productivity, and quality of life gains for patients, their caregivers, and society if provided to patients with rare hematologic diseases such as Multiple Myeloma (MM), Sickle Cell Disease (SCD), and Hemophilia A (Hem A).

- Combined, these blood disorders, which may be considered rare or genetic diseases, represent three conditions where new CGT products are likely to directly impact the healthcare costs and the ability of affected individuals to return to productive lives.

- A new Transformative Therapy Value Model (TVM) quantifies the cost savings and productivity gains from CGTs in each therapeutic area, offering a way to more fully examine the value of such life-changing therapies.

- **Access to CGTs for even a modest number of patients with MM, SCD, and Hem A each year can reduce overall disease costs by nearly 23% over a 10-year period. The savings from lowering healthcare costs and raising productivity are considerable, approaching $34 billion by 2029. Of the savings, $31 billion are from a reduction in healthcare costs and $3 billion are from productivity gains.**

- CGTs for MM produce the majority of the savings in both reclaimed healthcare costs and productivity if patients are provided access over 10 years. The savings in SCD and Hem A are reflective of the durable response that genetic therapies offer to dramatically improve the quality of life for the relatively smaller number of patients in those diseases versus MM.

- The value from productivity gains for patients and caregivers can be substantial in the TVM, reclaiming $3 billion of $7.5 billion of lost productivity over a ten-year period.

- A price sensitivity analysis suggests that if CGTs were priced comparable to current gene therapies, savings to the healthcare system would be realized in approximately 5 years.

- The magnitude and timing of savings achieved in the TVM model is driven by eligibility and access to therapy more than pricing and underlying estimates of healthcare costs. Eligibility and access to GCT therapies were conservatively estimated to reflect those of therapies provided at specialized centers.

- This TVM analysis of three hematologic diseases demonstrates the value that CGTs can offer to patients and payers who take a 10-year view at overall costs.

A Transformative Therapy Value Model for Rare Blood Diseases

Background

Advances in molecular biology and genetics are leading to new treatments for rare diseases that require new ways of assessing value. CGTs are directed at the underlying cause of a condition and offer durable,[1] potentially curative, or near-curative benefits. These transformative therapies create challenges for current reimbursement frameworks, as they require significant upfront costs but are expected to provide a lifetime of benefits. The recurring treatment costs of chronically-managed patients can be greatly reduced and even eliminated with a one-time administration or short course of these novel therapies.

As CGTs arrive on the market, payers need new models for assessing their value. These treatments could potentially end the patient's burden of illness, resulting in cost offsets (eliminating or reducing the need for long-term treatment, hospitalizations, and other care) and productivity gains that span a lifetime. Manufacturers incur a high per-patient development cost for these therapies and payers who bear the cost of treatment may not realize the long-term financial benefits due to health plan switching.

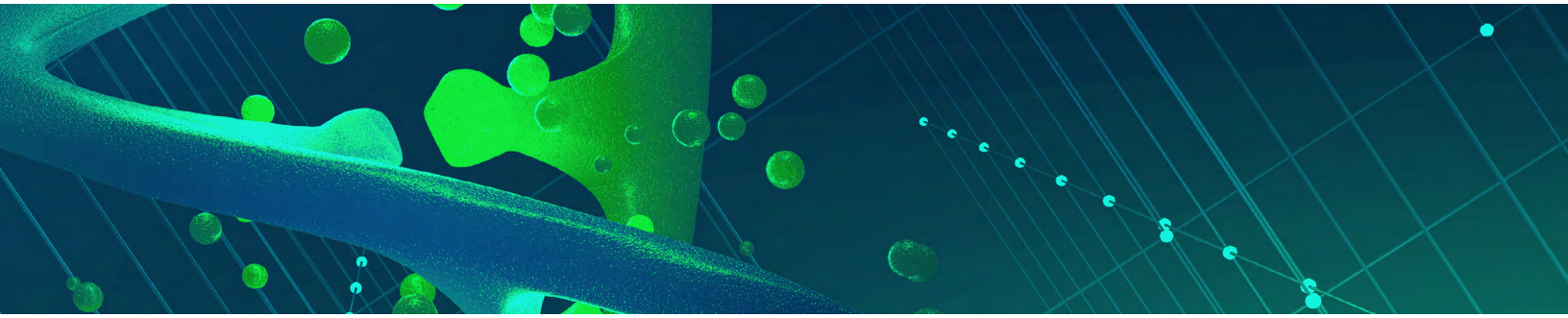
This paper proposes a simplified methodology that frames the economic value of cell and gene therapies in restoring patients to disease-free lives and productivity levels. Savings in medical and non-medical costs are modeled over 10 years for three rare diseases with limited current treatment options and promising CGTs — Multiple Myeloma (MM), Sickle Cell Disease (SCD), and Hemophilia A (Hem A). The decade timeframe is consistent with U.S. Congressional Budget Office measures for major health care policy changes. Over this period, patients given appropriate access to new CGTs can lead healthier, more productive, and potentially disease-free lives, resulting in reduced healthcare utilization.

Hematological Rare Disease Focus: Multiple Myeloma, Sickle Cell Disease, Hemophilia A

There are over 7,000 rare diseases affecting as many as 30 million Americans. The Orphan Drug Act of 1983 defined a rare disease as a condition that affects fewer than 200,000 persons in the United States.[2] Hematological diseases are disorders of the blood and include rare genetic diseases and blood cell cancers. These diseases are difficult to treat as no cure currently exists. They significantly impact the quantity and quality of life and are marked by high health care resource utilization.

Multiple Myeloma (MM) is a blood cancer that affects plasma cells (white blood cells) in the bone marrow and afflicts approximately 170,000 Americans. Sickle Cell Disease (SCD) is a group of inherited red blood cell disorders impacting approximately 100,000 persons and is more common in African Americans. Lastly, hemophilia A (Hem A) is a genetic disorder caused by missing or defective clotting protein, factor VIII, and affects approximately 20,000 Americans (Table 1).[3]

3 SEER, Cancer Database, 2019; CDC, 2019; National Hemophilia Foundation, 2019; Mayo Clinic, 2014; American Journal of Hematology, 2009; JME, 2015; Marwood analysis



Disease	Prevalent population	Incidence	Mortality	Mean survival	Annual health care costs/ patient
Multiple Myeloma (MM)	~170,000	~35,000	~13,000	5 yrs from dx	~$280,000
Sickle Cell Disease (SCD)	~100,000	~1,600	~400	45 yrs	~$30,000
Hemophilia A (Hem A)	~20,000	~240	~200	65 yrs	~$200,000*

Table 1: Epidemiology and costs, annual estimates for 2020 population
**Costs reflect those for patients with severe disease. This is a conservative estimate; a recent study estimates annual treatment costs can be much higher*[4]

These rare inherited blood disorders were selected because their patient populations are more readily identifiable, gene therapy treatments are in late-stage clinical development, and their treatment frequency often impedes patient and caregiver productivity. In addition, these diseases have been well-studied, providing the epidemiology and cost data needed for analysis. More than 600 peer-reviewed studies are available from the last ten years focusing on these diseases and their economic impact.[5]

Burden of Illness and Cost of Care

MM is a progressive, mostly incurable disease. It is associated with a variety of complications, such as anemia, infections, kidney impairment, and bone destruction, that impact therapy choices and quality of life. This cancer primarily affects the elderly, with diagnosis most common at 65-74 years. Patients routinely receive a combination of treatments spanning: targeted therapy drugs, including monoclonal antibodies; biological therapy; chemotherapy; corticosteroids; and radiation therapy. Some patients may be candidates for a stem cell transplant. Healthcare resource use is driven by (1) outpatient services such as the emergency room, physician visits, lab, radiology, and infusion and (2) a rise in hospitalizations due to the increasing use of stem cell transplantation.[6]

Individuals with SCD experience lifelong morbidity and premature mortality as a result of acute and chronic complications stemming from vaso-occlusion. These complications include anemia, infections, stroke, tissue damage, kidney failure, pulmonary hypertension, retinopathy, seizures, chronic pain, and episodes of intense acute pain. More than three-quarters of adults fail to receive hydroxyurea, the only FDA drug approved for adults with the disease.[7]

4 Stacy E. Croteau et al, *Regional Variation and Cost Implications of Prescribed Extended Half-Life Factor Concentrates among U.S. Haemophilia Treatment Centres for Patients with Moderate and Severe Haemophilia*, 25 Haemophilia 668, 673 table 2 (2019) describes annual cost of blood clotting factor therapy for severe hemophilia A patients as between $690,144 and $753,480, covering two to three prophylactic infusions per week.
5 NIH PubMed Database, accessed Sep. 2019
6 Leukemia & Lymphoma Aug 2019; Mayo Clinic Multiple myeloma
7 Rethink Sickle Cell Disease; JAMA Nov 2019; ASH State of Sickle Cell Disease 2018

Children and adolescents comprise 40% of the SCD population, and many do not receive the services needed to prevent complications. Patients and their families experience repeated disease episodes, known as "vaso-occlusive crises," and hospitalizations. In fact, a study of pediatric SCD patients showed that just 1,635 patients accounted for close to 600 hospitalizations per year.[8] The acute and chronic injuries SCD patients experience lead to pain and suffering, increased use of medical services, and functional physical, and cognitive and pyschological impairments. The debilitating disease often disrupts their education, limits their career opportunities, and diminishes their quality of life, resulting in income and productivity loss.

Hemophilia A mainly affects males (X-linked recessive disorder) and can be mild, moderate, or severe. An estimated three-fourths of all hemophilia patients have a severe or moderate form of the disease, with prolonged bleeding following injury, trauma, surgery, or dental procedures. The individual's baseline level of factor VIII determines the frequency, severity of bleeds, and age of symptom onset. The disease does not have a cure, but with education and treatment, affected individuals can live healthy, active lives. Patients with mild or moderate forms of the disease may be treated with factor VIII replacement therapy as needed. In contrast, those with severe hemophilia A may receive factor VIII infusions on a regular basis to prevent bleeding episodes and bleeding complications such as joint damage.[9]

The annual per patient healthcare costs for these rare hematological disorders are high, but vary greatly by disease. Medical costs for a patient with SCD amount to approximately $30,000 annually. Patients with either MM or severe Hem A and their families bear much higher annual health care costs, roughly $200k. Given that health care spending overall has generally outpaced both inflation and economic growth in the last 50 years and that from 2014-2015, health care spending on cancer grew by 5.3% and across all diseases/ conditions by 6.7%, the medical care costs for inherited blood diseases will likely only increase in the future.[10]

Cell and Gene Therapies (CGTs) and Potential Durable Response

In an environment of rising costs and increasing utilization, the durable responses from CGTs offer appreciable value for patients and their caregivers, reducing overall healthcare costs, restoring productivity, and improving quality of life. The frequent, often multiple

Disease	Current treatment	Frequency of treatment	No. of pipeline CGT drugs
MM	Dozens of Tx protocols, typically 3-4 drug combinations	Daily	9
SCD	Antimetabolite, hemoglobin	Daily, 3-9 month courses	4
Hem A	Blood clotting factor replacement	2-3x per week	3

Table 2: Current treatments and future pipeline CGTs for MM, SCD, and Hem A [10]

8 Blood, 2012; Am J Hematology, 2010
9 NORD rare disease database: Hemophilia A; NIH Genetic and Rare Disease Info Center: Hemophilia A; National Hemophilia Foundation
10 California Health Almanac May 2019 Health Care Costs 101

lines of therapies needed by these patients may be reduced or even eliminated by a single administration of a CGT, representing a major shift in treatment options (Table 2).[11]

As regenerative medicine technologies for MM, SCD and Hem A reach the final stages of clinical development and create optimism among patient communities, ensuring access for these populations is a policy priority. Government and commercial payers are beginning to grapple with how to reimburse novel therapies like CGTs. When addressing the issue of chimeric antigen receptor T-cell therapy (CAR-T) reimbursement for relapsed/refractory blood cancer patients, CMS Administrator Seema Verma acknowledged that "technology is moving faster than government policies," noting that it may take the agency until 2022 to create a framework that recognizes the value of these novel, expensive cancer therapies. In the coming years, public and private payers will need to evaluate CGTs and the durable efficacy they promise. This analysis is intended to be used as a starting point for that discussion.

Valuing a Disease-Free Life: Focus on Sickle-Cell

In March 2019, Mr. Lynndrick Holmes, a husband and father, underwent a one-time administration of a new gene therapy for sickle cell disease. By September, he was on the road to being declared "cured." He was not waiting for the declaration, though. He was already preparing for a different kind of life. "Now I have to rebuild myself and figure out what am I actually capable of, because I never got the chance to figure out who I am and what I can really do. Sickle cell was always a hindrance," he said. Current therapies for sickle cell disease and other genetic diseases have limited the ability of clinicians to help patients like Mr. Holmes. Until recently, treatments reduced the symptoms and the potential complications of the diseases without changing the course of the diseases. With the development of CGT treatments for inherited blood disorders growing, offering the potential for durable efficacy, clinicians, payers, and patients are starting to focus on what the world may look like when patients like Mr. Holmes can live symptom- and disease-free.

WBRC, Newscast, September 11, 2019

11 Hemophilia Society, 2019; Clinicaltrials.gov, accessed Oct 1, 2019; UpToDate, 2018; JAMA 2015; National Hemophilia Foundation, 2019

Challenges With Current Value Frameworks

Payers struggle to quantify the value of CGTs and other novel therapies because no universally accepted, standard definition of value exists. Current frameworks used for coverage and payment decisions aggregate clinical outcomes into a single measure of cost effectiveness. This approach has limitations: (1) a focus on late-stage disease and (2) a near-term perspective on cost effectiveness. These limitations overlook the life cycle of cancer therapies, where initial indications are often for advanced stages of cancer. However, as clinical evidence amasses over time, indications can expand and new therapies can become the standard of care in earlier stages.

Existing value frameworks do not adequately account for the likelihood that CGTs given earlier in the patient journey can create long-term savings. CGTs provided upon diagnosis, before a disease advances to a critical stage, or even as a preventive measure, can potentially confer years or decades of disease-free life, resulting in significantly reduced healthcare utilization and improved productivity for patients and caregivers. These therapies are transformative and offer a health trajectory not possible with conventional therapies (Figure 1). Thus, payer medical directors and policy makers can benefit from an additional framework when valuing CGTs that more accurately captures their value over an appropriate time frame.

Assessment of the financial and clinical value associated with CGTs should consider three key questions related to long-term benefits to patients and caregivers:

- Is overall healthcare utilization substantially reduced by CGTs?
- Can productivity lost by the patient and caregiver be regained with CGTs?
- How can payers value a patient's satisfaction with treatment, quality of life, and prolonged lifespan once they are "cured" or "nearly-cured" by CGTs?

A Proposed Value Framework That Includes Productivity

This paper proposes a simple and adaptable framework for addressing these questions and for valuing CGTs in three rare disease populations: MM, SCD, and Hem A. The purpose of this analysis is to quantify the value of CGTs when given to eligible patients over a ten-year window (2020-2029). Value is defined as savings in medical costs and gains in patient and caregiver productivity.

Figure 1 illustrates the framework for this analysis. In part one, the epidemiology, treatment patterns, and costs of care for each of the diseases, including population size, common treatment regimens, and inpatient and outpatient healthcare costs, are identified and quantified over time. In part two, the anticipated costs and potential value of implementing CGTs with durable 10-year effectiveness are estimated. The economic value is modeled for each disease from 2020-2029, comparing total costs against the predicted costs if patients had access to a durable CGT. Medium-term economic value is realized by replacing a substantial percentage of recurring maintenance treatment regimens with restored productivity to both patients and to caregivers.

By examining the cost savings for three different rare diseases, this model illustrates the broad range of value that CGTs with durable responses can create for the healthcare

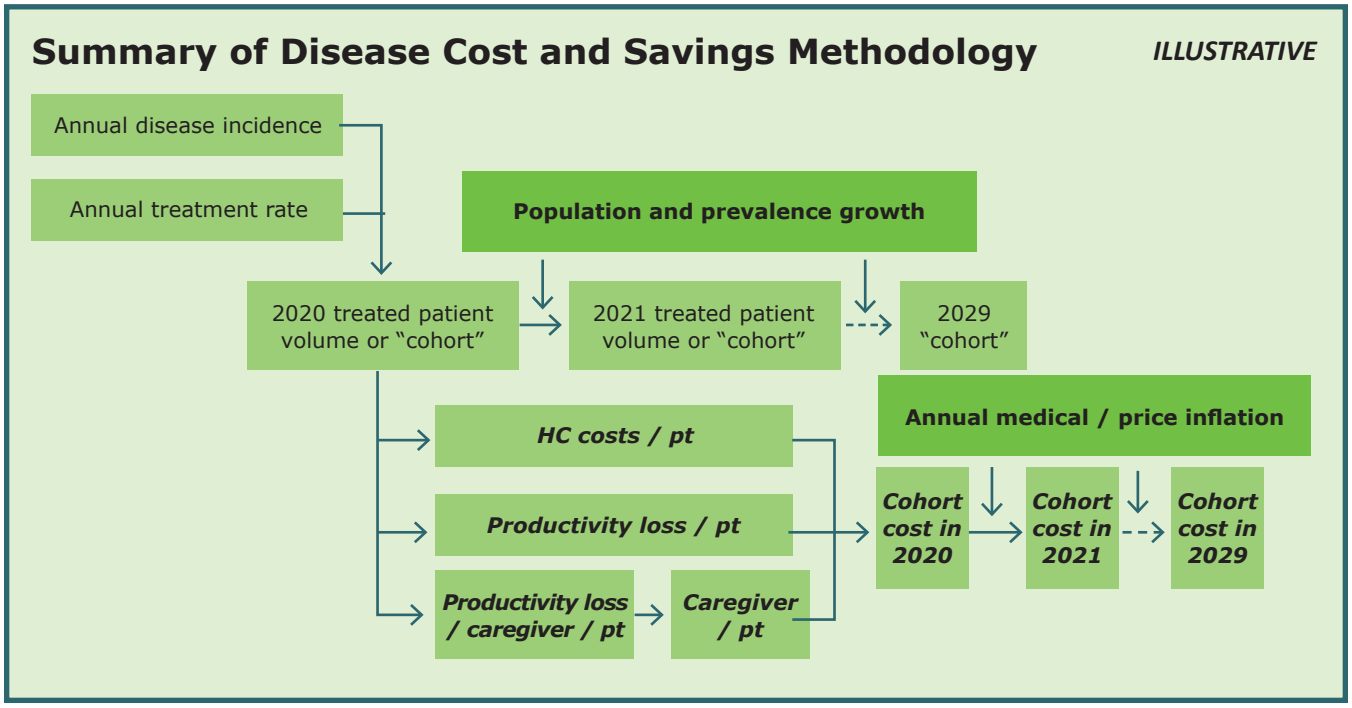


Figure 1: Methodology for calculating disease state costs in model

system in different clinical contexts, if patients are given access. While this analysis looks across the CBO window of 10 years, it is expected that the durability of clinical outcomes will generate significant economic benefits beyond this time frame. CGTs are expected to have a profound impact on patients, caregivers, and the healthcare system over the entire lifetimes of currently debilitated patients. As such, the cost savings modeled are conservative and likely understate their benefits, which would be significantly greater considering average patient lifespans.

Need for a New Value Analysis Framework

This analysis details savings in a Transformative Therapy Value Model (TVM) for rare diseases and contributes a new value framework to the ones already proposed in peer-reviewed literature and by third parties. It aggregates and simplifies population projections, cost projections, and patient impact from available, quantifiable, and verifiable published data. The model estimates populations, costs, and patient productivity in a user-friendly tool.

Several value analysis frameworks have been proposed. For example, the Institute for Clinical and Economic Review (ICER), a non-profit research institute has used spending per "quality-adjusted life year" (QALY) gained to determine value. ICER has completed analyses on multiple treatment regimens for Multiple Myeloma and found that only one available regimen met their threshold for value according to their definition of cost per QALY.[12] However, by focusing on cost per QALY gained, analyses may miss the full benefit that CGTs are expected to provide through a durable therapy. Standard cost-

12 ICER, 2016

effectiveness models do not account for both patient and caregiver QALYs gains in their base case analysis.

Through the TVM, payers can project trends in their own disease populations to assess these durable therapies, adjusting wage productivity for their covered lives. The transparency of the model allows payers to identify the relationship between the efficacy and the value of a new CGT. To maximize utility for a broad group of stakeholders, this analysis was created to be accessible, repeatable and flexible. New models such as this can be used to move the conversation on the value of CGTs forward, with consideration to their broader impact on patients, families, and caregivers.

Modeling Current and Future Costs of Care

Utilizing data from peer-reviewed articles and government sources, the model identifies the specific patient population sizes, growth rates, mortality rates, health care and treatment utilization, treatment eligibility, access, wage data, and inflationary data for each of the disease states. With this data, the model creates a dynamic view of the diseases and current estimated health care spending per incident patient per year. The annual cohort of patients can be followed for 10 years along with their growing costs. The outcomes and costs attributed to the cohort are divided into four key data sets: (1) population data, (2) treatment data, (3) healthcare costs, and (4) non-healthcare costs (Table 3).

Data set	Population data	Treatment data	Healthcare costs	Non-healthcare costs
Key metrics	Disease incidence and prevalence Mortality rates Growth rates	Current Txs Tx utilization Tx costs Growth rates	Inpatient costs Outpatient costs Pharmacy costs Cost growth	Lost lifetime wages Decreased patient & caregiver productivity
Sources	CDC, NIH, ACS, ASH[13], SEER	JAMA[14], NIH, Mayo Clinic[15], NEJM, JME[16]	JME, Mayo Clinic, AJH[17]	NIH, AJH, JMCP[18], SEER, AJMC[19]

Table 3: Key data sets and sources

13 ASH, 2018
14 JAMA, 2015
15 Mayo Clinic, 2014
16 JME, 2015
17 AJH, 2009
18 JMCP, 2018
19 AJMC, 2016

Cost Analyses by Total Disease Population and Cohort

The TVM completes the total cost of care picture with analyses on patients 9 years before and after the index year (2020), adjusting for changes in treatment rates, costs, medical inflation rates, and wage growth. The model creates a picture of current 2020 health care spending per disease, built from patient cohort data from 2011-2020. Similarly, the 2029 health care spending is derived from projected patient cohort data from 2020-2029.

The TVM decreases inpatient, pharmacy, and outpatient spending of patients with SCD, MM, and Hem A when they are treated with CGTs. Spend for these patients is reduced to the level of average patients' healthcare costs at the average age of patients with the respective diseases. In addition, the model conservatively estimates the number of treated patients who are clinically eligible for CGT and have access in any given year. Estimates of both the clinically eligible population and patient access are in line with currently marketed CAR-T therapies, the most recently introduced cellular therapies. Due to their labeling and distribution through specialized Comprehensive Cancer Centers, CAR-T therapies are expected to be accessible to only a small percent of the overall eligible cancer population. The model, again, conservatively estimates that the initial eligibility and access would not expand significantly over the 10-year time frame. This is a highly conservative estimate, but is reflective of potential challenges that cell and gene therapies may face if providers are concerned with immunogenic response to therapies, if patients require specialized monitoring, or if regulators and payers restrict allowable care settings.

Importantly, the model assumes CGTs will reduce a patient's annual medical costs to average annual medical costs associated with patients in the general population without the disease. Thus, medical costs are not completely eliminated, but rather reduced for patients treated with CGT. The model also considers changes in the sizes of the patient cohorts each year by factoring in the number of newly diagnosed patients and adjusting for all-cause mortality.

To compare the growing costs for each disease state on a constant dollar value basis, the model also adjusts for expected average annual inflation. The intent of the model is to provide policy makers and payers with a view of the potential savings of CGT if access was available for a portion of the addressable SCD, MM, and Hem A patient populations at the start of 2020. The analysis shows both the overall annual costs as well as the impact of costs accumulating over the 10-year time frame for each disease cohort, factoring in their different survival rates. The TVM provides stakeholders a more complete picture of the costs and savings when valuing new CGTs that could dramatically change the course of care for rare diseases.

Drivers of Disease Costs

The model examines and dissects health care spending for the nearly 37,000 patients who are projected to be diagnosed with one of these diseases in 2020. For each disease state, the patient costs are categorized as medical costs or non-medical costs. Analyzing the costs associated with these three disease states reveals significant variation in the drivers that influence care and health care spend. Disease states like MM are heavily impacted by numerous and costly treatment regimens, many of which require multiple drug combinations. The remaining medical costs, broken down by inpatient and outpatient services, represent a similar cost challenge for the MM community. MM patients tend to be in and out of hospital care due to their advanced age and many comorbidities.

Growth in health care spending is driven by factors such as price inflation of medical therapies, utilization rates of therapies, and a shift in the utilization mix of outpatient and inpatient services over time. The annual growth in medical costs was modeled at 5.3% for the MM disease cohort, 4.6% for the SCD disease cohort, and 4.2% for the Hem A disease cohort. From 2014-2015, health care spending for cancer care increased 5.3%; from 2016-2017 health care spending for hospital care increased 4.6%; and from 2016-2017 health care spending for physician and clinical services increased 4.2%. The model assumes that the care costs for the sickest Hem A patients will increase at the same rate as for cancer patients. However, since SCD patients often manage their pain crises through ER visits, the model used the growth in hospital spending as a proxy. Lastly, since Hem A patients manage their disease through treatment in outpatient heme centers, the growth in spending for physician and clinical services was used as a proxy.[20]

For each of the disease states, there are two key categories of health care costs: (1) therapy and inpatient stays associated with current treatment of the disease and (2) ongoing therapies and outpatient management of care. These two components vary across disease states based on the estimated utilization of acute and outpatient services in 2020. Annual outpatient cost estimates for these patients include provider and facility charges and the associated cost of any treatment they receive at the facility. Similarly, the costs associated with inpatient care are typically the facility charges and the costs any treatments received in an acute care setting.

For each disease state, the annual costs for inpatient and outpatient health care spending were modeled based on costs that were triangulated across peer reviewed studies. In 2020, multiple myeloma patients had a per patient inpatient, outpatient, and treatment annual cost of approximately $280,000, sickle cell patients had a cost of $30,000, and hemophilia A patients, most of whom had a severe form of the disease, had a cost of $200,000. Given the differences in patient demographics, disease progression, disease severity, health care coverage, access and utilization of healthcare, clinical eligibility, treatment type/frequency, and costs for each of the rare diseases should be viewed independently.

20 California Health Almanac May 2019, Health Care Costs 101

Non-medical costs were simplified into costs associated with lost productivity per patient and caregiver and projected over a 10-year period. The model also accounts for the long-term repercussions of lost productivity, as estimated by loss of earnings. Peer-reviewed studies and census data provided average values of missed work days and lost wages per day for the relevant age ranges associated with each disease state.

Most caregivers of patients with rare diseases are immediate relatives. Taking care of family members can be demanding and have an economic impact, resulting in lost income or diminished earning potential. The majority (two-thirds) work while providing care and report that their responsibilities impact their workplace. Significant numbers of caregivers reduced their work hours, took time off or a leave of absence, turned down a promotion, or gave up working entirely to care for a family member. Consequently, nearly all caregivers experienced a negative financial impact, with more than half reporting a high level of financial strain.[21]

Figure 2 below estimates the cumulative dollar value of productivity gains through lost wages for patients and caregivers for each of the three diseases from 2020-2029, totaling $7.5 billion.

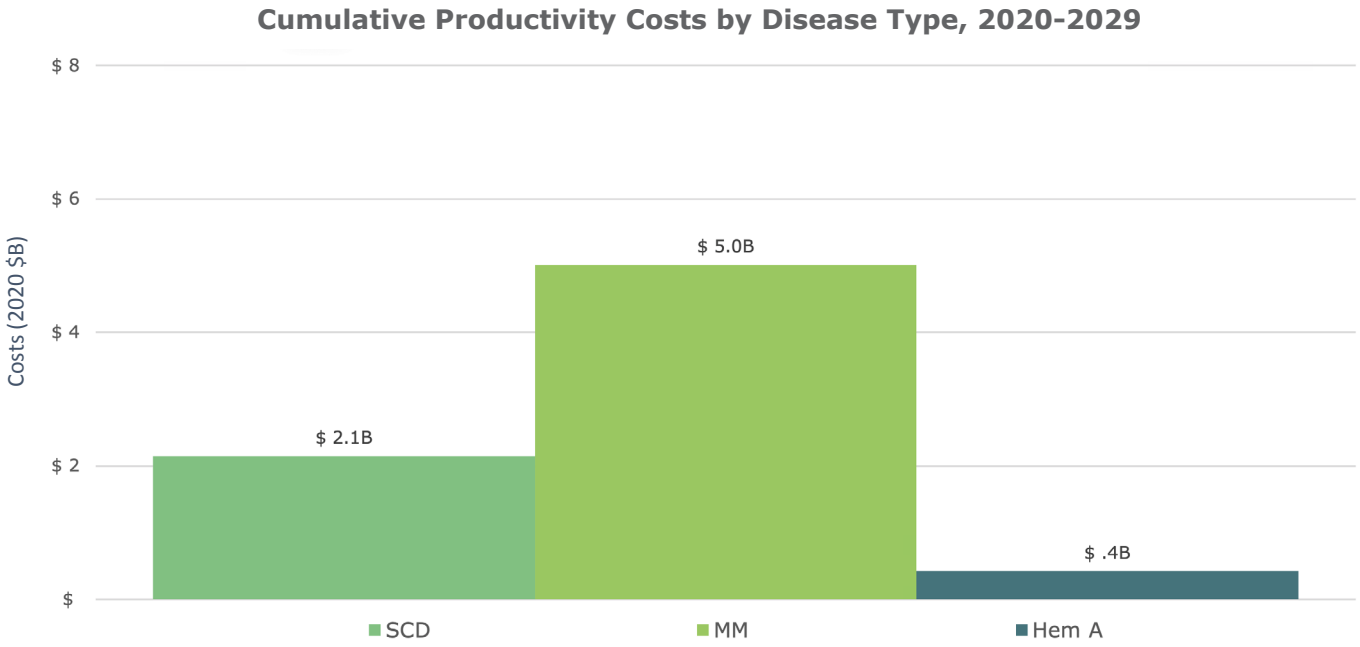


Figure 2: Cumulative patient and caregiver productivity gains by disease state

The combined medical and non-medical costs for the three hematologic disease cohorts totaled approximately $53 billion in 2020, with SC comprising approximately $4 billion of this cost, MM approximately $46 billion, and Hem A approximately $3 billion (Figure 3). These costs balloon to approximately $151 billion in 2029 as a result of increases in each of the cost components (e.g., growth in the affected populations, health care costs, utilization, and wage growth).

21 National Alliance for Caregiving and Global Genes. Rare disease caregiving in America. Feb 2018.

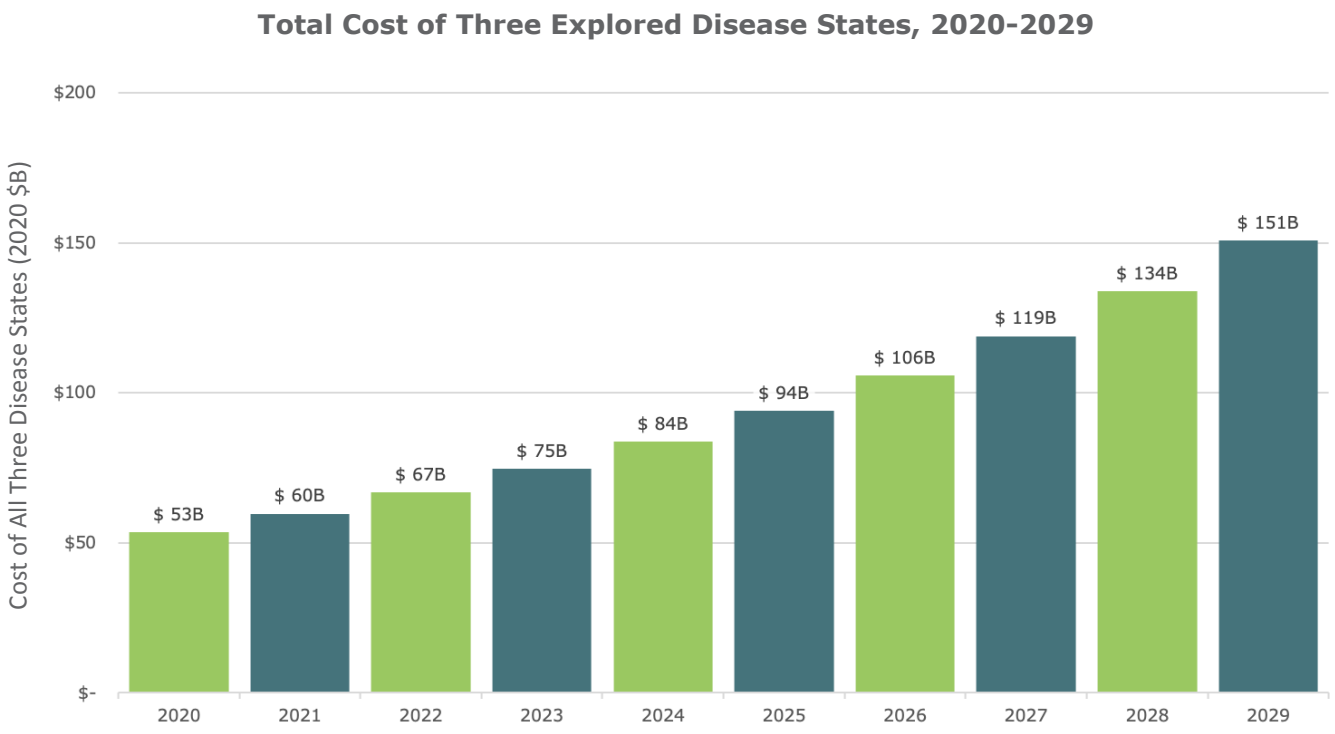


Figure 3: Medical and non-medical cost growth from 2020-2029 of SCD, MM, and Hem A

Modeling Costs in the 2020 Cohort From a Cell and Gene Therapy (CGT)

In 2020, the model introduces a CGT that has a durable response, obtained by eligible patients in each of the three disease cohorts likely to receive treatment. This durable response is assumed for the entire 10-year period. Although evidence of durability remains to be seen, CGT therapies are expected to be curative or near-curative. Therapy administration costs that are in line with those for CAR-T cell therapy are also accounted for in the model (Figure 4).

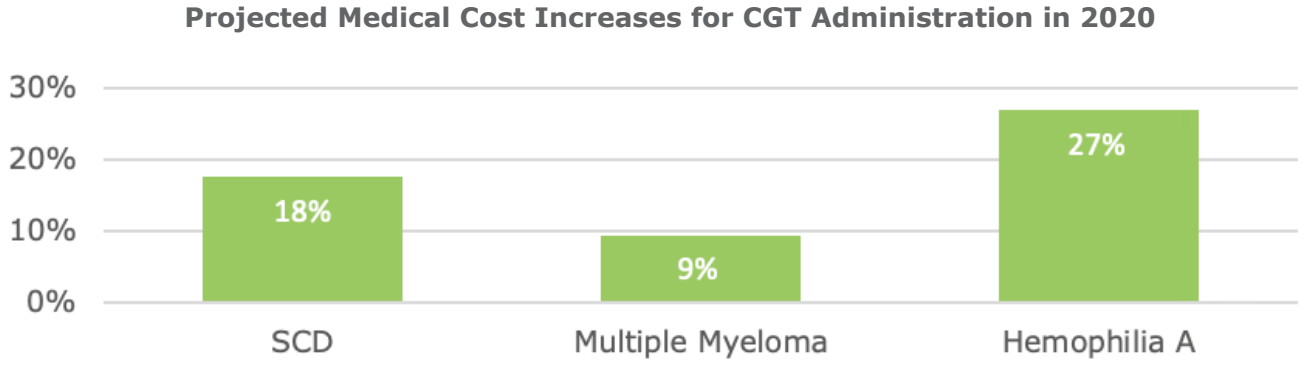


Figure 4: Medical costs for CGT eligible patients including additional administration costs for the 2020 patient population

Total Savings of CGTs From 2020-2029

By 2029, an estimated 53,000 SCD patients, 108,000 MM patients, and 11,000 Hem A patients will have received CGT gene therapy. The use of CGT, averaged across a range of prices as shown in Appendix C resulted in significant cost savings for each of the three rare diseases, with total costs decreasing by 18% for SCD, 23% for Hem A, and 30% for MM (Figures 5-7). While only a small number of Hem A patients benefited from CGT therapy, this cohort realized a significant increase in savings, most likely due to their high annual costs. All but the mildest forms of hemophilia are expensive to treat. This analysis focused exclusively on hemophilia A patients with moderate to severe disease. In the overall hemophilia population, 60% of cases are severe, 15% moderate, and 25% mild.[8] Patients with more severe forms of the disease are likely to have a higher need for replacement clotting factors and can develop immunity to clotting factors, requiring more advanced and expensive treatments.[22]

The largest savings was seen for MM in terms of dollars and as a percentage (30%). Although only 40% of the MM cohort was eligible for durable treatment with CGT versus 70% for either of the other rare diseases, the size of the initial patient cohort was significantly larger than for either of the other two disease groups. Additionally, the inpatient, outpatient, and treatment per patient costs were very high for this population, nearing the per patient cost of severe hemophilia A patients.

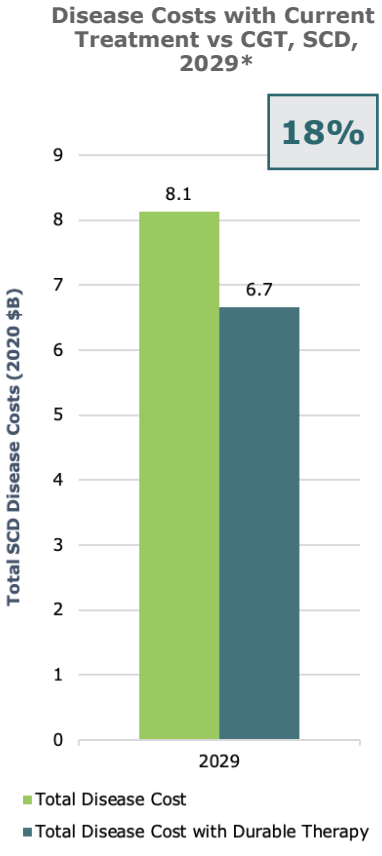


Fig 5: SCD Disease Cost, Current State vs CGT

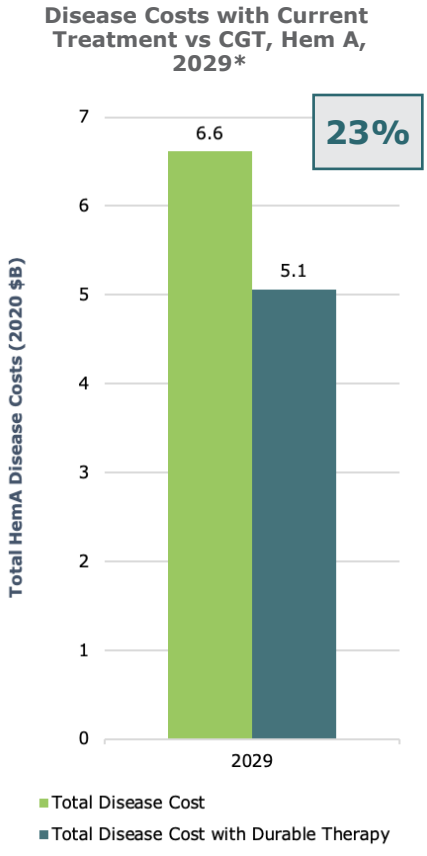


Fig 6: Hem A Disease Cost, Current State vs CGT

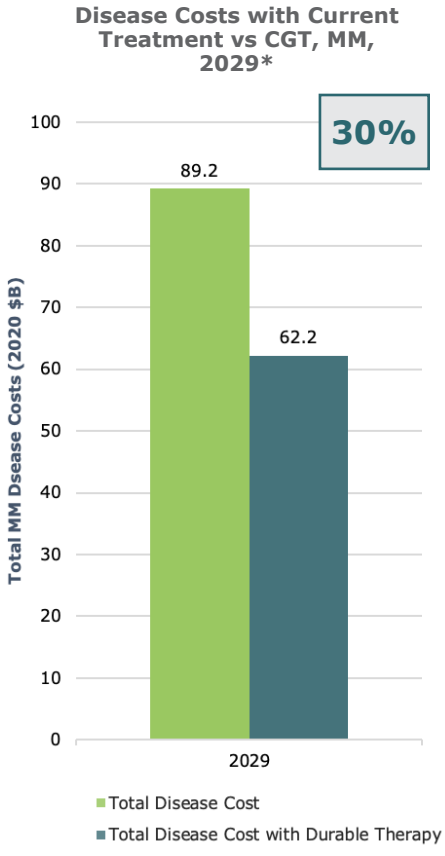


Fig 7: MM Disease Cost, Current State vs CGT

* Expected price increases removed for these calculcations only.

22 Optum Rx. Hemophilia. Drug Class Insight. 2015.

Even at high prices for CGT in SCD and Hem A, savings in medical costs for the three diseases reached $33.6 billion in 2029. Both inpatient and outpatient costs decreased at similar rates. Figure 8 shows that in 2024, four years after CGT therapies are provided to patients with MM, SCD, and Hem A, a reduction in healthcare spending and increase in productivity is realized. The savings are realized when access to the cell and gene therapies have repeatedly and annually taken patients out of the population and reduced that eligible, accessible patient's costs.

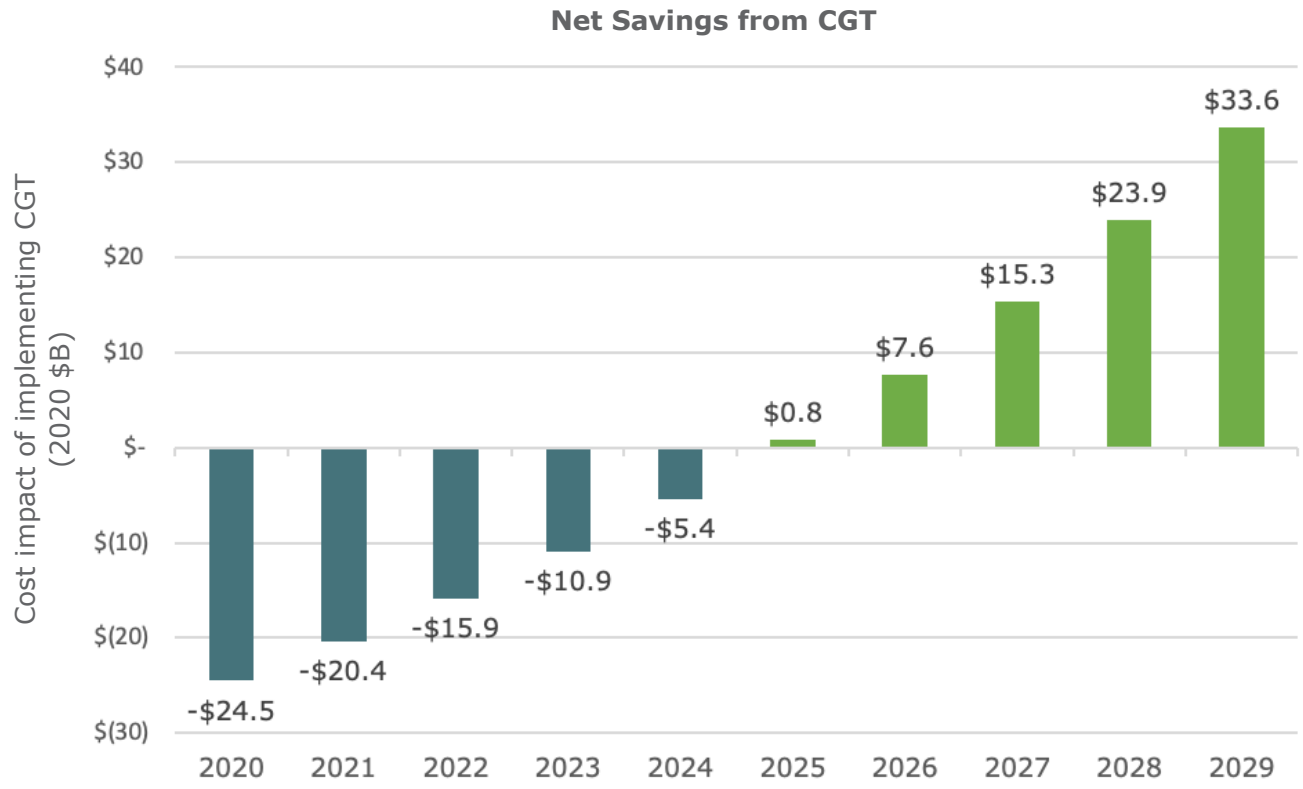


Figure 8: Cost savings from a reduction in healthcare spend over time for patients with access to SCD, MM, and Hem A populations

Improvements in patient productivity equate to $3.5 billion savings in 2029, with the SCD and MM disease cohorts achieving the highest gains in the model. SCD patients tend to be a relatively younger patient population with higher earning potential. MM patients when cured are older but are also the largest disease population examined in this model.

Impact Beyond the 2020 Cohort

Overall, substantial cost savings in the magnitude of billions of dollars was realized across all three diseases cohorts with only a modest uptake of CGT therapy across eligible patient populations from 2020-2029. If an even higher percentage of eligible patients receive access to these transformative therapies, the savings to our health care systems and economy would be even greater. Health care stakeholders should advocate for access to and coverage of CGTs for populations with genetic diseases who would benefit from this transformative therapy. Policies that encourage utilization and reimbursement for the cost and administration of these life changing therapies can help patients attain productive levels of health.

Pricing for CGT

The costs associated with administering CGTs have a significant impact on the net savings associated with their value. In the model, access to CGT by a modest-sized group of patients can significantly increase the medical costs of treatment. The model uses historical prices for CGTs based on recent company decisions on similar pipeline product categories. For example, genetic therapies for SCD and Hem A are priced in the model at list prices comparable to Zolgensma ($2.1 million), a gene therapy for spinal muscular atrophy, a rare pediatric disorder, and Zynteglo ($1.8 million), a gene therapy for beta-thalassemia (approved by the EMA in June 2019; not yet approved in the United States at the time of this writing), a rare blood disorder.[23] A cellular therapy for MM has model pricing that is similar to existing CAR-T cell treatment prices.

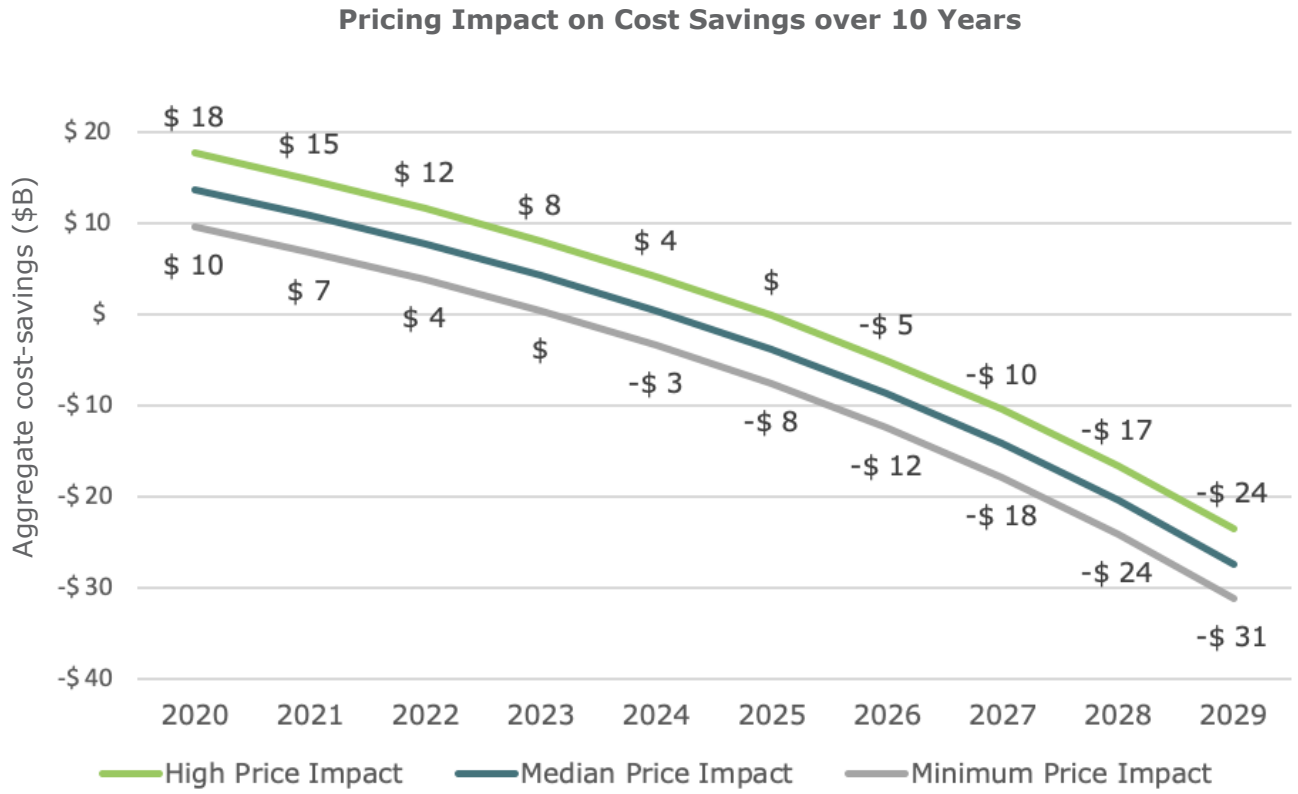


Figure 9: Summary of 180 pricing scenarios spend and savings across all three disease states treated with CGTs

Drug list prices have been rising, resulting in scrutiny from government agencies, pharmacy benefit managers, private payers, and the general public. ARM does not intend to recommend price points to industry or governments. Rather, this analysis demonstrates the value of CGTs. CGTs decrease health care utilization, resulting in savings for patients and their families, payers, and employers.

As Figure 9 shows, CGT prices impacts the time to value realization. At a hypothetical high price of approximately$2 million for diseases like SCD and Hem A, CGT will still result in savings by 2025 across all three disease populations. At a hypothetical minimum price scenario, CGTs will produce net savings by 2023.

23 Forbes June 2019; BioSpace June 2019

Sensitivity Testing

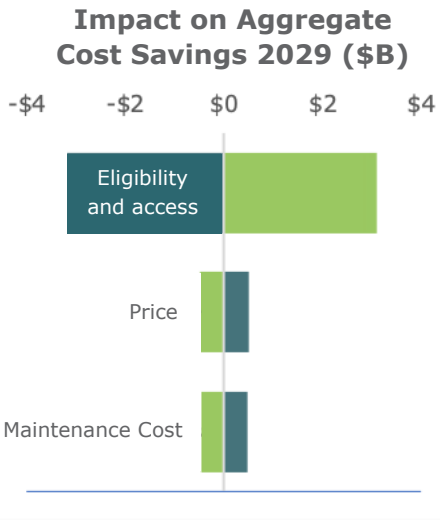


Figure 10: Increase in savings (blue) due to increase by 10% in key parameters in the model

Through the model, it is possible to understand the impact of a pricing corridor on the overall value of CGTs. For each 10% decrease in the average price, payers are likely to experience a $500M increase in their savings. Across two other parameters in the model, eligibility and access to the new therapies and maintenance costs, the savings resulting from CGTs varies considerably.

The tornado chart at the left (Figure 10) shows the impact that changing CGT price, eligibility/access, or maintenance costs by +/-10% has on cost savings for MM, SCD, and Hem A. **Changes in patient eligibility and access have the greatest impact on savings, with expansion leading to an estimated increase of greater than $3 billion by 2029.**

The impact of access is an important finding in this analysis. While there has been an intense discussion surrounding CGT price, access also has an important impact on cost savings. Access enables long term cost offsets and relieves patients and families of financial strain. In fact, the TVM suggests that the advent of CGTs creates urgency for payers to address short-term budget challenges that may impede immediate patient access.

Value Benefit of CGT Access

The model proposed herein provides a framework for payers across the public and private insurance sectors to use when evaluating new CGTs. Many frameworks have been proposed to assess value. Yet few have quantified the value of new therapies in restoring productivity to patients and their caregivers. This model attempts to supplement the conventional use of QALY with a more comprehensive measure — potential wage earnings that are lost from chronic diseases.

For patients who are impacted by genetic diseases, the primary objective of their treatment is to save them from the debilitating effects of the disease. With current treatments for diseases like SCD, MM, and Hem A, patients may be able to ameliorate the symptoms of their diseases but must return to the hospital when symptoms return. Over time, these symptoms lead to additional degenerative conditions that have an increasingly negative impact on patients' quality of life, their ability to engage in society, healthcare utilization, and lifespan. If even a small to moderate proportion of patients have access to CGTs, there could be profound economic, psychological and social impact on how these patients and their families live and work.

As with all investments, access to these CGTs will likely increase costs in the near-term, and this model demonstrates that these new therapies could be successful at decreasing cumulative costs and increasing patient and caregiver productivity within just 3-5 years. In an environment where cost sharing has increasingly shifted toward patients, the ability to increase productivity and earning power benefits both the patient and the payer.

Alternative Payment Structures for Access

Access and eligibility are the most impactful factors in the TVM, assuming that CGTs are effective and durable. More patients that are given a chance to stop the cycle of repeated inpatient or outpatient care associated with their disease can eventually lead to more patients successfully completing therapy. However, expensive therapies carry financial challenges for payers. Payers want patients to access new therapies if they are consistent with how they are approved for use by the U.S. Food and Drug Administration (FDA) and at a cost per member that will be sustainable.

Payers have been exploring alternative payment models for currently available CGTs, including CAR-T cell therapies. In September 2019, Cigna announced that it would institute a per-member, per-month fee to participate in a gene therapy network group that would be able to provide more access to drugs like Yescarta and Kymriah.[24] Because a model that addresses patient productivity is likely to be leveraged by closed networks and public payers like Medicaid, it is worthwhile for payers to consider alternative payment models. Payers today are conditioned to paying for debilitating diseases through annualized budgets that maintain a standard for chronic treatment. The approach of providing a "bolus payment" that can provide long-term savings to patients is challenging to adopt when neither patient eligibility nor access to treatment are foregone conclusions.

Whereas the typical payer approach to medical and therapeutic care is to reimburse services as they are performed, other models allow payers to spread the cost of an expensive treatment over longer periods of time, as the payer can begin to accrue the savings associated with a reduction in treatment costs. A payer "subscribing" to a treatment would gain continuous access to a curative therapy, which could be delivered as needed to members with diseases treatable with a durable CGT. When considering groups of patients with a given condition the subscription model allows payers to more seamlessly transition into paying for curative therapies that benefit their members immediately, while reducing the sticker-shock associated with the cost of expensive treatment. In addition, the subscription model allows public payers, such as Medicaid programs, to incorporate curative therapy costs more easily into long-term budget projections.

Paying for treatments to the extent they prove to be effective, also known as value-based payments, is emerging as a new method for reimbursing high-cost medical treatments. In the case of curative therapies, value-based payments can reduce the risk of paying for expensive treatments that may fail to effectively treat particular patients while allowing payers the opportunity to recoup part of the cost of the treatment. Manufacturers and payers have begun testing this model for new potentially curative treatments including Novartis's Zolgensma.[25] Similarly, state Medicaid agencies are in the early stages of assessing alternative payment models and care programs that can provide access to high cost therapies in a way that will not overburden state budgets.[26]

24 Fierce Healthcare, September 6, 2019
25 MedCity News, September 8, 2019
26 Marwood interviews and analysis

Conclusion

Access to CGTs can represent a profound change for patients who have been resigned to managing their disease with frequent trips to medical facilities and rely on chronic and potentially less effective treatments. A single-administration therapy which has a durable effect spanning to the 10 years — and more, hopefully many more years — can free patients and caregivers from repeated interactions with the healthcare system and to reclaim their lives. The potential to achieve a normal, healthy lifespan may be the most underrated value of CGTs and needs to be considered when assessing the potential of these future therapies and the possibility that some of the durable benefits can last longer than 10 years.

Payers and policy makers have seen precedents for some of the arguments presented in this white paper. Personalized therapies posed similar considerations to the calculations proposed by the TVM. PD-1 and PD-L1 pathways, when accurately identified as a key contributor to malignant cancers, enable patients to receive inhibitor immunotherapy treatments that give patients a chance to live cancer free. Realizing that diagnostics will increase the short term cost of care for relevant cancer patient populations, the Personalized Medicine Coalition recommended a framework that focused on the value of individualized treatment.[27]

The TVM offers a simplified model that includes patients' and caregivers' potential productivity in the calculation of the the overall cost of treatment. In the future, additional frameworks may emerge to assess the value of new CGTs. At present, this model will allow stakeholders, including payers, to evaluate with conservative and transparent rate of access assumptions that may yield reasonable projections that support more immediate and widespread access to care.

It is important to understand that the current cost of therapy plays a significant role in establishing the overall value of single-administration CGTs. As the results of this study reveal, the current environment of rising prices and expensive therapeutic approaches makes considering new mechanisms that expand access to single-administration CGTs even much more urgent. As the TVM shows, administration to the prevalent populations of three hematologic disease states early within the next decade can reduce costs of care by 20-25% even with conservative access assumptions.

27 Personalized Medicine Coalition, 2018

Appendix A

The TVM was informed by several direct interviews with experts in Sickle Cell Disease, Multiple Myeloma, and Hemophilia A. Experts provided clinical insights into how patients with these diseases are managed chronically and how treatments may be evolving in the next 10 years based on their experience with products in clinical trials.

In addition, the model design was informed by research and feedback from, patient support organizations, research support organizations, and several expert agencies such as:

- **NYC Hemophilia Chapter**
- **Multiple Myeloma Research Foundation**
- **American Society of Hematology**
- **The Marwood Group**

With the support of these experts and agencies, the TVM was developed to drive a simplified view that could be utilized between payers and policy makers. Because the model is meant to be a starting point in discussions it makes several assumptions that are worth enumerating and the impact those assumptions are likely to have on the model output.

Category of Assumption	Model Assumption	Impact on Model Savings
Patient eligibility and access to CGT	◆ 70% of incident and prevalent patients in each year are assumed eligible for CGT for SCD and Hem A and 40% for MM ◆ 20% are given access to CGT ◆ Prevalent patient volume growth / decline is expected to continue at historical rates	Very low combined eligibility and access to CGT is expected to have a significantly conservative impact on savings
Pricing for CGT	◆ Prices for non-CGT therapies are expected to increase at historical rates ◆ Loss of exclusivity is not factored in for non-CGT therapies	High prices, historical pricing growth and maintenance of pricing through patent protection is likely to inflate savings
Competition among CGT providers	◆ Price/volume competition for CGT is not included in the model	Lack of competition in post-CGT makes savings more challenging in the short term, but does not significantly affect longer term savings

Appendix B

Value frameworks and models have been proposed but few of them directly address productivity and wages as value measures associated with use of new therapies.

Framework	Perspective	Value Measures
American Society of Clinical Oncology (ASCO) Value Framework	Physician/Patient	Clinical benefit; toxicity; bonus points (i.e. survival, palliation, QoL, treatment-free interval); Costs Derived from population-based evidence
Memorial Sloan Kettering Cancer Center (MSKCC) DrugAbacus	Payer/Policymaker	Life year gain; toxicity; novelty; development cost; rarity; burden, unmet need; prognosis Derived from population-based evidence
Institute for Clinical and Economic Review (ICER) Reports	Payer/Policymaker	Efficacy; harms; quality of evidence; "additional benefits/ harm" "contextual considerations" Derived from population-based evidence
National Comprehensive Care Network (NCCN) Evidence Blocks	Physician/Patient	Efficacy; safety; quality of evidence; consistency of evidence; affordability Derived from population-based evidence
Avalere/FasterCures Patient-Perspective Value Framework (PPVF)	Patient/Physician	"Domains;" patient preferences; patient-centered outcomes; patient & family costs; quality and applicability of evidence; usability & transparency
CHOICE Institute, University of Washington/University of Mississippi Cost-Effectiveness Threshold	Payer/Policymaker	Value of statistical life; welfare economics; revealed preferences; uncertainty in insurance and medical care purchases; case severity; equity; value of hope
Marwood Productivity Loss/Recovery Model	Payer/Policymaker	Inpatient and outpatient treatment, drug, workforce productivity, caregiver productivity Derived from population-based evidence, projections

Appendix C

A variety of pricing scenarios were selected and examined for the model which assesses value across a wide range of possible prices for CGTs. The model has tested more than 180 different prices across the three potential CGTs that ranged from a minimum test price of $150,000 and up to a maximum price test of $2,000,000. The prices entered into the model created 60 different cost savings curves for all three of drugs in this model.

Prices were distributed with more than 50% of test prices in the $100,000-$600,000 price per administration range. The figure below shows the distribution of prices.



Based on the analysis, the following prices were utilized to assess the pricing corridor.

	SCD	MM	Hem A
Base Case	$1,570,526	$373,000	$1,570,526
High Case	$2,000,000	$475,000	$2,000,000
Low Case	$1,141,053	$271,000	$1,141,053



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